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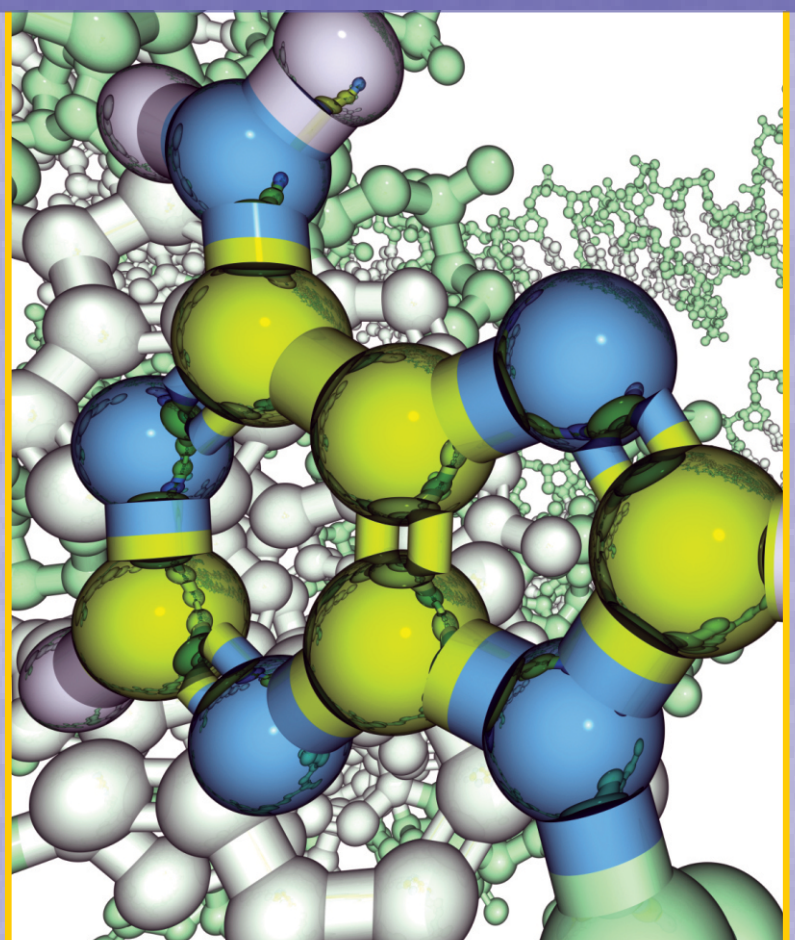
ORGANIC CHEMISTRY

FOR JEE (MAIN & ADVANCED)



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Organic Chemistry For JEE (Main & Advanced)

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Adapted by
M.S. Chouhan

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Solomons, Fryhle and Snyder Organic Chemistry for JEE (Main & Advanced)
Third Edition

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Preface to the Original Edition

"IT'S ORGANIC CHEMISTRY!"

That's what we want students to exclaim after they become acquainted with our subject. Our lives revolve around organic chemistry, whether we all realize it or not. When we understand organic chemistry, we see how life itself would be impossible without it, how the quality of our lives depends upon it, and how examples of organic chemistry leap out at us from every direction. That's why we can envision students enthusiastically exclaiming "It's organic chemistry!" when, perhaps, they explain to a friend or family member how one central theme—organic chemistry—pervades our existence. We want to help students experience the excitement of seeing the world through an organic lens, and how the unifying and simplifying nature of organic chemistry helps make many things in nature comprehensible.

Our book makes it possible for students to learn organic chemistry well and to see the marvelous ways that organic chemistry touches our lives on a daily basis. Our book helps students develop their skills in critical thinking, problem solving, and analysis—skills that are so important in today's world, no matter what career paths they choose. The richness of organic chemistry lends itself to solutions for our time, from the fields of health care, to energy, sustainability, and the environment. After all, it's organic chemistry!

Guided by these goals, and by wanting to make our book even more **accessible to students** than it has ever been before, we have brought many changes to this edition.

NEW TO THIS EDITION

With this edition we bring Scott Snyder on board as a co-author. We're very excited to have Scott join our team. Scott brings a rich resource of new perspectives to the book, particularly in the arena of complex molecule synthesis. Scott has infused new examples and applications of exciting chemistry that help achieve our goals. In addition to adding his perspectives to the presentation of core chemistry throughout the book, Scott's work is manifest in most of this edition's chapter openers and in all of the chapter closers, couched in a new feature called "Why do these topics matter?".

"Why do these topics matter?" is a new feature that bookends each chapter with a teaser in the opener and a captivating example of organic chemistry in the closer. The chapter opener seeks to whet the student's appetite both for the core chemistry in that chapter as well as a prize that comes at the end of the chapter in the form of a "Why do these topics matter?" vignette. These new closers consist of fascinating nuggets of organic chemistry that stem from research relating to medical, environmental, and other aspects of organic chemistry in the world around us, as well as the history of the science. They show the rich relevance of what students have learned to applications that have direct bearing on our lives and wellbeing. For example, in Chapter 6, the opener talks about the some of the benefits and drawbacks of making substitutions in a recipe, and then compares such changes to the nucleophilic displacement reactions that similarly allow chemists to change molecules and their properties. The closer then shows how exactly such reactivity has enabled scientists to convert simple table sugar into the artificial sweetener Splenda which is 600 times as sweet, but has no calories!

Laying the foundation earlier Certain tools are absolutely key to success in organic chemistry. Among them is the ability to draw structural formulas quickly and correctly.

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In this edition, we help students learn these skills even sooner than ever before by moving coverage of structural formulas and the use curved arrows earlier in the text (Section 3.5). We have woven together instruction about Lewis structures, covalent bonds, and dash structural formulas, so that students build their skills in these areas as a coherent unit, using organic examples that include alkanes, alkenes, alkynes, and alkyl halides. One could say that it's a "use organic to teach organic" approach.

Getting to the heart of the matter quicker Acid-base chemistry, and electrophiles and nucleophiles are at the heart of organic chemistry. Students cannot master the subject if they do not have a firm and early grasp of these topics. In this edition, we cut to the chase with these topics earlier in Chapter 3 than ever before, providing a streamlined and highly efficient route to student mastery of these critical concepts.

Improving a core area: substitution reactions All organic instructors know how important it is for their students to have a solid understanding of substitution reactions. This is one reason our text has proven its lasting value. In this edition we have even further enhanced the presentation of substitution reactions in several ways, including a revised introduction of S_N1 reactions (Section 6.10) through the classic hydrolysis experiments of Hughes, and a newly organized presentation of solvent effects on the rate of substitution reactions.

Striking a strong balance of synthetic methods Students need to learn methods of organic synthesis that are useful, as environmentally friendly as possible, and that are placed in the best overall contextual framework. In this edition we incorporate the Swern oxidation (Section 11.4B), long held as a useful oxidation method and one that provides a less toxic alternative to chromate oxidations in some cases. We also restore coverage of the Wolff-Kishner reduction (Section 15.8C) and the Baeyer-Villiger oxidation (Section 15.12), two methods whose importance has been proven by the test of time. The chemistry of radical reactions has also been refocused and streamlined by reducing thermochemistry content and by centralizing the coverage of allylic and benzylic radical substitutions (including NBS reactions) in one chapter (Sections 9.7 and 9.8), instead of distributing it between two, as before. The addition of sulfuric acid to alkenes and the Kolbe reaction have been deleted from the text, since these have little practical use in the laboratory.

Maintaining an eye for clarity With every edition we improve the presentation of topics, reactions, and diagrams where the opportunity arises. This edition includes improved mechanism depictions for aromatic sulfonation and thionyl chloride substitution.

Showing how things work A mechanistic understanding of organic chemistry is key to student success in organic chemistry. Mechanisms have always been central to the book, and in this edition the authors have added a mechanistic framework for the Swern and chromate alcohol oxidations (Section 11.4) by presenting elimination of the carbinol hydrogen and a leaving group from oxygen as the common theme.

TRADITIONAL PEDAGOGICAL STRENGTHS

Solved Problems Knowing "where to begin" to solve organic chemistry problems is one of the greatest challenges faced by today's students. By modeling problem solving strategies, students begin to understand the patterns inherent in organic chemistry and learn to apply that knowledge to new situations. In this edition we have added even more Solved Problems. They are **usually paired with a related Practice Problem**.

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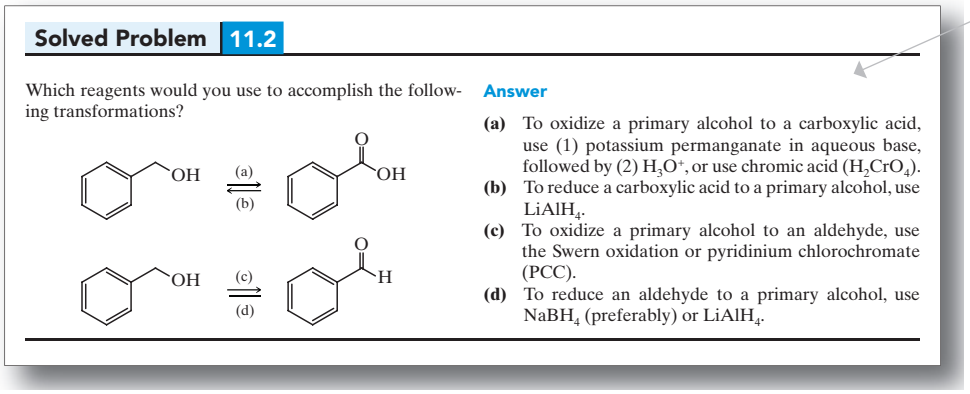
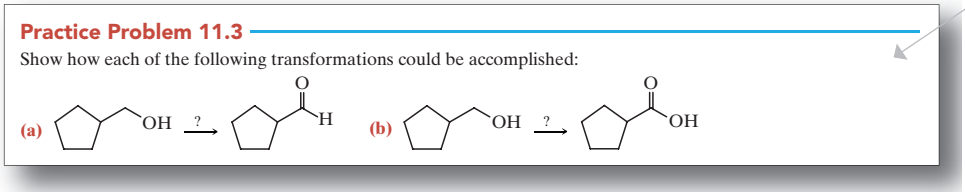
Practice Problems Students need ample opportunities to practice and apply their new found strategies for solving organic chemistry problems. We've added to our rich array of in-text Practice Problems to provide students with even more opportunities to check their progress as they study. If they can work the practice problem, they should move on. If not, they should review the preceding presentation.

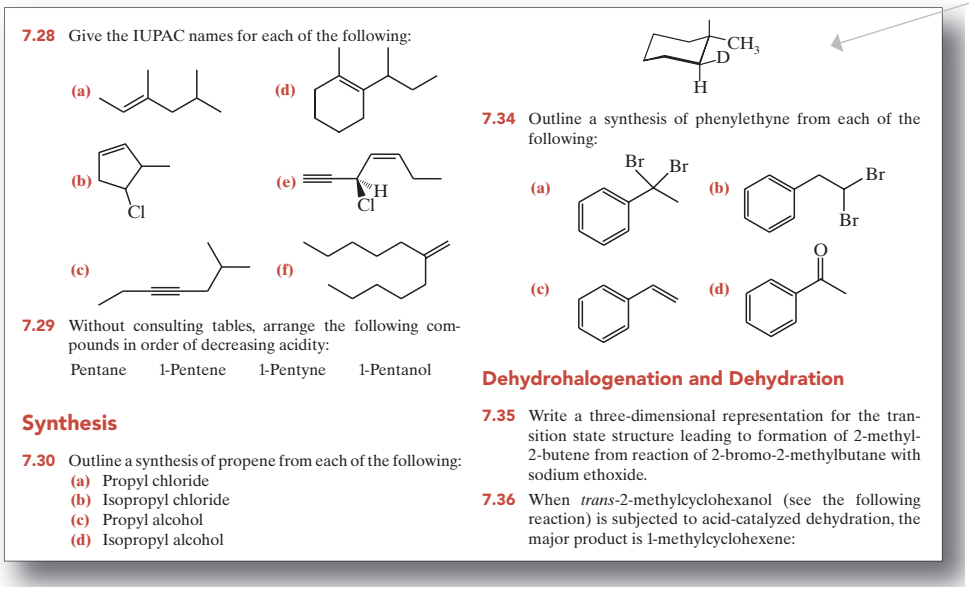


SOLVED PROBLEMS model problem solving strategies.



PRACTICE PROBLEMS provides opportunities to check progress.

End-of-Chapter Problems As athletes and musicians know, practice makes perfect. The same is true with organic chemistry. The End of Chapter problems, categorized by topic, provide essential practice for students and help them build mastery of both concepts and skills presented throughout the chapter. Many of the End of Chapter problems are cast in a visual format using structures, equations, and schemes.



END-OF-CHAPTER PROBLEMS are grouped and labeled by topic. Students and instructors can more easily select problems for specific purposes.

A Mechanism for the Reaction Understanding mechanisms and the ability to recognize patterns among them is a key component in determining student success in organic chemistry. We provide A Mechanism for the Reaction boxes that show step-by-step details about how reactions take place so that students have the tools to understand rather than memorize organic reactions.

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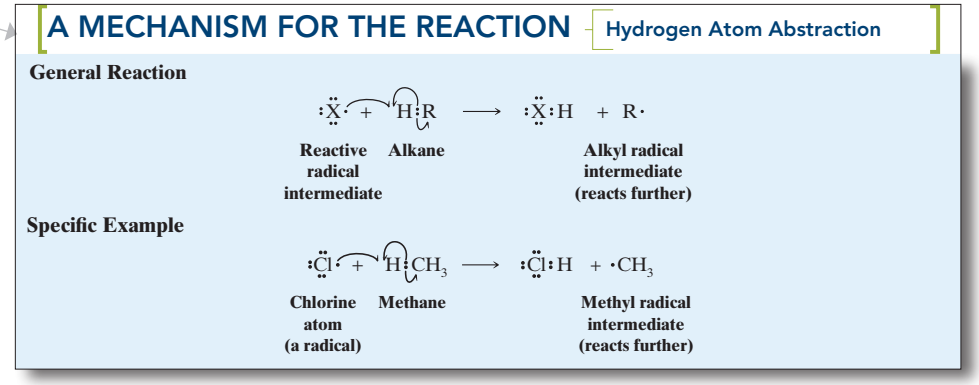
A MECHANISM FOR THE REACTION Stepped out reactions with just the right amount of detail provides the tools for students to understand rather than memorize reaction mechanisms



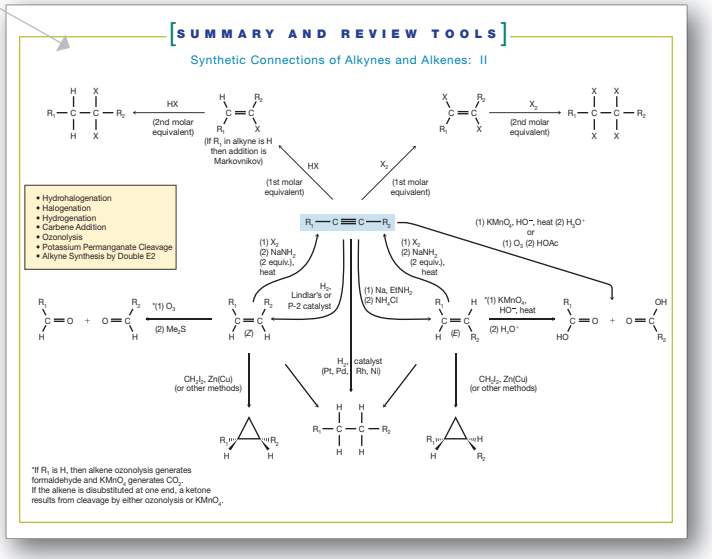
Key Ideas as Bullet Points The amount of content covered in organic chemistry can be overwhelming to students. To help students focus on the most essential topics, key ideas are emphasized as bullet points in every section. In preparing bullet points, we have distilled appropriate concepts into simple declarative statements that convey core ideas accurately and clearly. No topic is ever presented as a bullet point if its integrity would be diminished by oversimplification, however.

"How to" Sections Students need to master important skills to support their conceptual learning. "How to" Sections throughout the text give step-by-step instructions to guide students in performing important tasks, such as using curved arrows, drawing chair conformations, planning a Grignard synthesis, determining formal charges and writing Lewis structures.

The Chemistry of . . . . Virtually every instructor has the goal of showing students how organic chemistry relates to their field of study and to their everyday life experience. The authors assist their colleagues in this goal by providing boxes titled "The Chemistry of …" that provide interesting and targeted examples that engage the student with chapter content.

Summary and Review Tools At the end of each chapter, Summary and Review Tools provide visually oriented roadmaps and frameworks that students can use to help organize and assimilate concepts as they study and review chapter content. Intended to accommodate diverse learning styles, these include Synthetic

SUMMARY AND REVIEW TOOLS Visually oriented study tools accommodate diverse learning styles.



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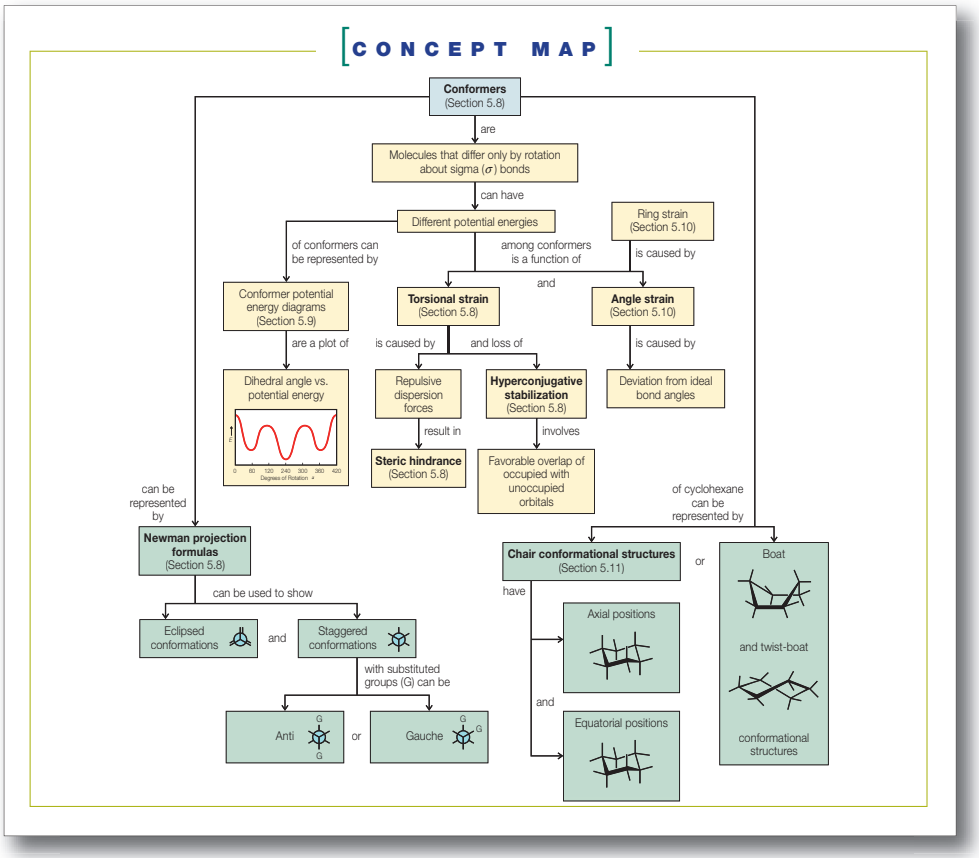

Connections, Concept Maps, Thematic Mechanism Review Summaries, and the detailed Mechanism for the Reaction boxes already mentioned. We also provide Helpful Hints and richly annotated illustrations throughout the text.

COVERAGE

Throughout the book, we have streamlined or reduced content to match the modern practice of organic chemistry, and we have provided new coverage of current reactions, while maintaining our commitment to an appropriate level and breadth of coverage.

- Chapters on carbonyl chemistry that are organized to emphasize mechanistic themes of nucleophilic addition, acyl substitution, and reactivity at the α-carbon.

ORGANIZATION—An Emphasis on the Fundamentals

So much of organic chemistry makes sense and can be generalized if students master and apply a few fundamental concepts. Therein lays the beauty of organic chemistry. If students learn the essential principles, they will see that memorization is not needed to succeed.

Most important is for students to have a solid understanding of structure—of hybridization and geometry, steric hindrance, electronegativity, polarity, formal charges, and resonance—so that they can make intuitive sense of mechanisms. It is with these topics that we begin in Chapter 1. In Chapter 2 we introduce the families of functional groups—so that students have a platform on which to apply these concepts.

We begin our study of mechanisms in the context of acid-base chemistry in Chapter 3. Acid-base reactions are fundamental to organic reactions, and they

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lend themselves to introducing several important topics that students need early in the course: (1) curved arrow notation for illustrating mechanisms, (2) the relationship between free-energy changes and equilibrium constants, and (3) the importance of inductive and resonance effects and of solvent effects.

In Chapter 3 we present the first of many "A Mechanism for the Reaction" boxes, using an example that embodies both Brønsted-Lowry and Lewis acid-base principles. All throughout the book, we use boxes like these to show the details of key reaction mechanisms. All of the Mechanism for the Reaction boxes are listed in the Table of Contents so that students can easily refer to them when desired.

A central theme of our approach is to emphasize the relationship between structure and reactivity. This is why we choose an organization that combines the most useful features of a functional group approach with one based on reaction mechanisms. Our philosophy is to emphasize mechanisms and fundamental principles, while giving students the anchor points of functional groups to apply their mechanistic knowledge and intuition. The structural aspects of our approach show students what organic chemistry is. Mechanistic aspects of our approach show students how it works. And wherever an opportunity arises, we show them what it does in living systems and the physical world around us.

In summary, our writing reflects the commitment we have as teachers to do the best we can to help students learn organic chemistry and to see how they can apply their knowledge to improve our world. The enduring features of our book have proven over the years to help students learn organic chemistry.

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Preface to the Adapted Version

This book is dedicated to the lotus feet of Revered Guruji

SHRI KESARAM JI MAHARAJ

It is a matter of great pleasure for me to present the second edition of the book before engineering aspirants. This book was written because I felt the need for a textbook that corresponds closely to the course that I teach. Although the book is organized along tried-and- true functional-group lines, it contains some unique features that have served me well in both my teaching and understanding of Organic Chemistry.

My four major concerns in both the initial writing and the revision of this text were readability, presentation, organization, and accuracy. In the current scenario of stiff competition especially for engineering entrances, one must be clear that almost all the sincere applicants are well equipped with the facts of subject; yet, the winner is the one who knows how to use these facts with accuracy and efficiency. As an experienced teacher, I would like to suggest students three golden rules to score high in Organic Chemistry:

1. Do not lag behind in schedule.
2. Work out a number of problems of different types.
3. Revise through short notes.

I hope that the present book will cater to the needs of engineering aspirants. As a matter of fact, they will enjoy the present venture and I would feel rewarded if this book is helpful for the students and teachers in real terms. All efforts have been made to make the book error-free; however, a few misprints may inadvertently creep.

I acknowledge the blessing and support of my mother Smt. Raj Kanwar, father Shri B.S. Chouhan, brother Dr. V. S. Chouhan, wife Ms. Meena Chouhan and daughter. They inspired me all the time during the preparation of this book.

The support and valuable suggestions from Mr. V.K. Jaiswal, Mr. N. Avasthi, Mr. Akshay Chawdhary, Dr. S. Kothari, Mr. Navneet Jethwani, Ms. Neha Joshi, Mr. Ashish Mishra, Mr. Kumud Ranjan, Mr. Mohit Sayal, Mr. Hanuman Prasad Sahay, Mr. Vineet Khatri, Mr. Govind Khadelwal, Mr. Manish Arora, Mr. Rahul Malay, Mr. Rahul Pareek, Mr. Divyesh Tiwari, Mr. Omkar Kelapure, Mr. Mayank Pareek, Mr. Gurpreet Singh, Mr. Yogesh Jain, Ms. Anjana Kamal, Mr. Anit Chaudhry, Mr. Shaliwahan Singh Rathore and Mr. Kishore Kilani, are highly acknowledged. I also pay my sincere thanks to all the esteemed members of Wiley India and specially Ms. Anjali Chadha, Ms. Seema Sajwan and Mr. Rakesh Poddar in bringing out this book in such a nice form.

In the end, constructive criticism and valuable suggestions from the readers are most welcome to make the book more useful.

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T. W. GRAHAM SOLOMONS did his undergraduate work at The Citadel and received his doctorate in organic chemistry in 1959 from Duke University where he worked with C. K. Bradsher. Following this he was a Sloan Foundation Postdoctoral Fellow at the University of Rochester where he worked with V. Boekelheide. In 1960 he became a charter member of the faculty of the University of South Florida and became Professor of Chemistry in 1973. In 1992 he was made Professor Emeritus. In 1994 he was a visiting professor with the Faculté des Sciences Pharmaceutiques et Biologiques, Université René Descartes (Paris V). He is a member of Sigma Xi, Phi Lambda Upsilon, and Sigma Pi Sigma. He has received research grants from the Research Corporation and the American Chemical Society Petroleum Research Fund. For several years he was director of an NSF-sponsored Undergraduate Research Participation Program at USF. His research interests have been in the areas of heterocyclic chemistry and unusual aromatic compounds. He has published papers in the *Journal of the American Chemical Society*, the *Journal of Organic Chemistry*, and the *Journal of Heterocyclic Chemistry*. He has received several awards for distinguished teaching. His organic chemistry textbooks have been widely used for 30 years and have been translated into French, Japanese, Chinese, Korean, Malaysian, Arabic, Portuguese, Spanish, Turkish, and Italian. He and his wife Judith have a daughter who is a building conservator and a son who is a research biochemist.

CRAIG BARTON FRYHLE is Chair and Professor of Chemistry at Pacific Lutheran University. He earned his B.A. degree from Gettysburg College and Ph.D. from Brown University. His experiences at these institutions shaped his dedication to mentoring undergraduate students in chemistry and the liberal arts, which is a passion that burns strongly for him. His research interests have been in areas relating to the shikimic acid pathway, including molecular modeling and NMR spectrometry of substrates and analogues, as well as structure and reactivity studies of shikimate pathway enzymes using isotopic labeling and mass spectrometry. He has mentored many students in undergraduate research, a number of who have later earned their Ph.D. degrees and gone on to academic or industrial positions. He has participated in workshops on fostering undergraduate participation in research, and has been an invited participant in efforts by the National Science Foundation to enhance undergraduate research in chemistry. He has received research and instrumentation grants from the National Science Foundation, the M J. Murdock Charitable Trust, and other private foundations. His work in chemical education, in addition to textbook coauthorship, involves incorporation of student-led teaching in the classroom and technology-based strategies in organic chemistry. He has also developed experiments for undergraduate students in organic laboratory and instrumental analysis courses. He has been a volunteer with the hands-on science program in Seattle public schools, and Chair of the Puget Sound Section of the American Chemical Society. His passion for climbing has led to ascents of high peaks in several parts of the world. He resides in Seattle with his wife, where both enjoy following the lives of their two daughters as they unfold in new places.

SCOTT A. SNYDER is Associate Professor of Chemistry at Columbia University. He grew up in the suburbs of Buffalo NY and was an undergraduate at Williams College, where he graduated summa cum laude in 1999, before pursuing his doctoral studies at The Scripps Research Institute under the tutelege of K. C. Nicolaou as an NSF, Pfizer,

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and Bristol-Myers-Squibb predoctoral fellow. While there, he co-authored the graduate textbook *Classics in Total Synthesis II* with his doctoral mentor. Scott was then an NIH postdoctoral fellow in the laboratories of E. J. Corey at Harvard University before assuming his current position in 2006. His research interests lie in the arena of natural products total synthesis, especially in the realm of unique polyphenols and halogenated materials, and to date he has trained more than 60 students at the high school, undergraduate, graduate, and postdoctoral levels and co-authored more than 40 research and review articles. Scott has received a number of awards and honors, including a Camille and Henry Dreyfus New Faculty Award, Amgen New Faculty and Young Investigator Awards, Eli Lilly New Faculty and Grantee Awards, a Bristol-Myers Squibb Unrestricted Grant Award, an NSF CAREER Award, an Alfred P. Sloan Foundation Fellowship, a DuPont Young Professor Award, and an Arthur C. Cope Scholar Award from the American Chemical Society. He has also received recognition for his teaching through a Cottrell Scholar Award from the Research Corporation for Science Advancement and a Columbia Presidential Teaching Award. He is a member of the international advisory board for *The Chemical Record* and the editorial board of *Chirality*. He lives north of New York City with his wife Cathy where he enjoys gardening, cooking, and watching movies.

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About the Adapting Author

Mahendra Singh Chouhan (MSC Sir) is a renowned name in the realm of Organic Chemistry. Though a Chemical engineer from Mumbai University, he has great passion for the subject that led him to impart guidance to engineering aspirants on a regular basis. His in-depth knowledge and vast teaching experience has helped innumerable students to achieve their dream of excelling in engineering and other such tough challenges.

He has launched a website to extend the benefits of his expertise beyond the geographical barriers to all those who dare to dream and seek—www.winvall.com and www.shivwin.com. The website provides expert guidance in all areas of the subject in a most skillful manner. There are quizzes, challenging questions, notes, e-books, videos, etc. This website is a complete guide in itself for organic chemistry and has been designed for engineering, keeping in mind CBSE syllabus and various other syllabi. Highly recommended for high flyers!

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To the Student

Contrary to what you may have heard, organic chemistry does not have to be a difficult course. It will be a rigorous course, and it will offer a challenge. But you will learn more in it than in almost any course you will take—and what you learn will have a special relevance to life and the world around you. However, because organic chemistry can be approached in a logical and systematic way, you will find that with the right study habits, mastering organic chemistry can be a deeply satisfying experience. Here, then, are some suggestions about how to study:

1. **Keep up with your work from day to day—never let yourself get behind.** Organic chemistry is a course in which one idea almost always builds on another that has gone before. It is essential, therefore, that you keep up with, or better yet, be a little ahead of your instructor. Ideally, you should try to stay one day ahead of your instructor's lectures in your own class preparations. The lecture, then, will be much more helpful because you will already have some understanding of the assigned material. Your time in class will clarify and expand ideas that are already familiar ones.

2. **Study material in small units, and be sure that you understand each new section before you go on to the next.** Again, because of the cumulative nature of organic chemistry, your studying will be much more effective if you take each new idea as it comes and try to understand it completely before you move on to the next concept.

3. **Work all of the in-chapter and assigned problems.** One way to check your progress is to work each of the in-chapter problems when you come to it. These problems have been written just for this purpose and are designed to help you decide whether or not you understand the material that has just been explained. You should also carefully study the Solved Problems. If you understand a Solved Problem and can work the related in-chapter problem, then you should go on; if you cannot, then you should go back and study the preceding material again. Work all of the problems assigned by your instructor from the end of the chapter, as well. Do all of your problems in a notebook and bring this book with you when you go to see your instructor for extra help.

4. **Write when you study.** Write the reactions, mechanisms, structures, and so on, over and over again. Organic chemistry is best assimilated through the fingertips by writing, and not through the eyes by simply looking, or by highlighting material in the text, or by referring to flash cards. There is a good reason for this. Organic structures, mechanisms, and reactions are complex. If you simply examine them, you may think you understand them thoroughly, but that will be a misperception. The reaction mechanism may make sense to you in a certain way, but you need a deeper understanding than this. You need to know the material so thoroughly that you can explain it to someone else. This level of understanding comes to most of us (those of us without photographic memories) through writing. Only by writing the reaction mechanisms do we pay sufficient attention to their details, such as which atoms are connected to which atoms, which bonds break in a reaction and which bonds form, and the three-dimensional aspects of the structures. When we write reactions and mechanisms, connections are made in our brains that provide the long-term memory needed for success in organic chemistry. We virtually guarantee that your grade in the course will be directly proportional to the number of pages of paper that your fill with your own writing in studying during the term.

5. **Learn by teaching and explaining.** Study with your student peers and practice explaining concepts and mechanisms to each other. Use the exercises your instructor may assign as vehicles for teaching and learning interactively with your peers.

6. **Use the answers to the problems in the Study Guide in the proper way.** Refer to the answers only in two circumstances: (1) When you have finished a problem, use the Study Guide to check your answer. (2) When, after making a real effort to solve the problem, you find that you are completely stuck, then look at the answer for a clue and go back to work out the problem on your own. The value of a problem is in solving it. If you simply read the problem and look up the answer, you will deprive yourself of an important way to learn.

7. **Use molecular models when you study.** Because of the three-dimensional nature of most organic molecules, molecular models can be an invaluable aid to your understanding of them.

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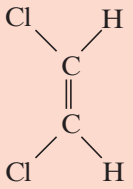
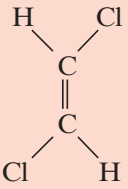
1

The Basics: Bonding and Molecular Structure



cis-1,2-Dichloroethene



trans-1,2-Dichloroethene

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1.6 | Hyperconjugation
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1.9 | The Structure of Ethyne (Acetylene): *sp* Hybridization
1.10 | HOW TO Interpret and Write Structural Formulas

Organic chemistry is a part of our lives at every moment. Organic molecules comprise the tissue of plants as mighty as the redwoods, convey signals from one neuron to the next in animals, store the genetic information of life, and are the food we eat each day. The growth of living things from microbes to elephants rests on organic reactions, and organic reactions provide the energy that drives our muscles and our thought processes.

Our lives depend on organic chemistry in many other ways as well. Every article of clothing we wear is a product of organic chemistry, whether the fibers are natural or synthetic. Hardly a minute goes by when we're not using something made of organic molecules, such as a pen, a computer keyboard, a music player, or a cellular phone. We view display screens made of organic liquid crystal arrays. Natural organic polymers comprise wood and the paper we read. Natural and synthetic organic molecules enhance our health. There is not a single aspect of our lives that is not in some way dependent on organic chemistry. But what is organic chemistry?

Organic chemistry is the chemistry of compounds that contain the element carbon.

Clearly, carbon compounds are central to life on this planet. Carbon as an element, however, has its origin elsewhere.

1.1 | DEVELOPMENT OF THE SCIENCE OF ORGANIC CHEMISTRY

The science of organic chemistry began to flower with the demise of a nineteenth century theory called vitalism. According to vitalism, organic compounds were only those that came from living organisms, and only living things could synthesize organic compounds through intervention of a vital force. Inorganic compounds were considered those compounds that came from nonliving sources.

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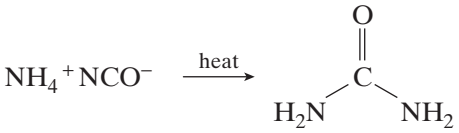
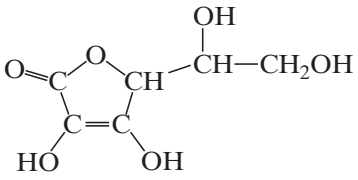
Friedrich Wöhler, however, discovered in 1828 that an organic compound called urea (a constituent of urine) could be made by evaporating an aqueous solution of the inorganic compound ammonium cyanate. With this discovery, the synthesis of an organic compound, began the evolution of organic chemistry as a scientific discipline.



Ammonium cyanate **Urea**

Despite the demise of vitalism in science, the word "organic" is still used today by some people to mean "coming from living organisms" as in the terms "organic vitamins" and "organic fertilizers." The commonly used term "organic food" means that the food was grown without the use of synthetic fertilizers and pesticides. An "organic vitamin" means to these people that the vitamin was isolated from a natural source and not synthesized by a chemist. While there are sound arguments to be made against using food contaminated with certain pesticides, while there may be environmental benefits to be obtained from organic farming, and while "natural" vitamins may contain beneficial substances not present in synthetic vitamins, it is impossible to argue that pure "natural" vitamin C, for example, is healthier than pure "synthetic" vitamin C, since the two substances are identical in all respects. In science today, the study of compounds from living organisms is called natural products chemistry.



Vitamin C

1.2 | ATOMIC STRUCTURE

Before we begin our study of the compounds of carbon we need to Practice some basic but familiar ideas about the chemical elements and their structure.

- The **compounds** we encounter in chemistry are made up of **elements** combined in different proportions.
- **Elements** are made up of **atoms**. An atom consists of a dense, positively charged *nucleus* containing **protons** and **neutrons** and a surrounding cloud of **electrons**.

Each proton of the nucleus bears one positive charge; electrons bear one negative charge. Neutrons are electrically neutral; they bear no charge. Protons and neutrons have nearly equal masses (approximately 1 atomic mass unit each) and are about 1800 times as heavy as electrons. Most of the **mass** of an atom, therefore, comes from the mass of the nucleus; the atomic mass contributed by the electrons is negligible. Most of the **volume** of an atom, however, comes from the electrons; the volume of an atom occupied by the electrons is about 10,000 times larger than that of the nucleus.

The elements commonly found in organic molecules are carbon, hydrogen, nitrogen, oxygen, phosphorus, and sulfur, as well as the halogens: fluorine, chlorine, bromine, and iodine.

Each **element** is distinguished by its **atomic number** (***Z***), a **number equal to the number of protons in its nucleus**. Because an atom is electrically neutral, **the atomic number also equals the number of electrons surrounding the nucleus**.

1.2A Isotopes

Before we leave the subject of atomic structure and the periodic table, we need to examine one other observation: **the existence of atoms of the same element that have different masses**.

For example, the element carbon has six protons in its nucleus giving it an atomic number of 6. Most carbon atoms also have six neutrons in their nuclei, and because each proton and each neutron contributes one atomic mass unit (1 amu) to the mass of the atom, carbon atoms of this kind have a mass number of 12 and are written as ^{12}C.

- **Although all the nuclei of all atoms of the same element will have the same number of protons**, some atoms of the same element **may have different masses** because they have **different numbers of neutrons**. Such atoms are called **isotopes**.

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For example, about 1% of the atoms of elemental carbon have nuclei containing 7 neutrons, and thus have a mass number of 13. Such atoms are written ^{13}C. A tiny fraction of carbon atoms have 8 neutrons in their nucleus and a mass number of 14. Unlike atoms of carbon-12 and carbon-13, atoms of carbon-14 are radioactive. The ^{14}C isotope is used in *carbon dating*. The three forms of carbon, ^{12}C, ^{13}C, and ^{14}C, are isotopes of one another.

Most atoms of the element hydrogen have one proton in their nucleus and have no neutron. They have a mass number of 1 and are written ^{1}H. A very small percentage (0.015%) of the hydrogen atoms that occur naturally, however, have one neutron in their nucleus. These atoms, called *deuterium* atoms, have a mass number of 2 and are written ^{2}H. An unstable (and radioactive) isotope of hydrogen, called *tritium* (^{3}H), has two neutrons in its nucleus.

Practice Problem 1.1

There are two stable isotopes of nitrogen, ^{14}N and ^{15}N. How many protons and neutrons does each isotope have?

1.2B Valence Electrons

We discuss the electron configurations of atoms in more detail in Section 1.10. For the moment we need only to point out that the electrons that surround the nucleus exist in **shells** of increasing energy and at increasing distances from the nucleus. The most important shell, called the **valence shell**, is the outermost shell because the electrons of this shell are the ones that an atom uses in making chemical bonds with other atoms to form compounds.

- How do we know how many electrons an atom has in its valence shell? We look at the periodic table. The number of electrons in the valence shell (called **valence electrons**) is equal to the group number of the atom. For example, carbon is in group **IVA** and carbon has *four* valence electrons; oxygen is in group **VIA** and oxygen has *six* valence electrons. The halogens of group **VIIA** all have *seven* electrons.

Practice Problem 1.2

How many valence electrons does each of the following atoms have?

(a) Na **(b)** Cl **(c)** Si

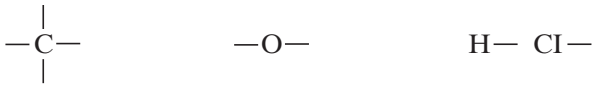
(d) B **(e)** Ne **(f)** N

1.3 | THE STRUCTURAL THEORY OF ORGANIC CHEMISTRY

Between 1858 and 1861, August Kekulé, Archibald Scott Couper, and Alexander M. Butlerov, working independently, laid the basis for one of the most important theories in chemistry: the **structural theory**.

Two central premises are fundamental:

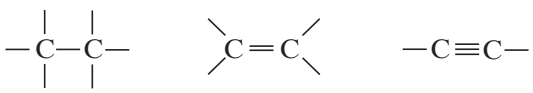
1. The atoms in organic compounds can form a fixed number of bonds using their outermost shell (valence) electrons. Carbon is *tetravalent*; that is, carbon atoms have four valence electrons and can form four bonds. Oxygen is *divalent*, and hydrogen and (usually) the halogens are *monovalent*:



Carbon atoms are tetravalent | **Oxygen atoms are divalent** | **Hydrogen and halogen atoms are monovalent**

2. A carbon atom can use one or more of its valence electrons to form bonds to other carbon atoms:

Carbon–carbon bonds



Single bond | **Double bond** | **Triple bond**

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In his original publication Couper represented these bonds by lines much in the same way that most of the formulas in this book are drawn. In his textbook (published in 1861), Kekulé gave the science of organic chemistry its modern definition: ***a study of the compounds of carbon***.

1.3A Isomers: The Importance of Structural Formulas

The structural theory allowed early organic chemists to begin to solve a fundamental problem that plagued them: the problem of **isomerism**. These chemists frequently found examples of **different compounds that have the same molecular formula**. Such compounds are called **isomers**.

Helpful Hint: Terms and concepts that are fundamentally important to your learning organic chemistry are set in bold blue type. You should learn them as they are introduced. These terms are also defined in the glossary.

Let us consider an example involving two compounds that have practical uses: acetone, used in nail polish remover and as a paint solvent, and propylene oxide, used with seaweed extracts to make food-grade thickeners and foam stabilizers for beer (among other applications). Both of these compounds have the molecular formula C_3H_6O and therefore the same molecular weight. Yet acetone and propylene oxide have distinctly different boiling points and chemical reactivity that, as a result, lend themselves to distinctly different practical applications. Their shared molecular formula simply gives us no basis for understanding the differences between them. We must, therefore, move to a consideration of their **structural formulas**.

On examining the structures of acetone and propylene oxide several key aspects are clearly different (Fig. 1.1). Acetone contains a double bond between the oxygen atom and the central carbon atom. Propylene oxide does not contain a double bond, but has three atoms joined in a ring. The connectivity of the atoms is clearly different in acetone and propylene oxide. Their structures have the same molecular formula but a different constitution. We call such compounds constitutional isomers.

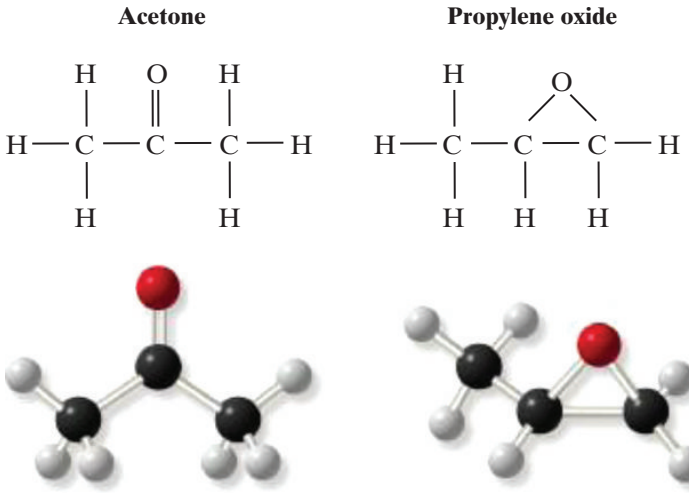

Figure 1.1 Ball-and-stick models and chemical formulas show the different structures of acetone and propylene oxide.

1. **Constitutional isomers** are different compounds that have the same molecular formula but differ in the sequence in which their atoms are bonded, that is, in their connectivity.
2. Constitutional isomers usually have different physical properties (e.g., melting point, boiling point, and density) and different chemical properties (reactivity).

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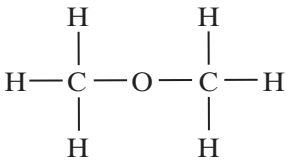
Solved Problem 1.1

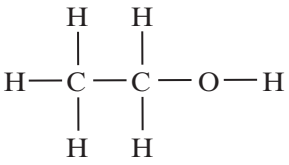
There are two constitutional isomers with the formula C_2H_6O. Write structural formulas for these isomers.

Answer

If we recall that carbon can form four covalent bonds, oxygen can form two, and hydrogen only one, we can arrive at the following constitutional isomers.



Dimethyl ether



Ethanol

It should be noted that these two isomers are clearly different in their physical properties. At room temperature and 1 atm pressure, dimethyl ether is a gas. Ethanol is a liquid.

1.3B The Tetrahedral Shape of Methane

In 1874, the structural formulas originated by Kekulé, Couper, and Butlerov were expanded into three dimensions by the independent work of J. H. van't Hoff and J. A. Le Bel. van't Hoff and Le Bel proposed that the four bonds of the carbon atom in methane, for example, are arranged in such a way that they would point toward the corners of a regular tetrahedron, the carbon atom being placed at its center (Fig. 1.2). The necessity for knowing the arrangement of the atoms in space, taken together with an understanding of the order in which they are connected, is central to an understanding of organic chemistry, and we shall have much more to say about this later, in Chapters 4 and 5.

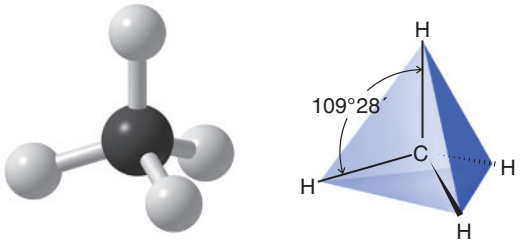


Figure 1.2 The tetrahedral structure of methane.

1.4 | CHEMICAL BONDS: THE OCTET RULE

The first explanations of the nature of chemical bonds were advanced by G. N. Lewis (of the University of California, Berkeley) and W. Kössel (of the University of Munich) in 1916. Two major types of chemical bonds were proposed:

1. **Ionic** (or electrovalent) bonds are formed by the transfer of one or more electrons from one atom to another to create ions.
2. **Covalent** bonds result when atoms share electrons.

The central idea in their work on bonding is that atoms without the electronic configuration of a noble gas generally react to produce such a configuration because these configurations are known to be highly stable. For all of the noble gases except helium, this means achieving an octet of electrons in the valence shell.

- The tendency for an atom to achieve a configuration where its valence shell contains eight electrons is called the **octet rule**.

The concepts and explanations that arise from the original propositions of Lewis and Kössel are satisfactory for explanations of many of the problems we deal with in organic chemistry today. For this reason we shall Practice these two types of bonds in more modern terms.

1.4A Ionic Bonds

Atoms may gain or lose electrons and form charged particles called **ions**.

- An **ionic bond** is an attractive force between oppositely charged ions.

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One source of such ions is a reaction between atoms of widely differing electronegativities (Table 1.1).

Table 1.1 Electronegativities of Some of the Elements

Increasing electronegativity →

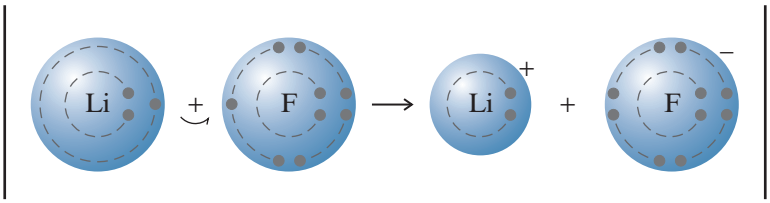
			H			
			2.1			
Li	**Be**	**B**	**C**	**N**	**O**	**F**
1.0	1.5	2.0	2.5	3.0	3.5	4.0
Na	**Mg**	**Al**	**Si**	**P**	**S**	**Cl**
0.9	1.2	1.5	1.8	2.1	2.5	3.0
K						**Br**
0.8						2.8

↑ Increasing electronegativity

- **Electronegativity** ***is a measure of the ability of an atom to attract electrons.***
- Electronegativity increases as we go across a horizontal row of the periodic table from left to right and it increases as we go up a vertical column (Table 1.1).

Helpful Hint: We will use electronegativity frequently as a tool for understanding the properties and reactivity of organic molecules.

An example of the formation of an ionic bond is the reaction of lithium and fluorine atoms:



Lithium, a typical metal, has a very low electronegativity; fluorine, a nonmetal, is the most electronegative element of all. The loss of an electron (a negatively charged species) by the lithium atom leaves a lithium cation (Li^+); the gain of an electron by the fluorine atom gives a fluoride anion (F^-).

- Ions form because atoms can achieve the electronic configuration of a noble gas by gaining or losing electrons.

The lithium cation with two electrons in its valence shell is like an atom of the noble gas helium, and the fluoride anion with eight electrons in its valence shell is like an atom of the noble gas neon. Moreover, crystalline lithium fluoride forms from the individual lithium and fluoride ions. In this process negative fluoride ions become surrounded by positive lithium ions, and positive lithium ions by negative fluoride ions. In this crystalline state, the ions have substantially lower energies than the atoms from which they have been formed. Lithium and fluorine are thus "stabilized" when they react to form crystalline lithium fluoride.

We represent the formula for lithium fluoride as LiF, because that is the simplest formula for this ionic compound.

Ionic substances, because of their strong internal electrostatic forces, are usually very high melting solids, often having melting points above 1000°C. In polar solvents, such as water, the ions are solvated (see Section 2.13D), and such solutions usually conduct an electric current.

- Ionic compounds, often called **salts**, form only when atoms of very different electronegativities transfer electrons to become ions.

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1.4B Covalent Bonds and Lewis Structures

When two or more atoms of the same or similar electronegativities react, a complete transfer of electrons does not occur. In these instances the atoms achieve noble gas configurations by *sharing electrons*.

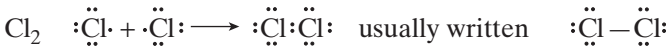
- **Covalent bonds** form by sharing of electrons between atoms of similar electronegativities to achieve the configuration of a noble gas.
- **Molecules** are composed of atoms joined exclusively or predominantly by covalent bonds.

Molecules may be represented by electron-dot formulas or, more conveniently, by bond formulas where each pair of electrons shared by two atoms is represented by a line. Some examples are shown here:

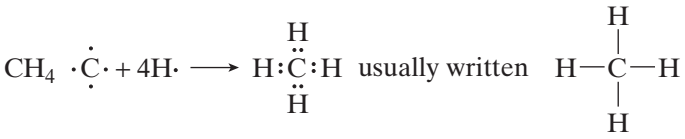
1. Hydrogen, being in group IA of the periodic table, has one valence electron. Two hydrogen atoms share electrons to form a hydrogen molecule, H_2.



2. Because chlorine is in group VIIA, its atoms have seven valence electrons. Two chlorine atoms can share electrons (one electron from each) to form a molecule of Cl_2.



3. And a carbon atom (group IVA) with four valence electrons can share each of these electrons with four hydrogen atoms to form a molecule of methane, CH_4.

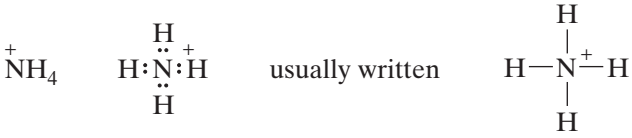


These formulas are often called **Lewis structures**; in writing them we show only the electrons of the valence shell.

4. Atoms can share *two or more pairs of electrons* to form **multiple covalent bonds**. For example, two nitrogen atoms possessing five valence electrons each (because nitrogen is in group VA) can share electrons to form a triple bond between them.



5. Ions, themselves, may contain covalent bonds. Consider, as an example, the ammonium ion.

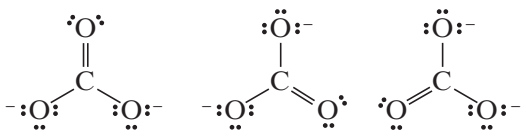


Practice Problem 1.3

Consider the following compounds and decide whether the bond in them would be ionic or covalent.
(a) LiH **(b)** KCl **(c)** F_2 **(d)** PH_3

1.5 | RESONANCE THEORY

Many times more than one *equivalent* Lewis structure can be written for a molecule or ion. Consider, for example, the carbonate ion (CO_3^{2-}). We can write three *different* but *equivalent* structures, 1–3:



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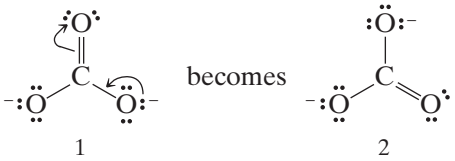
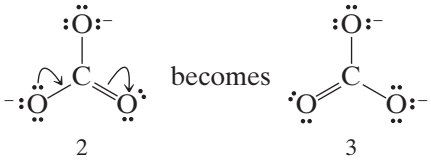
Notice two important features of these structures. First, each atom has the noble gas configuration. Second, *and this is especially important*, we can convert one structure into any other by *changing only the positions of the electrons*. We do not need to change the relative positions of the atomic nuclei. For example, if we move the electron pairs in the manner indicated by the **curved arrows** in structure 1, we change structure 1 into structure 2:



1 2

In a similar way we can change structure 2 into structure 3:



2 3

Structures 1–3, although not identical on paper, *are equivalent*. None of them alone, however, fits important data about the carbonate ion.

Helpful Hint: Curved arrows (Section 3.5) show movement of electron pairs, not atoms. The tail of the arrow begins at the current position of the electron pair. The head of the arrow points to the location where the electron pair will be in the next structure. Curved-arrow notation is one of the most important tools that you will use to understand organic reactions.

X-Ray studies have shown that carbon–oxygen double bonds are shorter than single bonds. The same kind of study of the carbonate ion shows, however, that all of its carbon–oxygen bonds *are of equal length*. One is not shorter than the others as would be expected from representations 1, 2, and 3. Clearly none of the three structures agrees with this evidence. In each structure, 1–3, one carbon–oxygen bond is a double bond and the other two are single bonds. None of the structures, therefore, is correct. How, then, should we represent the carbonate ion?

One way is through a theory called **resonance theory**. This theory states that whenever a molecule or ion can be represented by two or more Lewis structures *that differ only in the positions of the electrons*, two things will be true:

1. None of these structures, which we call **resonance structures or resonance contributors**, will be a realistic representation for the molecule or ion. None will be in complete accord with the physical or chemical properties of the substance.
2. The actual molecule or ion will be better represented by a *hybrid (average) of these structures*.

- **Resonance structures, then, are not real structures for the actual molecule or ion; they exist only on paper**. As such, they can never be isolated. No single contributor adequately represents the molecule or ion. In resonance theory we view the carbonate ion, which is, of course, a real entity, as having a structure that is a **hybrid** of the three **hypothetical** resonance structures.

What would a hybrid of structures 1–3 be like? Look at the structures and look especially at a particular carbon–oxygen bond, say, the one at the top. This carbon–oxygen bond is a double bond in one structure (1) and a single bond in the other two (2 and 3). The actual carbon–oxygen bond, since it is a hybrid, must be something in between a double bond and a single bond. Because the carbon–oxygen bond is a single bond in two of the structures and a double bond in only one, it must be more like a single bond than a double bond. It must be like a one and one-third bond. We

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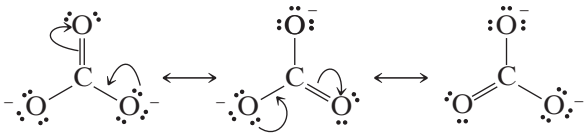
could call it a partial double bond. And, of course, what we have just said about any one carbon–oxygen bond will be equally true of the other two. Thus all of the carbon–oxygen bonds of the carbonate ion are partial double bonds, and *all are equivalent*. All of them *should be* the same length, and this is exactly what experiments tell us. The bonds are all 1.28 Å long, a distance which is intermediate between that of a carbon–oxygen single bond (1.43 Å) and that of a carbon–oxygen double bond (1.20 Å). One angstrom equals 1×10^{-10} meter.

- One other important point: By convention, when we draw resonance structures, we connect them by double-headed arrows (↔) to indicate clearly that they are hypothetical, not real. For the carbonate ion we write them this way:



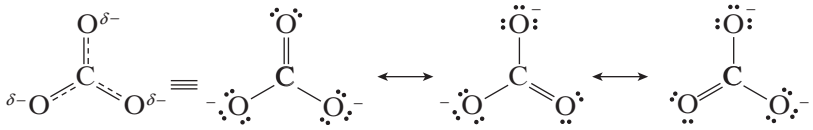
We should not let these arrows, or the word "resonance," mislead us into thinking that the carbonate ion fluctuates between one structure and another. These structures individually do not represent reality and exist only on paper; therefore, the carbonate ion cannot fluctuate among them because it is a hybrid of them.

- It is also important to distinguish between resonance and an **equilibrium**.

Helpful Hint: Each type of arrow in organic chemistry (e.g., ↷, ⇌, and ↔) has a specific meaning. It is important that you use each type of arrow only for the purpose for which it is defined.

In an equilibrium between two, or more, species, it is quite correct to think of different structures and moving (or fluctuating) atoms, *but not in the case of resonance* (as in the carbonate ion). Here the atoms do not move, and the "structures" exist only on paper. **An equilibrium is indicated by ⇌ and resonance by ↔.**

How can we write the structure of the carbonate ion in a way that will indicate its actual structure? We may do two things: we may write all of the resonance structures as we have just done and let the reader mentally fashion the hybrid, or we may write a non-Lewis structure that attempts to represent the hybrid. For the carbonate ion we might do the following:



The bonds in the structure on the left are indicated by a combination of a solid line and a dashed line. This is to indicate that the bonds are something in between a single bond and a double bond. As a rule, we use a solid line whenever a bond appears in all structures, and a dashed line when a bond exists in one or more but not all. We also place a $\delta-$ (read partial minus) beside each oxygen to indicate that something less than a full negative charge resides on each oxygen atom. (In this instance each oxygen atom has two-thirds of a full negative charge.) Calculations from theory show the equal charge density at each oxygen in the carbonate anion.

1.5A HOW TO Write Resonance Structures

1. **Resonance structures exist only on paper.** Although they have no real existence of their own, **resonance structures** are useful because they allow us to describe molecules and ions for which a single Lewis structure is inadequate. We write two or more Lewis structures, calling them resonance structures or resonance contributors. We connect these structures by double-headed arrows (↔), and we say that the real molecule or ion is a hybrid of all of them.

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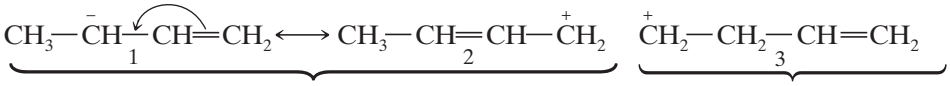
2. **We are only allowed to move electrons in writing resonance structures.** The positions of the nuclei of the atoms must remain the same in all of the structures. Structure 3 is not a resonance structure of 1 or 2, for example, because in order to form it we would have to move a hydrogen atom and this is not permitted:

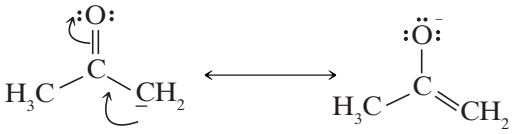


These are resonance structures.

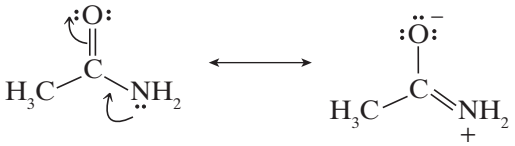
This is not a proper resonance structure of 1 or 2 because a hydrogen atom has been moved.

Generally speaking, when we move electrons, we move only those of multiple bonds (as in the example above) and those of nonbonding electron pairs.

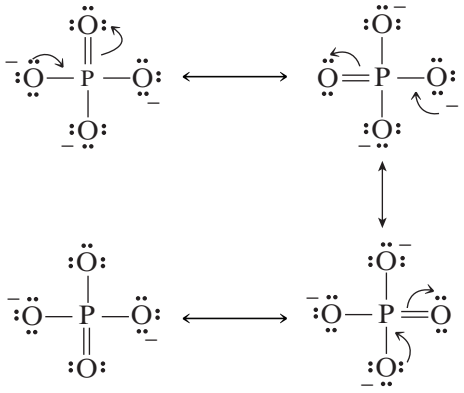
3. While drawing the resonance structures, a lone pair can be moved in the same manner as an electron. The carbon bearing the lone pair and negative charge acts as a donor atom, while the carbon atom of a carbonyl group (C=O) serves as the acceptor atom. A molecule that bears a negative charge next to the carbonyl group is termed as an enolate. The resonance involving a lone pair of electrons or a positive charge next to the bond is also exhibited in many cases



However, the lone pair does not necessarily have to be on an atom that bears a formal negative charge as indicated in the previous point. For example:



Phosphorous is a third-row element and therefore, it can expand its octet to accomodate 10 valence electrons. It is the only atom commonly encountered in organic chemistry that routinely expands its octet to accomodate 10 valence electrons. The oxygen atoms can lend a lone pair each to the phosphorus and atom and the following resonance structures are possible:



The resonance of phosphate ion has important biochemical consequences.

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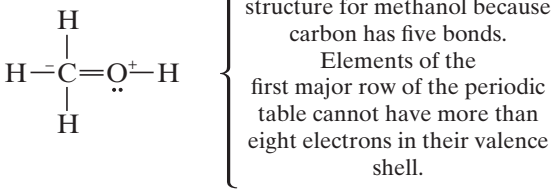
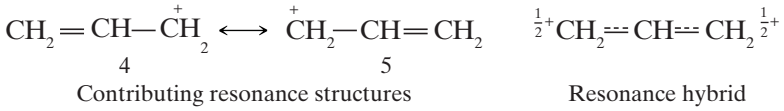
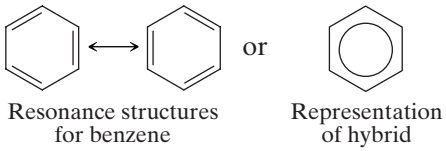
4. **All of the structures must be proper Lewis structures.** We should not write structures in which carbon has five bonds, for example:



5. **The energy of the resonance hybrid is lower than the energy of any contributing structure.** Resonance stabilizes a molecule or ion. This is especially true when the resonance structures are equivalent. Chemists call this stabilization *resonance stabilization*.
6. **Equivalent resonance structures make equal contributions to the hybrid, and a system described by them has a large resonance stabilization.** The following cation, for example, is more stable than either contributing resonance structure taken separately:



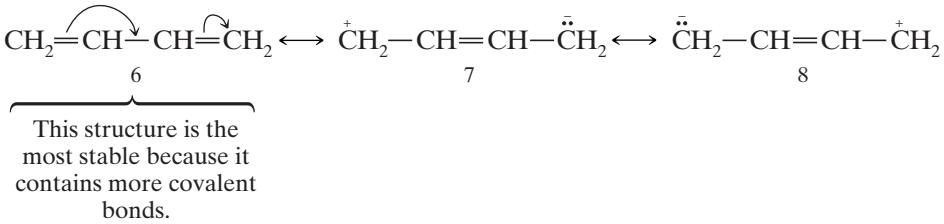
Benzene is highly resonance stabilized because it is a hybrid of the two equivalent forms that follow:



7. **The more stable a structure is (when taken by itself), the greater is its contribution to the hybrid.**

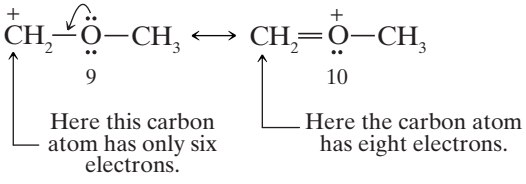
How do we decide whether one resonance structure is more stable than another? The following rules will help us:

1. **The more covalent bonds a structure has, the more stable it is.** This is exactly what we would expect because we know that forming a covalent bond lowers the energy of atoms. This means that of the following structures for 1,3-butadiene, 6 is by far the most stable and makes by far the largest contribution because it contains one more bond.



These structures also illustrate two other considerations:

2. **Structures in which all of the atoms have a complete valence shell of electrons (i.e., the noble gas structure) are especially stable and make large contributions to the hybrid.** Again, this is what we would expect from what we know about bonding. This means, for example, that 10 makes a larger stabilizing contribution to the cation below than 9 because all of the atoms of 10 have a complete valence shell.



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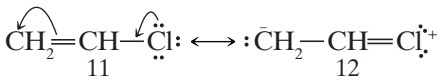
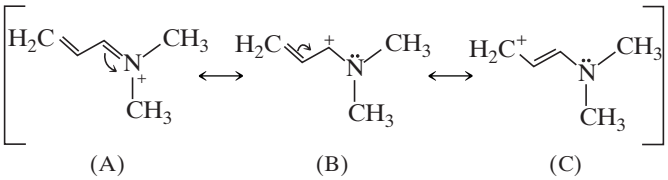
3. **Charge separation decreases stability.** It takes energy to separate opposite charges, and therefore a structure with separated charges is less stable. Structure B for formaldehyde has separated plus and minus charges; therefore, on this basis, too, it is the less stable contributor and makes a smaller contribution to the hybrid. Therefore, structures in which opposite charges are separated have greater energy (lower stability) than those that have no charge separation. This means that of the following two structures for vinyl chloride, structure 11 makes a larger contribution because it does not have separated charges. (This does not mean that structure 12 does not contribute to the hybrid; it just means that the contribution made by 12 is smaller.)



11 12

4. **Resonance contributors with negative charge on highly electronegative atoms are more stable than ones with negative charge on less or nonelectronegative atoms.** Conversely, resonance contributors with positive charge on highly electronegative atoms are less stable than ones with positive charge on nonelectronegative atoms.
5. **To predict the energies of the resonance structures, we consider the energy of resonance hybrid structure. Resonance hybrid is the weighted average of the resonance contributors.** The following structures are considered relatively stable:
   - **(i)** Structures having filled octets for second row elements (C, N, O, F) are stable.
   - **(ii)** Structures having minimum number of formal charges and maximum number of bonds.
   - **(iii)** Structure in which negative charge is on the most electronegative atom (C < N < O).
   - **(iv)** Structure in which there is minimal charge separation while keeping the formal charges closer together.

Solved Problem 1.2



(A) (B) (C)

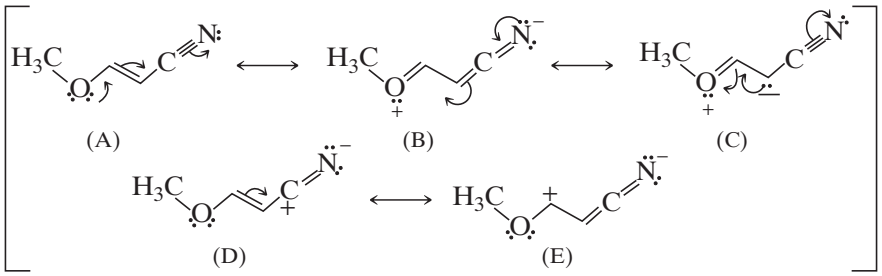
Which of the following structures is relatively stable?

Answer

Structure (A) is most stable as it follows all guidelines as per points (1) to (4).
Structure (B) is more stable as it violates point (1).
Structure (C) is least stable for violating point (1).
Stability order is A > B > C

Solved Problem 1.3

Predict the relative energies of the following resonating structures.



(A) (B) (C) (D) (E)

Answer

Structure (A) follows all the guidelines as per points (1) to (4) above.

Structure (B) violates point (2) because it has two formal charges.

Structure (C) violates points (2) and (3), because it has two formal charges and carries a negative charge on carbon atom, respectively.

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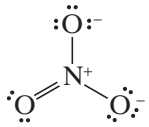
Structure (D) violates points (1) and (2), because it has 6 e^- on carbon atom and carries two formal charges, respectively.

Structure (E) violates points (1), (2) and (4) because it has 6 e^- on carbon atom, carries two formal charges and more charge separation than (D), respectively.

Thus, the relative energies of the structures are of the order A << B < C << D < E and their relative contribution to resonance hybrid is of the order A > B > C > D > E.

Solved Problem 1.4

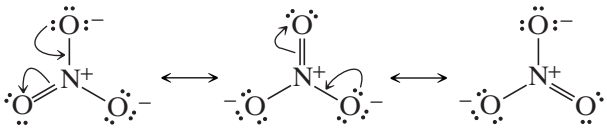
The following is one way of writing the structure of the nitrate ion:



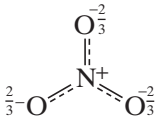
However, considerable physical evidence indicates that all three nitrogen–oxygen bonds are equivalent and that they have the same length, a bond distance between that expected for a nitrogen–oxygen single bond and a nitrogen–oxygen double bond. Explain this in terms of resonance theory.

Answer

We recognize that if we move the electron pairs in the following way, we can write three *different* but *equivalent* structures for the nitrate ion:



Since these structures differ from one another *only in the positions of their electrons*, they are *resonance structures* or *resonance contributors*. As such, no single structure taken alone will adequately represent the nitrate ion. The actual molecule will be best represented by a *hybrid of these three structures*. We might write this hybrid in the following way to indicate that all of the bonds are equivalent and that they are more than single bonds and less than double bonds. We also indicate that each oxygen atom bears an equal partial negative charge. This charge distribution corresponds to what we find experimentally.

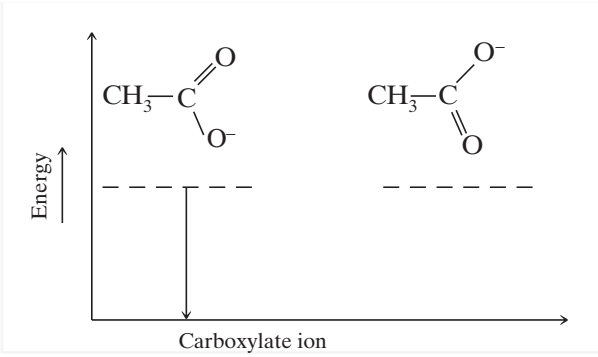


Hybrid structure for the nitrate ion

1.5B Schematic Energy Level Diagrams of Some Mesomeric Molecules/Ions

Energy diagrams of some resonating structures are given as follows. (*Note*: The downwards arrow marks the conventional mesomeric energies and indicates energy level).

Example 1: Carboxylate ion



Interpretation: The two equivalent resonating structures have the same energy.

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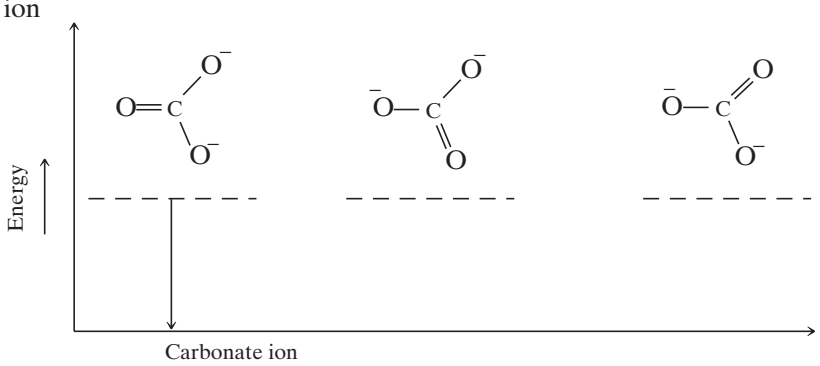
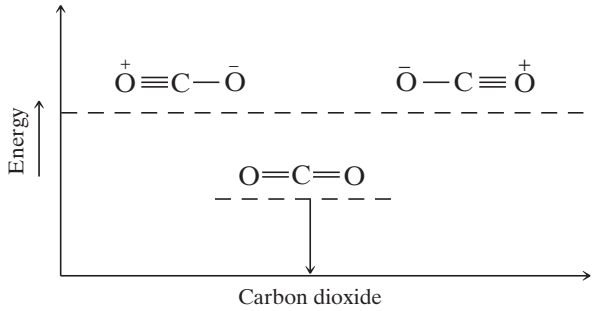
Example 2: Carbonate ion



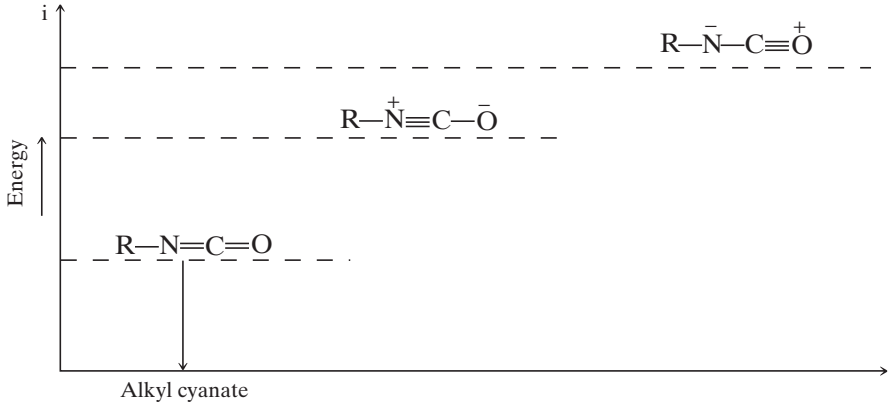
Interpretation: The three equivalent resonating structures have the same energy.

Example 3: Carbon dioxide



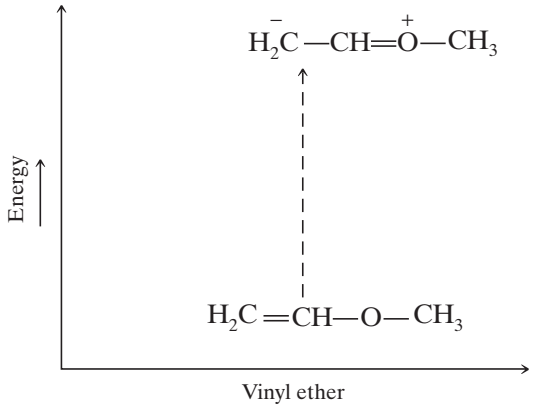
Interpretation: Polarized structures have higher energy because separation of opposite charges requires energy.

Example 4: Alkyl cyanate



Interpretation: Negative charge on the more electronegative element (oxygen) makes the structure more stable.

Example 5: Vinyl ether



Interpretation: Separation of opposite charges requires energy.

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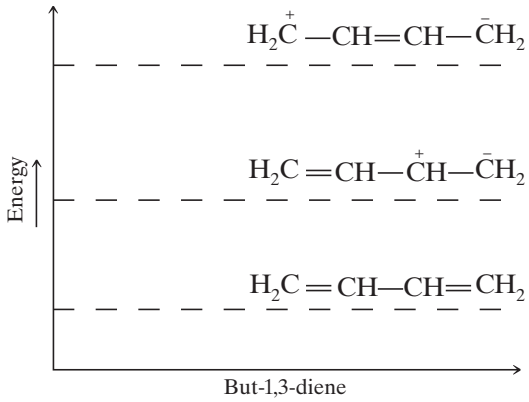
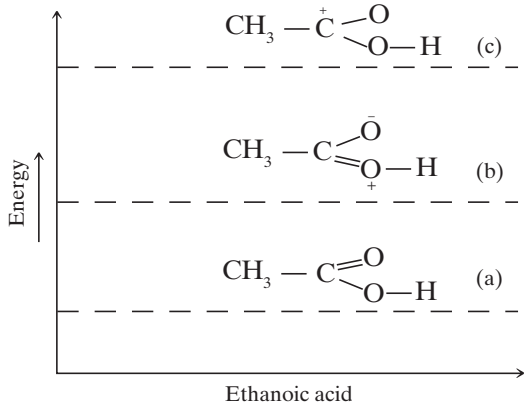
Example 6: But-1,3-diene



Interpretation: Unlike charges must be closer to each other for the structure to be more stable.

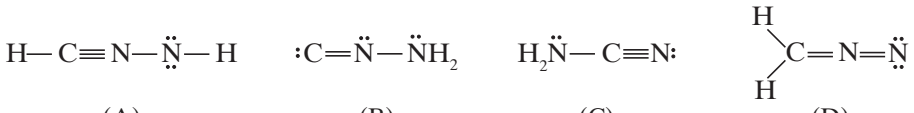
Example 7: Ethanoic acid

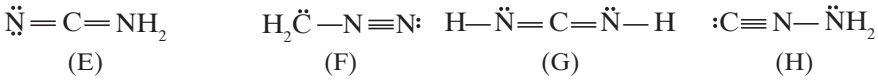


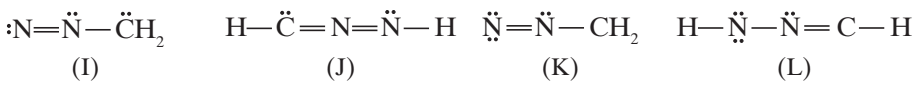
Interpretation: Structure (c) is unstable due to lesser covalent bonds and incomplete octet, while (b) is less stable than (a) because of separation of opposite charges.

Solved Problem 1.5

The following Lewis/Kekulé structures (A)–(L) are isomeric (with molecular formula CN_2H_2).







Which of these structures match the following properties? Indicate with letters (A) to (L). If no structure fits the property write the letter X.

1. Which of the structures have no atoms with formal charge?
2. Which of the structures have at least one nitrogen atom with a (+) formal charge?

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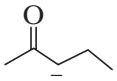
3. Which of the structures have at least one nitrogen atom with a (–) formal charge?
4. Which of the structures have at least one carbon atom with a (+) formal charge?
5. Which of the structures have at least one carbon atom with a (–) formal charge?
6. Which of the structures have electron deficient heavy atoms (N or C)?

Answer

1. (B,C,G); **2.** (A,D,E,F,H,I,J); **3.** (A,D,E,K,L); **4.** (K,L); **5.** (F,H,I,J); **6.** (B,I,K,L).

Solved Problem 1.6

Write the possible resonance structures for the following molecules. Show the direction of the movement of electrons with the help of arrows.

1. 

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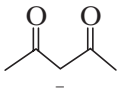
3. 

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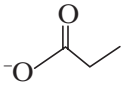
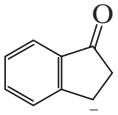
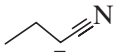
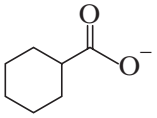
7. 

8. 

9. 

10. 

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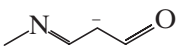
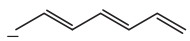
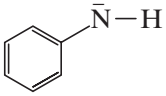
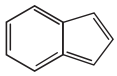
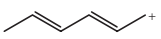
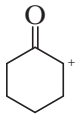
12. 

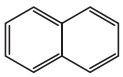
13. 

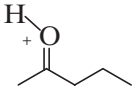
14. 

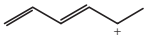
15. 

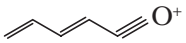
16. 

17. 

18. 

19. 

20. 

21. 

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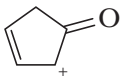
23. 

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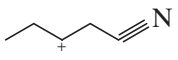
25. 

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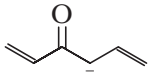
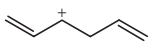
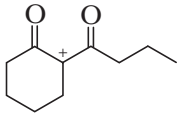
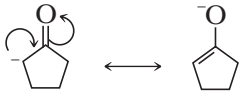
28. 

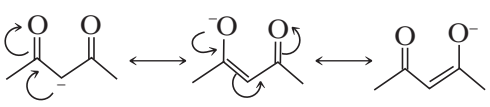
29. 

30. 

Answer

1. 

2. 

3. 

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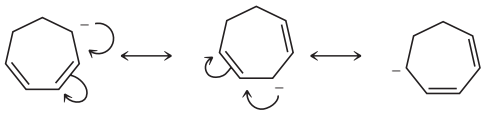
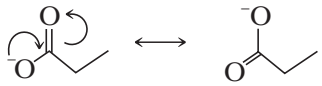
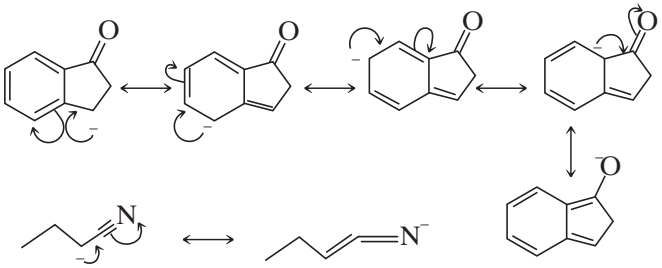
6. 

7. 

8. 

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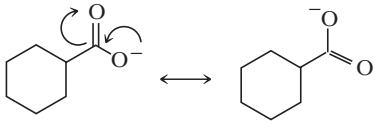
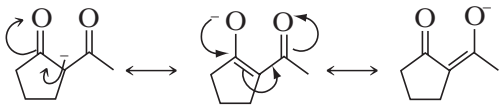
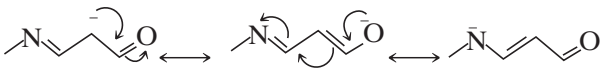
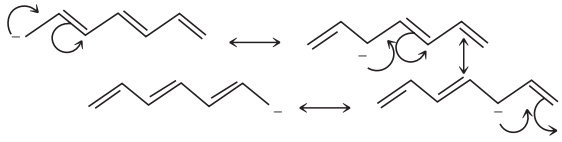
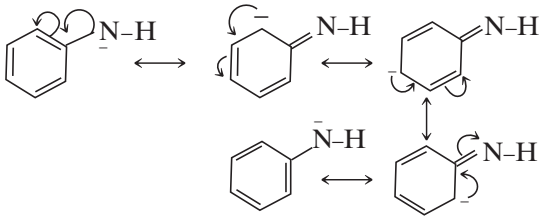
10. 

11. 

12. 

13. 

14. 

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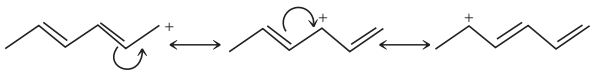
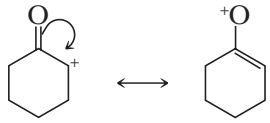
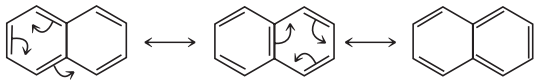
16. 

17. 

18. 

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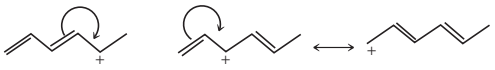
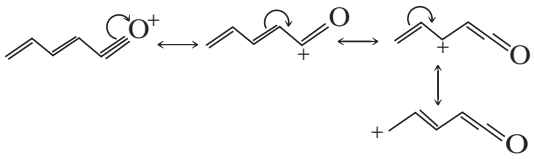
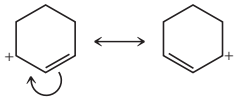
20. 

21. 

22. 

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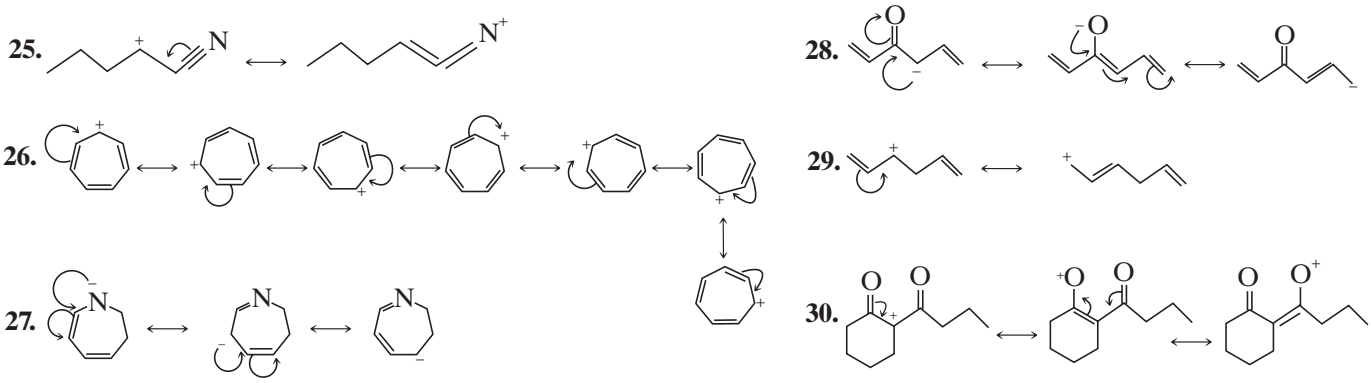


Practice Problem 1.4

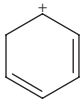
(a) Write two resonance structures for the formate ion HCO_2^-. (*Note*: The hydrogen and oxygen atoms are bonded to the carbon.) **(b)** Explain what these structures predict for the carbon–oxygen bond lengths of the formate ion, and **(c)**, for the electrical charge on the oxygen atoms.

Practice Problem 1.5

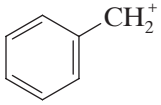
Write the contributing resonance structures and resonance hybrid for each of the following:

(a) $CH_3CH{=}CH{-}CH{=}\overset{+}{\underset{\cdot\cdot}{O}}H$

(b) $CH_2{=}CH{-}\overset{+}{C}H{-}CH{=}CH_2$

(c) 

(d) $CH_2{=}CH{-}Br$

(e) 

(f) $^-{:}CH_2{-}\overset{\overset{O}{\|}}{C}{-}CH_3$

(g) $CH_3{-}S{-}\overset{+}{C}H_2$

(h) $CH_3{-}NO_2$

Practice Problem 1.6

From each set of resonance structures that follow, designate the one that would contribute most to the hybrid and explain your choice:

(a) $\overset{+}{C}H_2{-}\ddot{N}(CH_3)_2 \longleftrightarrow CH_2{=}\overset{+}{N}(CH_3)_2$

(b) $CH_3{-}\overset{\overset{:O:}{\|}}{C}{-}\ddot{O}{-}H \longleftrightarrow CH_3{-}\overset{\overset{O^-}{|}}{C}{=}O^+{-}H$

(c) $:NH_2{-}C{\equiv}N: \longleftrightarrow \overset{+}{N}H_2{=}C{=}\ddot{N}^-$

1.6 | HYPERCONJUGATION

When σ-electrons of a C–H bond are in conjugation with an adjacent π-bond, then this type of conjugation is called hyperconjugation.

1.6A Condition for Hyperconjugation

The presence of α-hydrogen at an alkene, alkyl carbocation, alkyl free radical or a phenyl group is the main condition for hyperconjugation.

Hyperconjugation can be divided into five categories:

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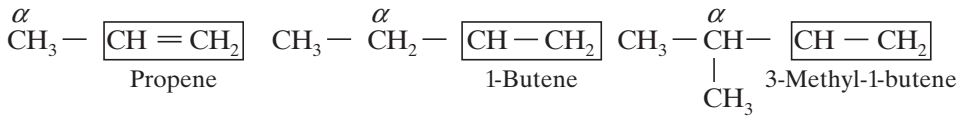
Type I: σ–π conjugation in alkene

The examples of this type of hyperconjugation are as follows:



(3α–hydrogens) **(2α–hydrogens)** **(1α–hydrogen)**

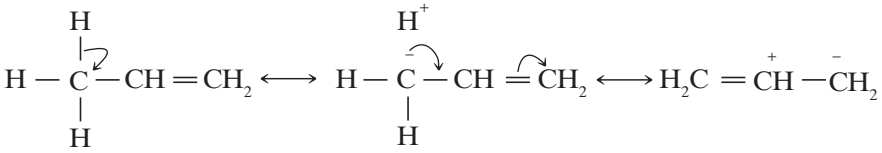
(a) **(b)** **(c)**

Solved Problem 1.7

How are the hyperconjugating structures drawn?

Answer

The hyperconjugating structures are drawn by separating the α-hydrogens from rest of the molecule. For example, the hyperconjugating structures of propene are drawn as follows.

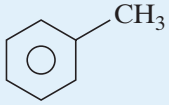


In the above resonating structures, there is no covalent bond between carbon and one of the hydrogens; that is why it is known as no-bond resonance.

The number of α-hydrogens of some simple compounds and number of resonating structures are given below. In case the compound carries a phenyl group attached to it, we have

Number of reasonating structures = Number of α-hydrogens + 1

The above expression is applicable to alkenes only.

Structure	Number of α-hydrogen	Number of reasonating structures
(1) $CH_3—CH=CH_2$	3α	4
(2) $CH_3—CH_2—CH=CH_2$	2α	3
(3) $CH_3—CH=CH—CH_3$	6α	7
(4) $CH_3—C(CH_3)_2—CH=CH_2$	0α	0
(5) 	3α	10

(*Continued*)

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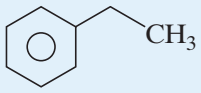
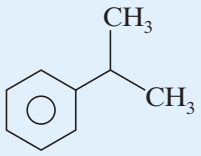
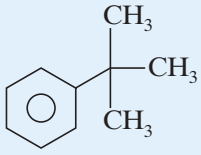
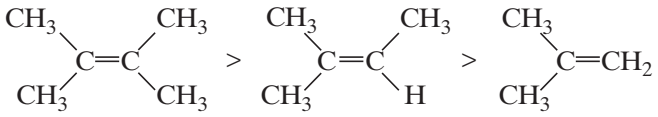
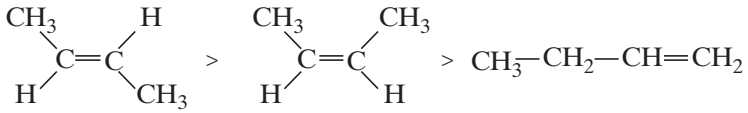
Structure	Number of α-hydrogen	Number of reasonating structures
(6) 	2α	7
(7) 	1α	4
(8) 	0α	0

Hyperconjugation explains the stability of alkenes. More the number of α-hydrogens in an alkene, more will be its stability. Thus, the order of stability some alkenes is as follows:



(12α-hydrogens) **(9α-hydrogens)** **(6α-hydrogens)**

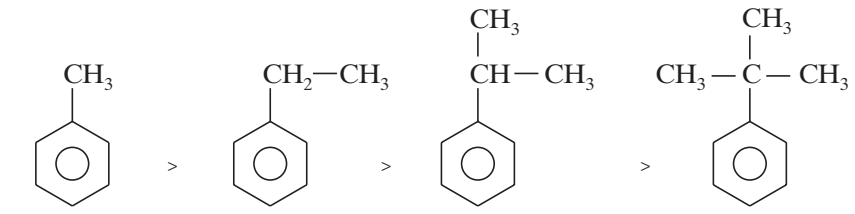


(6α-hydrogens) **(6α-hydrogens)** **(2α-hydrogens)**

Isobutene is the most stable isomer of butene. Hyperconjugation also explains the physical properties of butene isomers.



Type II: In 1935, Baker Nathan effect explained that hyperconjugation dominates inductive effect. The decreasing order of electron density on phenyl ring is as follows:



(3α-hydrogens) **(2α-hydrogens)** **(1α-hydrogen)** **(0α-hydrogen)**

Here, more the number of α-hydrogens, more will be the electron density on the phenyl ring. The electron donation of the alkyl groups is dominated by hyperconjugation effect rather than inductive effect.

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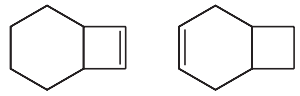
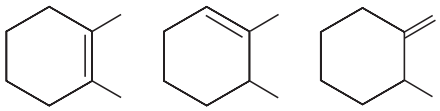
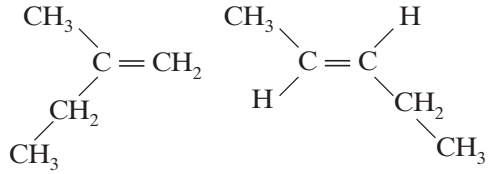
Solved Problem 1.8

Compare the stabilities of the following alkenes

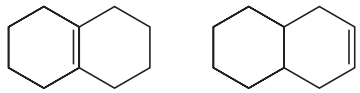
1. 
(a) (b)

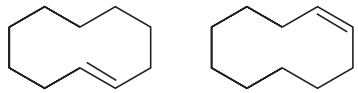
2. 
(a) (b) (c)

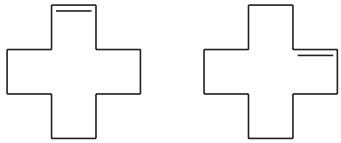
3. 

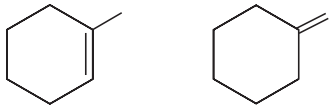
(a) (b)

4. 1-Hexene 2-Hexene 3-Hexene
(a) (b) (c)

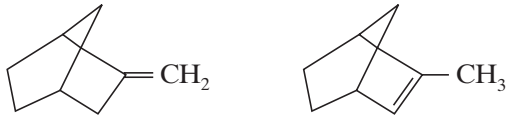
5. 
(a) (b)

6. 
(a) (b)

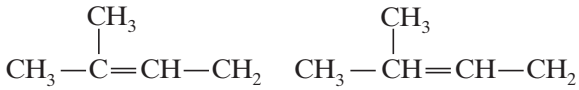
7. 
(a) (b)

8. 
(a) (b)

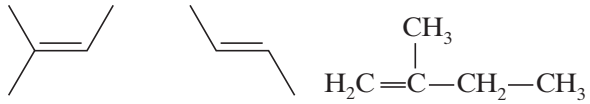
9. 
(a) (b)

10. 

(a) (b)

11. 

(a) (b)

12. 

(a) (b) (c)

13. $CH_3—O—CH=CH_2$ $CH_3—CH=CH—CH_3$
(a) (b)

Answer

The order of stabilities of the given alkenes is as follows:

1. (b) > (a). This is because there are more α-hydrogens in structure (b).
2. (a) > (b) > (c). This is because more the number of α-hydrogens, more will be the stability of alkene.
3. (a) > (b). This is because structure (a) is more stable because of a stable hyperconjugating structure.
4. (b) > (c) > (a). This is because more the number of α-hydrogens, more will be the stability of alkene.
5. (a) > (b). This is because there are more α-hydrogens (8α-hydrogens) in structure (a) than (b).
6. (b) > (a). This is because *cis* is more stable than *trans* when the number of constituent atoms of the ring is less than 11.
7. (b) > (a). This is because *trans* is more stable than *cis* when ring contains is more than 11 atoms.

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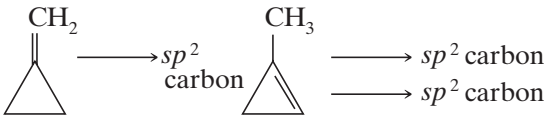
8. (a) > (b). This is because structure (a) is more substituted alkene than (b) and has more α-hydrogens. More the number of α-hydrogens, more will be the stability of alkene.

9. (a) > (b). Structure (b) is unstable because sp^2 carbon in a three-membered ring is unstable due to the ring strain.



There is 120° – 60° = 60° strain in two carbons.

10. (b) > (a). This is because structure (b) has more α-hydrogens.

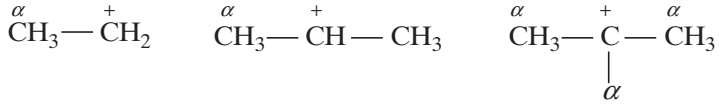
11. (a) > (c) > (b). This is because more the number of α-hydrogens, more will be the stability of alkene.

12. (a) > (b). This is because structure (a) has more α-hydrogens.

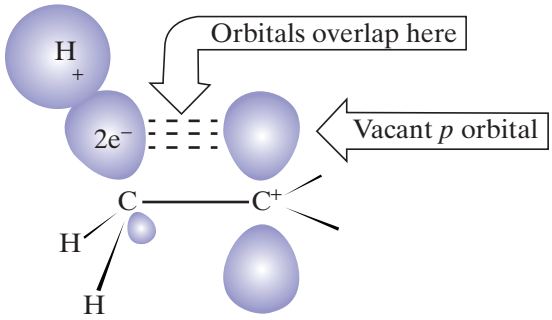
13. (a) > (b). This is because structure (a) is resonance stabilized.

Type III: Hyperconjugation in carbocations

In the carbocations, the conjugation is between σ-bond of C–H and positive charge on carbon.



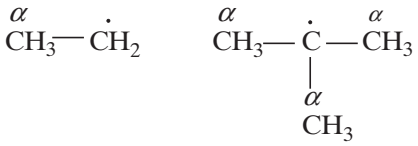
1° **(3α-hydrogens)** **2°** **(6α-hydrogens)** **3°** **(9α-hydrogens)**



The point to be noted here is that more the number of α-hydrogens, more will be the stability of carbocation. Thus, the stability of the above noted carbocations follows the order 3° > 2° > 1°.

Type IV: Hyperconjugation in free radical

Consider, for example, the following free radicals.

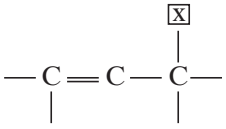


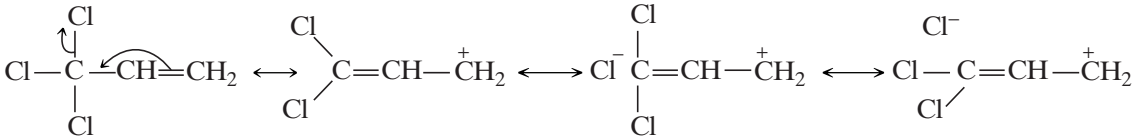
(A) **(3α-hydrogens)** **(B)** **(9α-hydrogens)**

Here again, more the number of α-hydrogens, more will be the stability of the radical. So, (B) is more stable than (A).

Type V: Hyperconjugation is also observed in systems of the following type:

In the above system, hyperconjugation will operate in reverse direction. Therefore, the above hyperconjugation is also known as reverse hyperconjugation. The important examples of this type of hyperconjugation are





(a)

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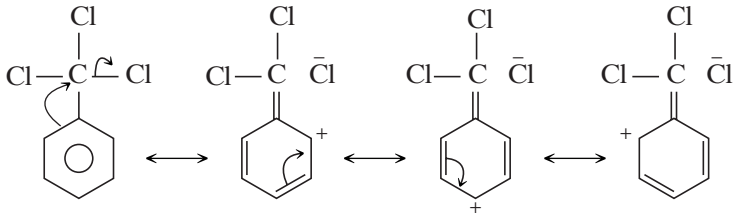
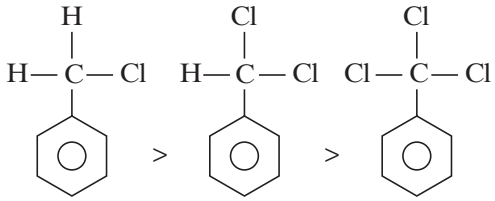


(b)

In case of reverse hyperconjugation, there is a decrease in electron density at π-bond. The decreasing order of electron density in phenyl ring is given below.

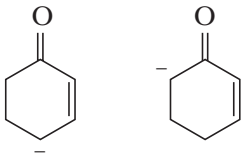


Solved Problem 1.9

Compare the stabilities of the following carbanions:

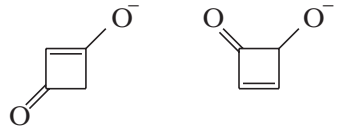
1. $CH_3-CH_2-\bar{C}H_2$ **(a)** $NO_2-CH_2-\bar{C}H_2$ **(b)**

2.



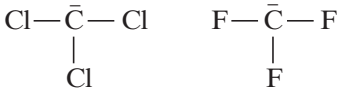
(a) **(b)**

3.



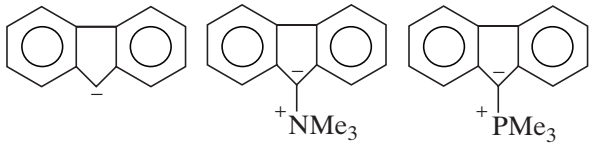
(a) **(b)**

4.



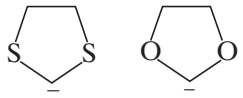
(a) **(b)**

5.



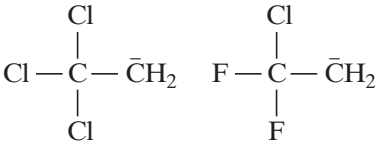
(a) **(b)** **(c)**

6.



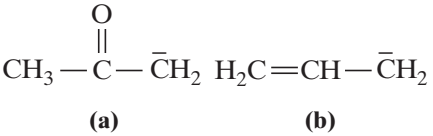
(a) **(b)**

7.



(a) **(b)**

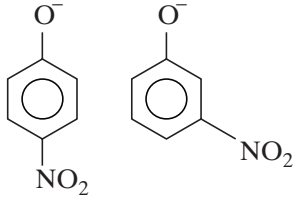
8.



(a) **(b)**

9. $H_2C=CH-\bar{N}H$ **(a)** $HN=CH-\bar{N}H$ **(b)**

10.



(a) **(b)**

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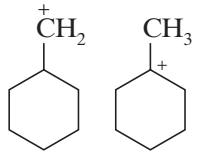
Answer

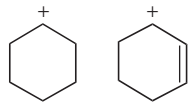
The comparison for the stability of carbanions is as follows:

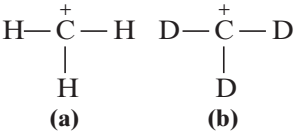
1. (b) > (a). This is because –I effect of $–NO_2$ is more than $–CH_3$.
2. (a) > (b). This is because greater number of resonating structures can be drawn for structure (a).
3. (a) > (b). This is because greater number of resonating structures can be drawn for structure (a).
4. (a) > (b). This is because negative charge is delocalized over the vacant *d*-orbital of chlorine.
5. (c) > (b) > (a). Structure (c) is more stable due to delocalization of charge over the vacant *d*-orbital of phosphorus.
6. (a) > (b). This is because negative charge is delocalized over the vacant *d*-orbital of sulphur.
7. (b) > (a). This is because –I effect exerted by fluorine is more than that of chlorine.
8. (a) > (b). Structure (a) is more stable because on drawing the resonating structure, there is negative charge on oxygen.
9. (b) > (a). Structure (b) is more stable because on drawing the resonating structure, there is negative charge on nitrogen.
10. (a) > (b). This is because negative charge is delocalized over $–NO_2$ group.

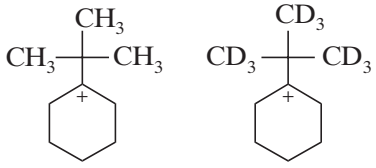
Solved Problem 1.10

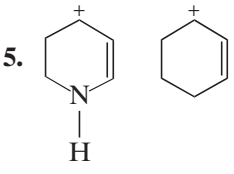
Compare the stabilities of the following intermediates:

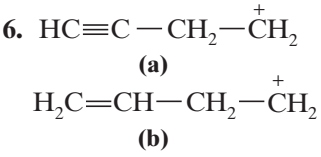
1. 
(a) (b)

2. 
(a) (b)

3. 
(a) (b)

4. 
(a) (b)

5. 
(a) (b)

6. 
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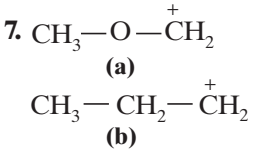
7. 
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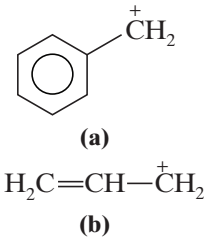
8. 
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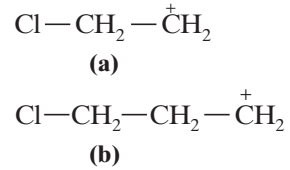
9. 
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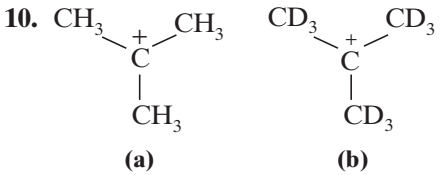
10. 
(a) (b)

Answer

The order of stabilities of the given intermediates is as follows:

1. (b) > (a). This is because tertiary carbocation is more stable than the primary.
2. (b) > (a). This is because structure (b) is more resonance stabilized than structure (a).
3. (b) > (a). This is because +I effect of D is more than H.
4. (b) > (a). This is because +I effect of D is more than H.
5. (a) > (b). This is because structure (a) has more resonating structures than (b).
6. (b) > (a). This is because –I effect of alkyne is more than that of alkene.
7. (a) > (b). This is because structure (a) is resonance stabilized.

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8. (a) > (b). This is because benzyl carbocation is more stable than allyl carbocation.

9. (b) > (a). This is because –I effect of chlorine is exerted to a greater extent in structure (a), which makes the carbocation less stable.

10. (a) > (b). This is because $-CH_3$ is more effective than $-CD_3$ in exhibiting hyperconjugation.

1.7 | THE STRUCTURE OF METHANE AND ETHANE: sp^3 HYBRIDIZATION

1.7A The Structure of Methane

Hybrid atomic orbitals that account for the structure of methane can be derived from carbon's second-shell s and p orbitals as follows (Fig. 1.3):

- Wave functions for the $2s$, $2p_x$, $2p_y$, and $2p_z$ orbitals of ground state carbon are mixed to form four new and equivalent $2sp^3$ hybrid orbitals.
- The designation sp^3 signifies that the hybrid orbital has one part *s* orbital character and three parts *p* orbital character.
- The mathematical result is that the four $2sp^3$ orbitals are oriented at angles of 109.5° with respect to each other. This is precisely the orientation of the four hydrogen atoms of methane. Each H—C—H bond angle is 109.5°.

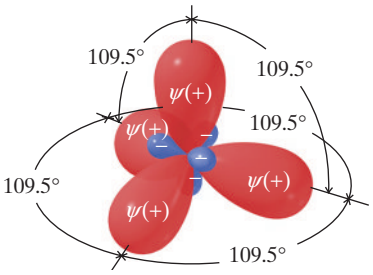

Figure 1.3 Hybridization of pure atomic orbitals of a carbon atom to produce sp^3 hybrid orbitals.

1.7B The Structure of Ethane

The bond angles at the carbon atoms of ethane, and of all alkanes, are also tetrahedral like those in methane. A satisfactory model for ethane can be provided by sp^3-hybridized carbon atoms. Figure 1.4 shows how we might imagine

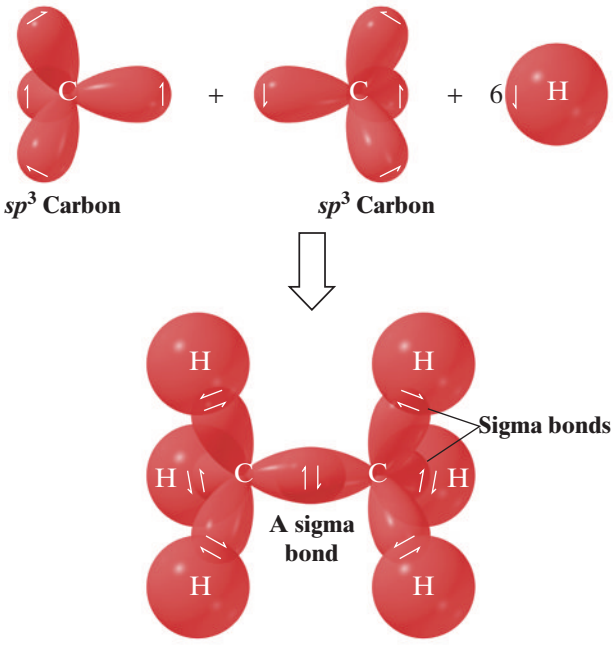

Figure 1.4 The hypothetical formation of the bonding molecular orbitals of ethane from two sp^3-hybridized carbon atoms and six hydrogen atoms. All of the bonds are sigma bonds. (Antibonding sigma molecular orbitals—called σ^* orbitals—are formed in each instance as well, but for simplicity these are not shown.)

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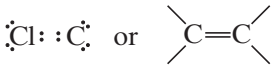
the bonding molecular orbitals of an ethane molecule being constructed from two sp^3-hybridized carbon atoms and six hydrogen atoms.

The carbon–carbon bond of ethane is a *sigma bond* with cylindrical symmetry, formed by two overlapping sp^3 orbitals. (The carbon–hydrogen bonds are also sigma bonds. They are formed from overlapping carbon sp^3 orbitals and hydrogen *s* orbitals.) Because a sigma bond (i.e., any nonmultiple bond) has cylindrical symmetry along the bond axis, *rotation of groups joined by a single bond does not usually require a large amount of energy.* Consequently, groups joined by single bonds rotate relatively freely with respect to one another.

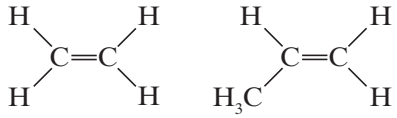
Helpful Hint: Rotation of groups joined by a single bond does not usually require a large amount of energy.

1.8 | THE STRUCTURE OF ETHENE (ETHYLENE): sp^2 HYBRIDIZATION

The carbon atoms of many of the molecules that we have considered so far have used their four valence electrons to form four single covalent (sigma) bonds to four other atoms. We find, however, that many important organic compounds exist in which carbon atoms share more than two electrons with another atom. In molecules of these compounds some bonds that are formed are multiple covalent bonds. When two carbon atoms share two pairs of electrons, for example, the result is a carbon–carbon double bond:



Hydrocarbons whose molecules contain a carbon–carbon double bond are called **alkenes**. Ethene (C_2H_4) and propene (C_3H_6) are both alkenes. (Ethene is also called ethylene, and propene is sometimes called propylene.)



Ethene **Propene**

In ethene the only carbon–carbon bond is a double bond. Propene has one carbon–carbon single bond and one carbon–carbon double bond.

The spatial arrangement of the atoms of alkenes is different from that of alkanes. The six atoms of ethene are coplanar, and the arrangement of atoms around each carbon atom is triangular (Fig. 1.5).

- Carbon–carbon double bonds are comprised of sp^2-hybridized carbon atoms.

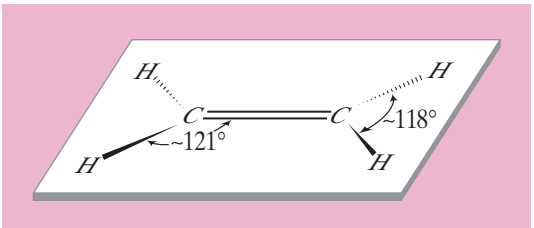


Figure 1.5 The structure and bond angles of ethene. The plane of the atoms is perpendicular to the paper. The dashed wedge bonds project behind the plane of the paper, and the solid wedge bonds project in front of the paper.

The mathematical mixing of orbitals that furnish the ***sp*² orbitals** for our model can be visualized in the way shown in Fig. 1.6. The 2*s* orbital is mathematically mixed (or hybridized) with two of the 2*p* orbitals. (The hybridization procedure applies only to the orbitals, not to the electrons.) One 2*p* orbital is left unhybridized. One electron is then placed in each of the sp^2 hybrid orbitals and one electron remains in the 2*p* orbital.

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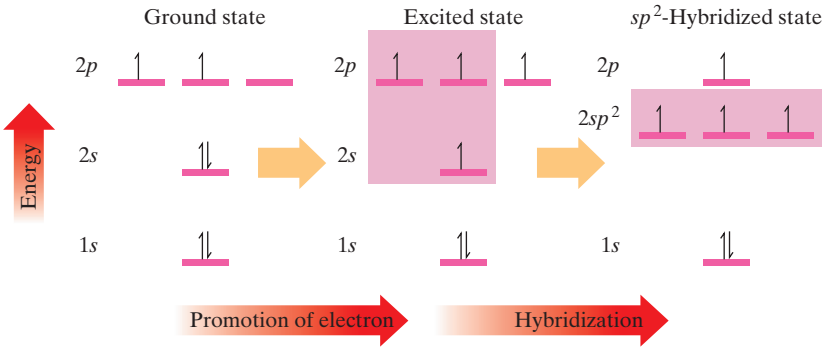

Figure 1.6 A process for deriving sp^2-hybridized carbon atoms.

The three sp^2 orbitals that result from hybridization are directed toward the corners of a regular triangle (with angles of 120° between them). The carbon p orbital that is not hybridized is perpendicular to the plane of the triangle formed by the hybrid sp^2 orbitals (Fig. 1.7).

In our model for ethene we see the following:

- Two sp^2-hybridized carbon atoms form a sigma **(σ)** bond between them by overlap of one sp^2 orbital from each carbon. The remaining carbon sp^2 orbitals form σ bonds to four hydrogens through overlap with the hydrogen 1s orbitals. These five σ bonds account for 10 of the 12 valence electrons contributed by the two carbons and four hydrogens, and comprise the **σ-bond framework** of the molecule.
- The remaining two bonding electrons are each located in an unhybridized p orbital of each carbon. Sideways overlap of these p orbitals and sharing of the two electrons between the carbons leads to a **pi (π) bond**.

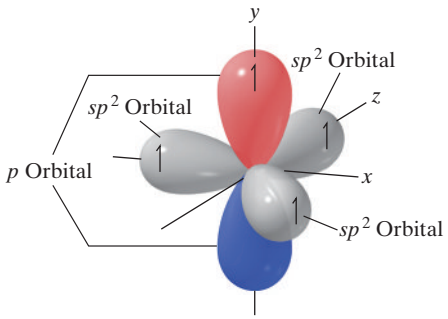

Figure 1.7 An sp^2-hybridized carbon atom.

The bond angles that we would predict on the basis of sp^2-hybridized carbon atoms (120° all around) are quite close to the bond angles that are actually found .

1.8A Restricted Rotation and the Double Bond

The σ–π model for the carbon–carbon double bond also accounts for an important property of the double bond:

- There is a large energy barrier to rotation associated with groups joined by a double bond.

Maximum overlap between the p orbitals of a π bond occurs when the axes of the p orbitals are exactly parallel. Rotating one carbon of the double bond 90° (Fig. 1.8) breaks the π bond, for then the axes of the p orbitals are perpendicular and there is no net overlap between them. Estimates based on thermochemical calculations indicate that the strength of the π bond is 264 kJ mol^{-1}. This, then, is the barrier to rotation of the double bond. It is markedly higher than the rotational barrier of groups joined by carbon–carbon single bonds (13–26 kJ mol^{-1}). While groups joined by single bonds rotate relatively freely at room temperature, those joined by double bonds do not.

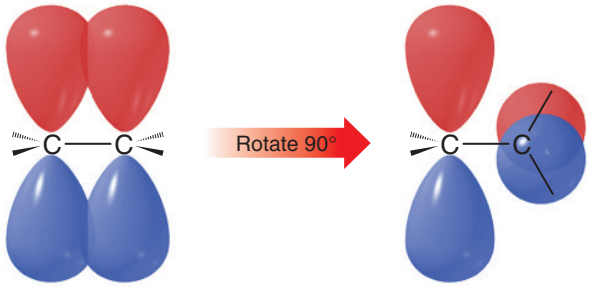

Figure 1.8 A stylized depiction of how rotation of a carbon atom of a double bond through an angle of 90° results in breaking of the π bond.

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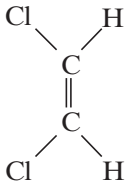
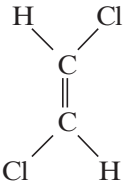
1.8B Cis–Trans Isomerism

Restricted rotation of groups joined by a double bond causes a new type of isomerism that we illustrate with the two dichloroethenes written as the following structures:



***cis*-1,2-Dichloroethene**



***trans*-1,2-Dichloroethene**

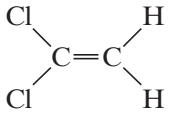
- These two compounds are isomers; they are different compounds that have the same molecular formula.

We can tell that they are different compounds by trying to place a model of one compound on a model of the other so that all parts coincide, that is, to try to **superpose** one on the other. We find that it cannot be done. Had one been **superposable**. On the other, all parts of one model would correspond in three dimensions exactly with the other model. (*The notion of superposition is different from simply superimposing one thing on another*. The latter means only to lay one on the other without the necessary condition that all parts coincide.)

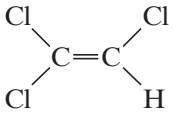
- We indicate that they are different isomers by attaching the prefix cis or trans to their names (*cis*, Latin: on this side; *trans*, Latin: across).

cis-1,2-Dichloroethene and *trans*-1,2-dichloroethene are not constitutional isomers because the connectivity of the atoms is the same in each. The two compounds ***differ only in the arrangement of their atoms in space***. Isomers of this kind are classified formally as **stereoisomers**, but often they are called simply *cis–trans* isomers. (We shall study stereoisomerism in detail in Chapter 4.)

The structural requirements for **cis–trans isomerism** will become clear if we consider a few additional examples. 1,1.Dichloroethene and 1,1,2-trichloroethene do not show this type of isomerism.

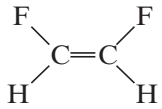


1,1-Dichloroethene
(no *cis–trans* isomerism)

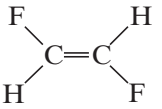


1,1,2-Trichloroethene
(no *cis–trans* isomerism)

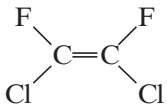
1,2-Difluoroethene and 1,2-dichloro-1,2-difluoroethene do exist as cis–trans isomers. Notice that we designate the isomer with two identical groups on the same side as being cis:



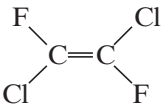
***cis*-1,2-Difluoroethene**



***trans*-1,2-Difluoroethene**



***cis*-1,2-Dichloro-1,2-difluoroethene**



***trans*-1,2-Dichloro-1,2-difluoroethene**

Clearly, then, ***cis–trans isomerism of this type is not possible if one carbon atom of the double bond bears two identical groups***.

Practice Problem 1.7

Which of the following alkenes can exist as *cis–trans* isomers? Write their structures. Build handheld models to prove that one isomer is not superposable on the other.

(a) $CH_2{=}CHCH_2CH_3$ **(b)** $CH_3CH{=}CHCH_3$ **(c)** $CH_2{=}C(CH_3)_2$ **(d)** $CH_3CH_2CH{=}CHCl$

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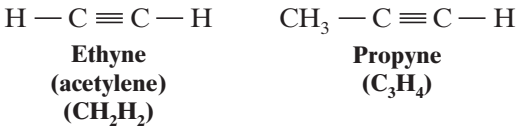
1.9 | THE STRUCTURE OF ETHYNE (ACETYLENE): *sp* HYBRIDIZATION

Hydrocarbons in which two carbon atoms share three pairs of electrons between them, and are thus bonded by a triple bond, are called **alkynes**. The two simplest alkynes are ethyne and propyne.



Ethyne, a compound that is also called acetylene, consists of a linear arrangement of atoms. The H—C≡C bond angles of ethyne molecules are 180°:

H—C≡C—H
180° 180°

We can account for the structure of ethyne on the basis of orbital hybridization as we did for ethane and ethene. In our model for ethane (Section 1.7B) we saw that the carbon orbitals are sp^3 hybridized, and in our model for ethene (Section 1.8) we saw that they are sp^2 hybridized. In our model for ethyne we shall see that the carbon atoms are *sp hybridized*.

The mathematical process for obtaining the *sp* hybrid orbitals of ethyne can be visualized in the following way (Fig. 1.9).

- The 2*s* orbital and one 2*p* orbital of carbon are hybridized to form two ***sp* orbitals**.

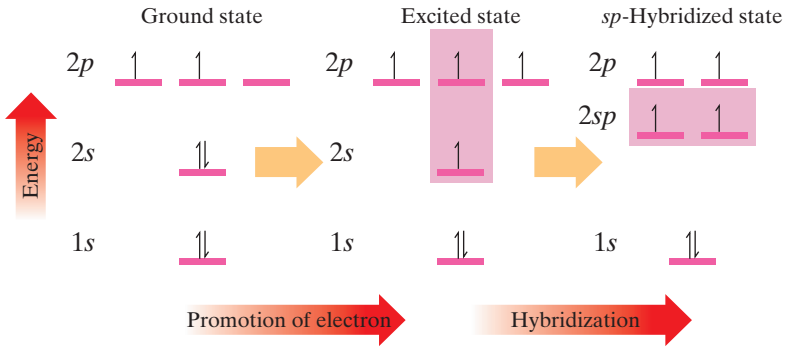


Figure 1.9 A process for deriving *sp*-hybridized carbon atoms.

The remaining two 2*p* orbitals are not hybridized.

Calculations show that the *sp* hybrid orbitals have their large positive lobes oriented at an angle of 180° with respect to each other. The two 2*p* orbitals that were not hybridized are each perpendicular to the axis that passes through the center of the two *sp* orbitals (Fig. 1.10). We place one electron in each orbital.

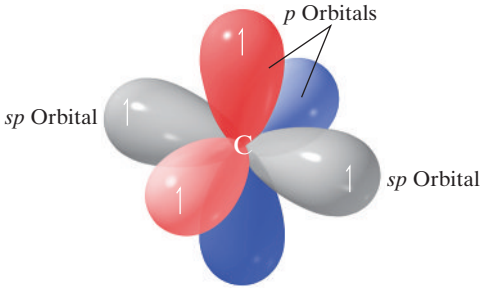


Figure 1.10 An *sp*-hybridized carbon atom.

We envision the bonding molecular orbitals of ethyne (Fig. 1.11) being formed in the following way.

1. Two carbon atoms overlap *sp* orbitals to form a sigma bond between them (this is one bond of the triple bond). The remaining two *sp* orbitals at each carbon atom overlap with *s* orbitals from hydrogen atoms to produce two sigma C—H bonds.
2. The two *p* orbitals on each carbon atom also overlap side to side to form two π bonds. These are the other two bonds of the triple bond.
3. The carbon–carbon triple bond consists of two π bonds and one σ bond.

Structures for ethyne based on calculated molecular orbitals and electron density are shown in Fig. 1.12. Circular symmetry exists along the length of a triple bond (Fig. 1.12). As a result, there is no restriction of rotation for groups joined by a triple bond (as compared with alkenes), and if rotation would occur, no new compound would form.

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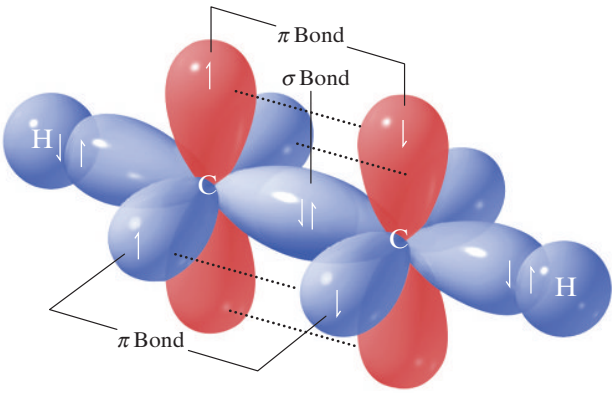

Figure 1.11 Formation of the bonding molecular orbitals of ethyne from two *sp*-hybridized carbon atoms and two hydrogen atoms. (Antibonding orbitals are formed as well, but these have been omitted for simplicity.)

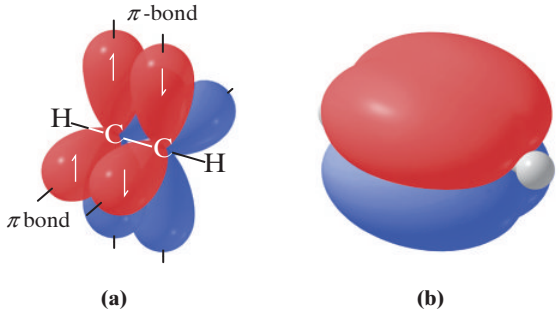

Figure 1.12 *(a)* The structure of ethyne (acetylene) showing the sigma-bond framework and a schematic depiction of the two pairs of *p* orbitals that overlap to form the two π bonds in ethyne. *(b)* A structure of ethyne showing calculated π molecular orbitals. Two pairs of π molecular orbital lobes are present, one pair for each π bond. The red and blue lobes in each π bond represent opposite phase signs. The hydrogen atoms of ethyne (white spheres) can be seen at each end of the structure (the carbon atoms are hidden by the molecular orbitals).

1.9A Bond Lengths of Ethyne, Ethene, and Ethane

The carbon–carbon triple bond of ethyne is shorter than the carbon–carbon double bond of ethene, which in turn is shorter than the carbon–carbon single bond of ethane. The reason is that bond lengths are affected by the hybridization states of the carbon atoms involved.

1. The greater the *s* orbital character in one or both atoms, the shorter is the bond. This is because *s* orbitals are spherical and have more electron density closer to the nucleus than do *p* orbitals.
2. The greater the *p* orbital character in one or both atoms, the longer is the bond. This is because *p* orbitals are lobe-shaped with electron density extending away from the nucleus.

In terms of hybrid orbitals, an *sp* hybrid orbital has 50% *s* character and 50% *p* character. An sp^2 hybrid orbital has 33% *s* character and 67% *p* character. An sp^3 hybrid orbital has 25% *s* character and 75% *p* character. The overall trend, therefore, is as follows:

- Bonds involving *sp* hybrids are shorter than those involving sp^2 hybrids, which are shorter than those involving sp^3 hybrids. This trend holds true for both C—C and C—H bonds.

The bond lengths and bond angles of ethyne, ethene, and ethane are summarized in Fig. 1.13.

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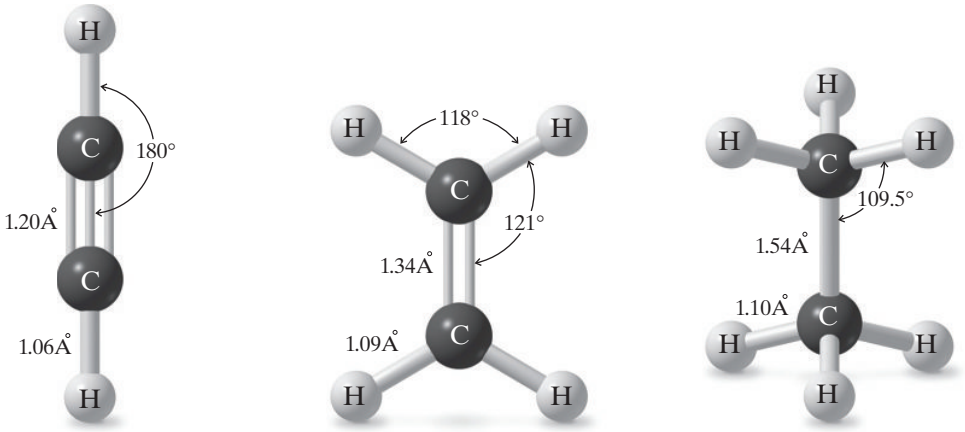


Figure 1.13 Bond angles and bond lengths of ethyne, ethene, and ethane.

1.10 | HOW TO INTERPRET AND WRITE STRUCTURAL FORMULAS

Organic chemists use a variety of ways to write structural formulas. The most common types of representations are shown in Fig. 1.14 using propyl alcohol as an example. The dot structure shows all of the valence electrons, but writing it is tedious and time-consuming. The other representations are more convenient and are, therefore, more often used.

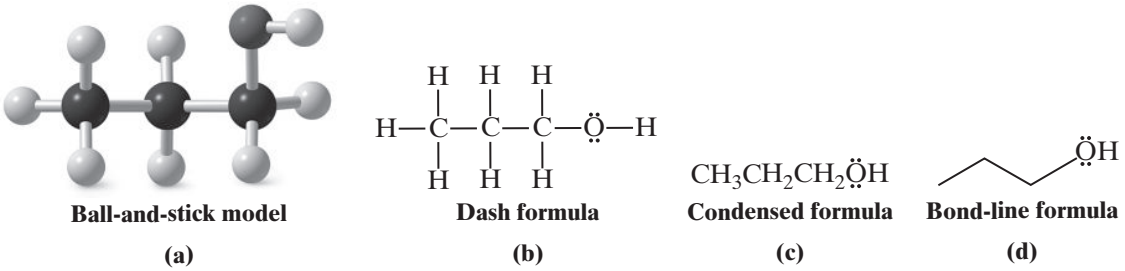
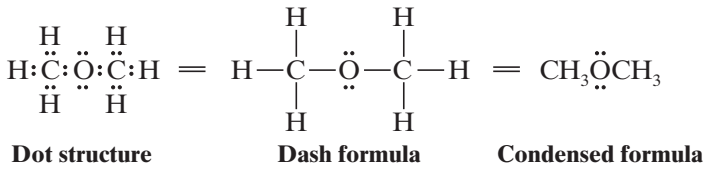


Figure 1.14 Structural formulas for propyl alcohol.

Sometimes we even omit unshared pairs when we write formulas. However, when we write chemical reactions, we see that it is necessary to include the unshared electron pairs when they participate in the reaction. It is a good idea, therefore, to get into the habit of writing the unshared (nonbonding) electron pairs in the structures you draw.



1.10A Dash Structural Formulas

If we look at the model for propyl alcohol given in Fig. 1.14*a* and compare it with the dash, and condensed formulas in Figs. 1.14*c–d* we find that the chain of atoms is straight in those formulas. In the model, which corresponds more accurately to the actual shape of the molecule, the chain of atoms is not at all straight. Also of importance is this: ***Atoms joined by single bonds can rotate relatively freely with respect to one another.*** (We discussed this point briefly in Section 1.7B.) This relatively free rotation means that the chain of atoms in propyl alcohol can assume a variety of arrangements like these:

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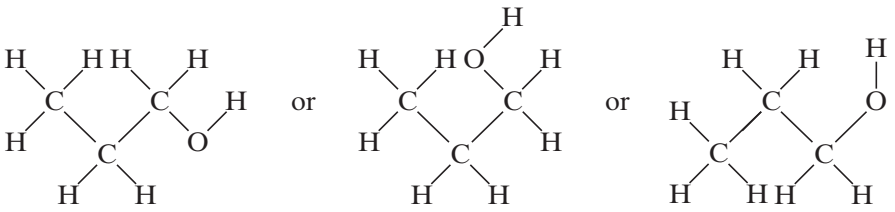
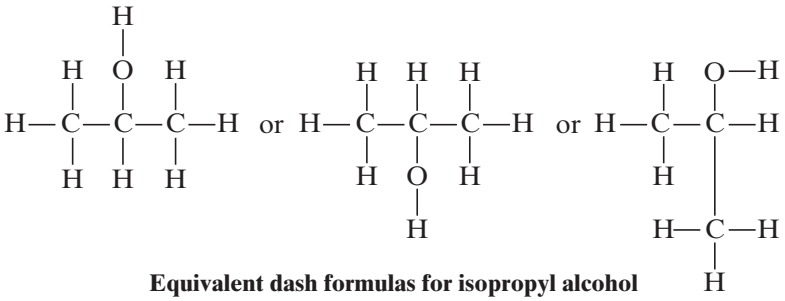


Equivalent dash formulas for propyl alcohol

It also means that all of the structural formulas above are *equivalent* and all represent propyl alcohol. **Dash structural formulas** such as these indicate the way in which the atoms are attached to each other and *are not* representations of the actual shapes of the molecule. (Propyl alcohol does not have 90° bond angles. It has tetrahedral bond angles.) Dash structural formulas show what is called the **connectivity** of the atoms. *Constitutional isomers (Section 1.3A) have different connectivities and, therefore, must have different structural formulas.*

Consider the compound called isopropyl alcohol, whose formula we might write in a variety of ways:



Equivalent dash formulas for isopropyl alcohol

Helpful Hint: It is important that you be able to recognize when a set of structural formulas has the same connectivity versus when they are constitutional isomers.

Isopropyl alcohol is a constitutional isomer (Section 1.3A) of propyl alcohol because its atoms are connected in a different order and both compounds have the same molecular formula, C_3H_8O. In isopropyl alcohol the OH group is attached to the central carbon; in propyl alcohol it is attached to an end carbon.

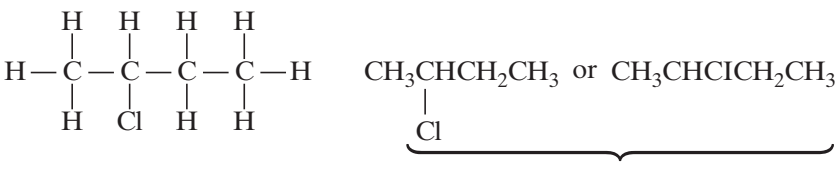
- In problems you will often be asked to write structural formulas for all the isomers that have a given molecular formula. Do not make the error of writing several equivalent formulas, like those that we have just shown, mistaking them for different constitutional isomers.

Practice Problem 1.8

There are actually three constitutional isomers with the molecular formula C_3H_8O. We have seen two of them in propyl alcohol and isopropyl alcohol. Write a dash formula for the third isomer.

1.10B Condensed Structural Formulas

Condensed structural formulas are somewhat faster to write than dash formulas and, when we become familiar with them, they will impart all the information that is contained in the dash structure. In condensed formulas all of the hydrogen atoms that are attached to a particular carbon are usually written immediately after the carbon. In fully condensed formulas, all of the atoms that are attached to the carbon are usually written immediately after that carbon, listing hydrogens first. For example,



Dash formula **Condensed formulas**

The condensed formula for isopropyl alcohol can be written in four different ways:

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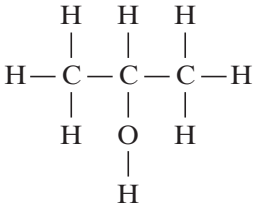


Dash formula

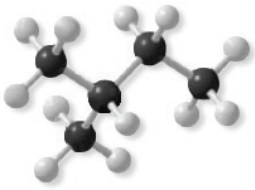
CH_3CHCH_3 (OH) $CH_3CH(OH)CH_3$

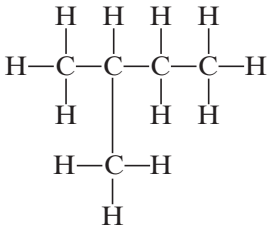
$CH_3CHOHCH_3$ or $(CH_3)_2CHOH$

Condensed formulas

Solved Problem 1.11

Write a condensed structural formula for the compound that follows:





Answer

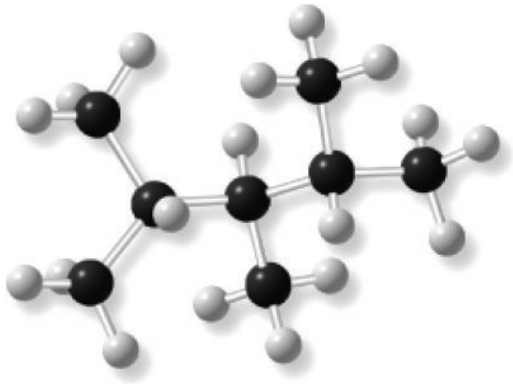
$CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_3$ or $CH_3CH(CH_3)CH_2CH_3$ or

$(CH_3)_2CHCH_2CH_3$ or $CH_3CH_2CH(CH_3)_2$

or $CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_3$

Practice Problem 1.9

Write a condensed structural formula for the following compound.



1.10C Bond-Line Formulas

The most common type of structural formula used by organic chemists, and the fastest to draw, is the **bond-line formula**. The formula in Fig. 1.14*d* is a bond-line formula for propyl alcohol. The sooner you master the use of bond-line formulas, the more quickly you will be able to draw molecules when you take notes and work problems. And, lacking all of the symbols that are explicitly shown in dash and condensed structural formulas, bond-line formulas allow you to more quickly interpret molecular connectivity and compare one molecular formula with another.

The efficiencies of drawing bond-line formulas come from the fact that no Cs are written for carbon atoms, and generally no Hs are shown for hydrogen atoms, unless they are needed to give a three-dimensional perspective to the molecule (and in that case we use solid or dashed wedges for bonds to the out-of-plane atoms, as described in the following section). Instead, in bond-line formulas ordinary lines represent bonds, and carbon atoms are inferred at each bend in the line and at the ends of lines.

The number of hydrogen atoms bonded to each carbon is also inferred, by assuming that as many hydrogen atoms are present as needed to fill the valence shell of each carbon, unless a charge is indicated. When an atom other than carbon is present, the symbol for that element is written in the formula at the appropriate location, i.e., in place of a bend or at the terminus of the line leading to the atom. Hydrogen atoms bonded to atoms other than carbon (e.g., oxygen or

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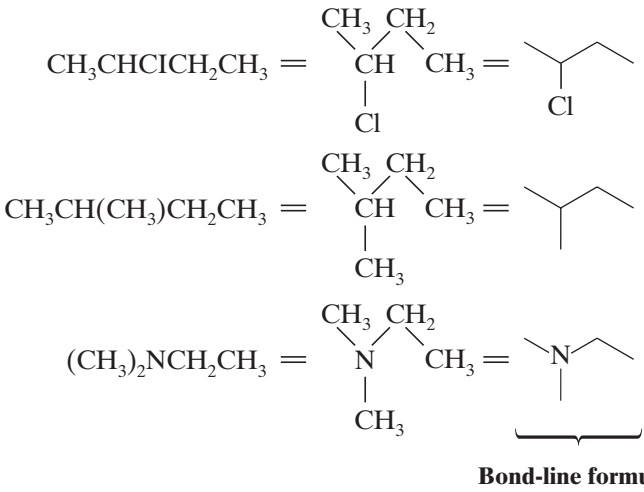
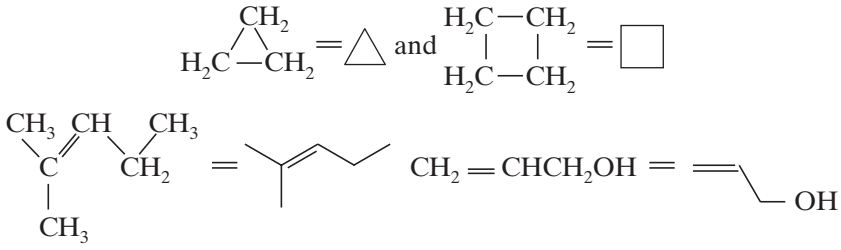
nitrogen) are written explicitly. And, as mentioned above, hydrogen atoms are shown where needed to help specify three dimensions using solid or dashed wedges. Consider the following examples of molecules depicted by bond-line formulas.



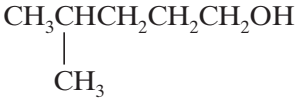
Helpful Hint: As you become more familiar with organic molecules, you will find bond-line formulas to be very useful tools for representing structures.

Bond-line formulas are easy to draw for molecules with multiple bonds and for cyclic molecules, as well. The following are some examples.



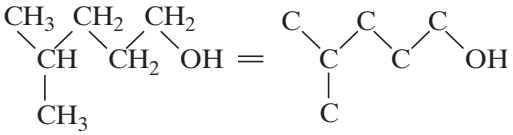
Solved Problem 1.12

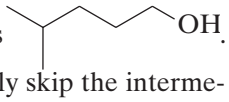
Write the bond-line formula for



Answer

First, for the sake of practice, we outline the carbon skeleton, including the OH group, as follows:



Then we write the bond-line formula as 

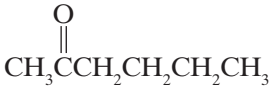
As you gain experience you will likely skip the intermediate steps shown above and proceed directly to writing bond-line formulas.

Practice Problem 1.10

Write each of the following condensed structural formulas as a bond-line formula:

(a) $(CH_3)_2CHCH_2CH_3$ **(b)** $(CH_3)_2CHCH_2CH_2OH$ **(c)** $(CH_3)_2C{=}CHCH_2CH_3$

(d) $CH_3CH_2CH_2CH_2CH_3$ **(e)** $CH_3CH_2CH(OH)CH_2CH_3$ **(f)** $CH_2{=}C(CH_2CH_3)_2$

(g) 

(h) $CH_3CHClCH_2CH(CH_3)_2$

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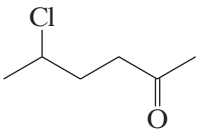
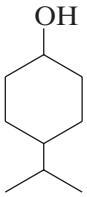
Practice Problem 1.11

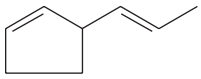
Which molecules in Practice Problem 1.10 form sets of constitutional isomers?

Practice Problem 1.12

Write a dash formula for each of the following bond-line formulas:

(a) 

(b) 

(c) 

Helpful Hint: Wedge and dashed-wedge formulas are a tool for unambiguously showing three dimensions.

1.10D Three-Dimensional Formulas

None of the formulas that we have described so far conveys any information about how the atoms of a molecule are arranged in space. There are several types of representations that do this. The types of formulas that we shall use most of the time are shown in Fig. 1.15. In these representations, bonds that project upward out of the plane of the paper are indicated by a solid wedge (◄), those that lie behind the plane are indicated with a dashed wedge (┈┈), and those bonds that lie in the plane of the page are indicated by a line (—). For tetrahedral atoms, notice that we draw the two bonds that are in the plane of the page with an angle of approximately 109° between them and that proper three-dimensional perspective then requires the wedge and dashed-wedge bonds to be drawn near each other on the page (i.e., the atom in front nearly eclipses the atom behind). We can draw trigonal planar atoms either with all bonds in the plane of the page separated by approximately 120° or with one of the three bonds in the plane of the page, one behind, and one in front (as in Fig. 1.5). Atoms with linear bonding geometry are best drawn with all bonds to those atoms in the plane of the page. Lastly, when drawing three-dimensional formulas is it generally best to draw as many carbon atoms as possible in the plane of the paper, allowing substituent groups or hydrogen atoms to be primarily those for which wedge or dashed-wedge bonds are used. Note that when using bond-line formulas we continue to omit hydrogen atoms unless they are relevant to clarifying the three-dimensional perspective of some other group. Figure 1.15 shows some examples of three-dimensional formulas.

Practice Problem 1.13

Write three-dimensional (wedge–dashed wedge–line) representations for each of the following:

(a) CH_3Cl **(b)** CH_2Cl_2 **(c)** CH_2BrCl **(d)** CH_3CH_2Cl

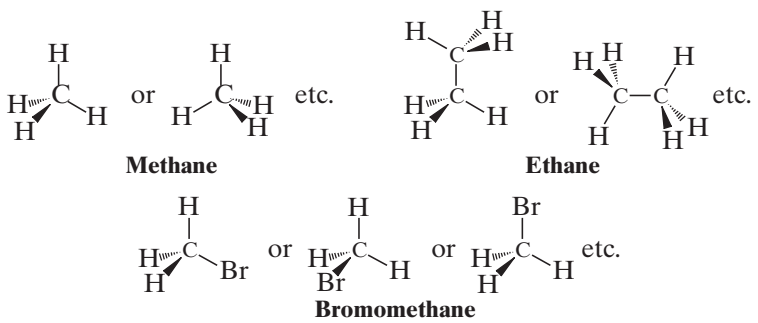


Figure 1.15 Three-dimensional formulas using wedge–dashed wedge–line formulas.

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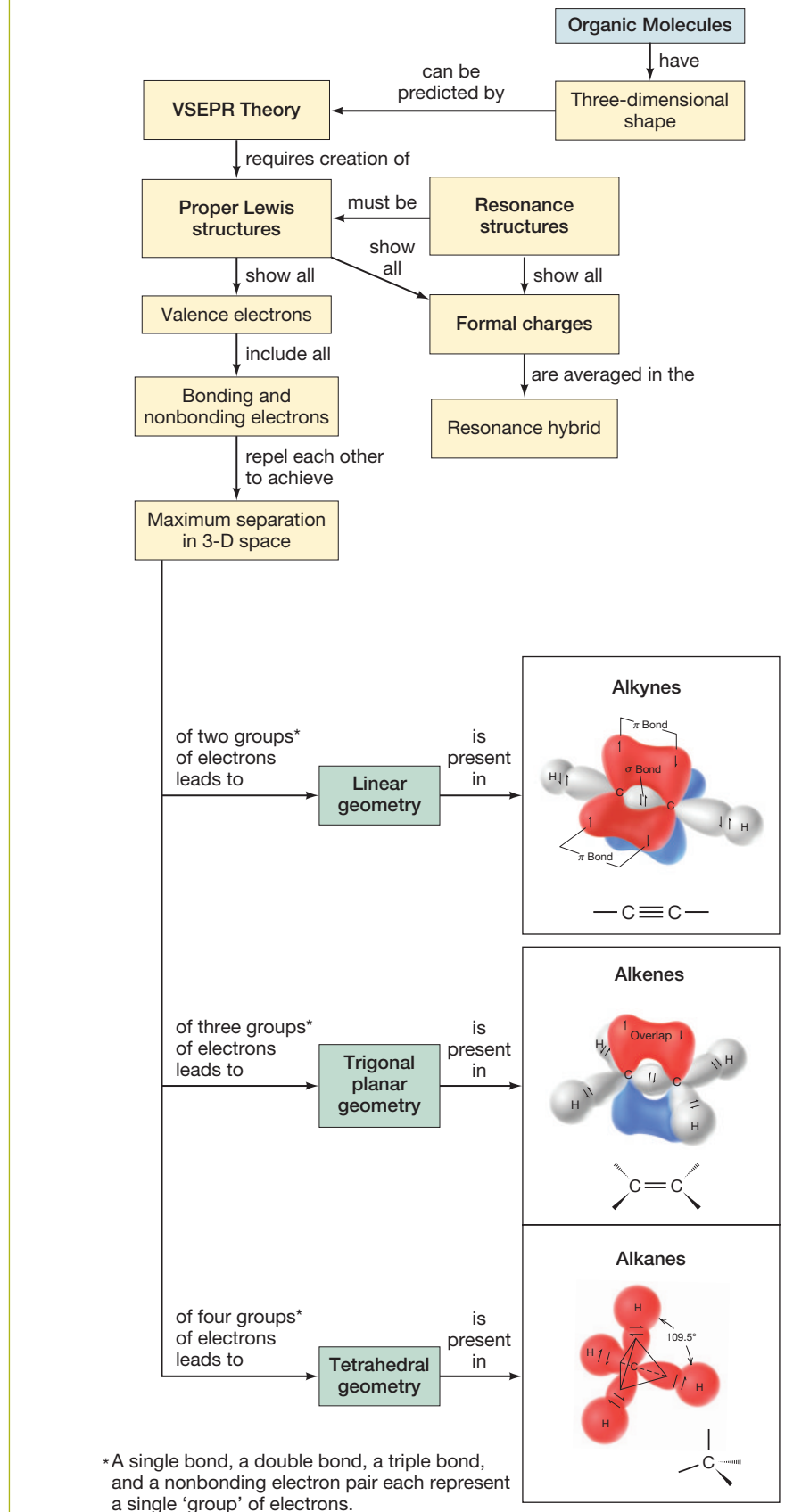
[CONCEPT MAP]



*A single bond, a double bond, a triple bond, and a nonbonding electron pair each represent a single 'group' of electrons.

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REVIEW PROBLEMS

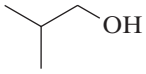
Electronic Configuration

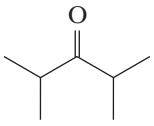
1.14 Which of the following ions possess the electron configuration of a noble gas?

(a) Na^+ **(b)** Cl^- **(c)** F^+ **(d)** H^-
(e) Ca^{2+} **(f)** S^{2-} **(g)** O^{2-} **(h)** Br^+

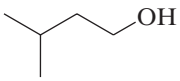
Structural Formulas and Isomerism

1.15 Write a condensed structural formula for each compound given here.

(a) 

(b) 

(c) 

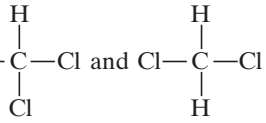
(d) 

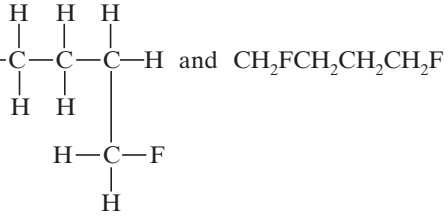
1.16 What is the molecular formula for each of the compounds given in the above questions?

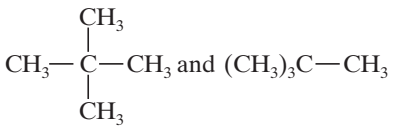
1.17 Consider each pair of structural formulas that follow and state whether the two formulas represent the same compound, whether they represent different compounds that are constitutional isomers of each other, or whether they represent different compounds that are not isomeric.

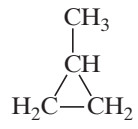
(a) 

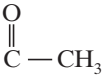
(b) $CH_3CH_2CH_2$ (with CH_2Cl branch) and $ClCH_2CH(CH_3)_2$

(c) 

(d) 

(e) 

(f) $CH_2{=}CHCH_2CH_3$ and 

(g) $CH_3OCH_2CH_3$ and 

(h) CH_3CH_2 (with CH_3CH_3 branch) and $CH_3CH_2CH_2CH_3$

1.18 Rewrite each of the following using bond-line formulas:

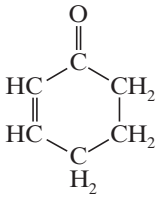
(a) $CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}CH_3$

(b) $CH_3CHCH_2CH_2CHCH_2CH_3$ (CH3 branches)

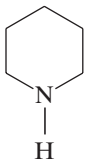
(c) $(CH_3)_3CCH_2CH_2CH_2OH$

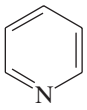
(d) $CH_3CH_2CHCH_2\overset{\overset{O}{\|}}{C}OH$ (CH_3 branch)

(e) $CH_2{=}CHCH_2CH_2CH{=}CHCH_3$

(f) 

1.19 Write a dash formula for each of the following showing any unshared electron pairs:

(a) 

(b) 

(c) $(CH_3)_2NCH_2CH_3$

(d) 

1.20 Consider the compound with the following condensed molecular formula:

$$CH_3CHOHCH{=}CH_2$$

(a) Write a full dash structural formula,
(b) show all nonbonding electron pairs,
(c) label the hybridization state of each carbon atom.

1.21 Write structural formulas of your choice for all the constitutional isomers with the molecular formula C_4H_8.

1.22 Write structural formulas for at least three constitutional isomers with the molecular CH_3NO_2. (In answering this question you should assign a formal charge to any atom that bears one.)

Resonance Structures

1.23 Cyanic acid (H—O—C≡N) and isocyanic acid (H—N=C=O) differ in the positions of their electrons but their structures do not represent resonance structures. **(a)** Explain. **(b)** Loss of a proton from cyanic acid yields the same anion as that obtained by loss of a proton from isocyanic acid. Explain.

1.24 Ozone (O_3) is found in the upper atmosphere where it absorbs highly energetic ultraviolet (UV) radiation and

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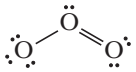
thereby provides the surface of Earth with a protective screen. One possible resonance structure for ozone is the following:



(a) Assign any necessary formal charges to the atoms in this structure.
(b) Write another equivalent resonance structure for ozone.
(c) What do these resonance structures predict about the relative lengths of the two oxygen–oxygen bonds of ozone?
(d) The structure above, and the one you have written, assume an angular shape for the ozone molecule. Is this shape consistent with VSEPR theory? Explain your answer.

1.25 Write resonance structures for the azide ion, N_3^-. Explain how these resonance structures account for the fact that both bonds of the azide ion have the same length.

Isomerism

1.26 Devise two structures, each having two *sp*-hybridized carbons and the molecular formula C_4H_6O. Create one of these structures such that it is linear with respect to all carbon atoms.

1.27 Write structural formulas of the type indicated: **(a)** bond-line formulas for seven constitutional isomers with the formula $C_4H_{10}O$; **(b)** condensed structural formulas for two constitutional isomers with the formula C_2H_7N; **(c)** condensed structural formulas for four constitutional isomers with the formula C_3H_9N; **(d)** bond-line formulas for three constitutional isomers with the formula C_5H_{12}.

ADDITIONAL OBJECTIVE QUESTIONS

Single Correct Choice Type

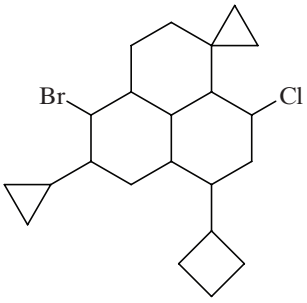
1. CH_2I_2 is a _____ halide.
(a) vicinal **(b)** secondary **(c)** geminal **(d)** vinyl

2. Identify the correct order of boiling point of the following compounds:

$CH_3CH_2CH_2CH_2OH$ $CH_3CH_2CH_2CHO$ $CH_3CH_2CH_2COOH$
1 **2** **3**

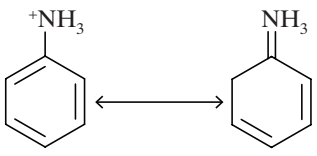
(a) 1 > 2 > 3 **(b)** 3 > 1 > 2 **(c)** 1 > 3 > 2 **(d)** 3 > 2 >1

3. Total number of 2° carbon present in given compound is x, so the value of $x - 7$ is



(a) 6 **(b)** 8 **(c)** 9 **(d)** None of these

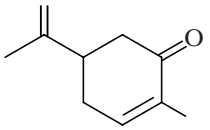
4. Choose the correct statement from the ones given below for the two anilinium ion structures.



(I) **(II)**

(a) II is not an acceptable canonical structure because carbonium ions are less stable than ammonium ions.
(b) II is not an acceptable canonical structure because it is non aromatic.
(c) II is not an acceptable canonical structure because the nitrogen has 10 valence shell electrons.
(d) II is an acceptable canonical structure.

5. What is the molecular formula of carvone?



Carvone
(responsible for odour of spearmint)

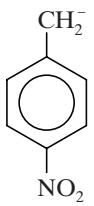
(a) $C_8H_{10}O$ **(b)** $C_{10}H_{14}O$
(c) $C_{10}H_{12}O$ **(d)** $C_9H_{12}O$

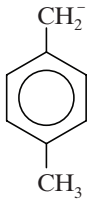
6. The number of sigma and pi-bonds in 1-butene-3-yne are
(a) 5 sigma and 5 pi **(b)** 7 sigma and 3 pi.
(c) 8 sigma and 2 pi **(d)** 6 sigma and 4 pi.

7. For 1–methoxy–1,3–butadiene, which of the following resonating structure is the least stable?

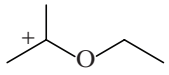
(a) $H_2\overset{+}{C}-\overset{+}{C}H-CH=CH-O-CH_3$
(b) $H_2\overset{+}{C}-CH=CH-CH=\overset{+}{O}-CH_3$
(c) $H_2\overset{+}{C}-\bar{C}H-\overset{+}{C}H-\overset{+}{C}H-O-CH_3$
(d) $H_2C=CH-\overset{+}{C}H-CH=\overset{+}{O}-CH_3$

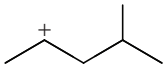
8. Most stable carbanion is
(a) CH_3^- **(b)** $CH_3CH_2^-$

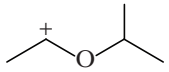
(c)


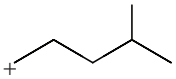
(d)


9. The correct stability order for the following species is

(I)


(II)


(III)


(IV)


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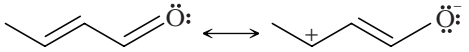
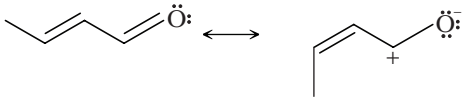
(a) II > IV > I > III (b) I > II > III > IV
(c) II > I > IV > III (d) I > III > II > IV

10. Select the structures that are not resonance structures of the same molecule.

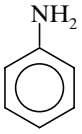
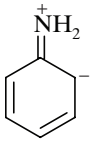
(a) 

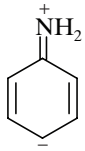
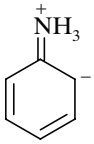
(b) 

(c) 

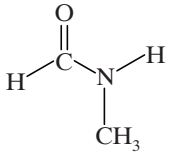
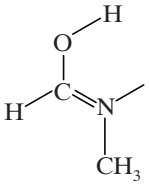
(d) 

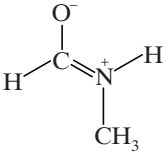
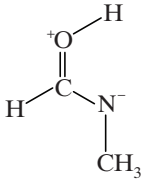
11. Which of the following is not a valid resonating structure?

(a)  (b) 

(c)  (d) 

12. Choose the incorrect statement about the following compounds.

(I)  (II) 

(III)  (III) 

(a) Compounds (I) and (II) are constitutional isomers.
(b) Compounds (I) and (III) are resonance structures.
(c) Compounds (I) and (IV) are resonance structures.
(d) Compounds (II) and (IV) are resonance structures.

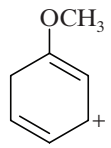
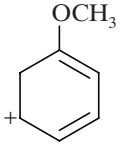
13. The correct stability order of the following resonance structures is

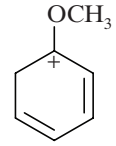
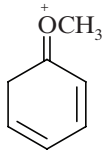
(I) $H_2\bar{C}-\overset{+}{N}\equiv N$ (II) $H_2C=\overset{+}{N}=\bar{N}$

(III) $H_2\overset{+}{C}-N=\bar{N}$ (IV) $H_2\bar{C}-N=\overset{+}{N}$

(a) (I) > (II) > (IV) > (III) (b) (I) > (III) > (II) > (IV)
(c) (II) > (I) > (III) > (IV) (d) (III) > (I) > (IV) > (II)

14. Which of the following resonance structures contribute the most to the resonance hybrid?

(a)  (b) 

(c)  (d) 

15. Among the given cations, the most stable carbonium ion is
(a) *sec*-butyl (b) *tert*-butyl.
(c) *n*-butyl (d) none of these.

16. $H_2C=CH-CH_2-\underset{\underset{CH_2}{\|}}{C}-\overset{+}{C}H_2$

Resonance hybrid of the carbocation is

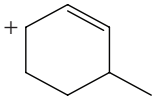
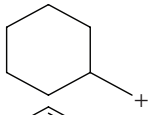
(a) $H_2\overset{\delta+}{C}=CH=\overset{\delta+}{C}H_2=\underset{\underset{\delta+}{\overset{\|}{CH_2}}}{C}=\overset{\delta+}{C}H_2$

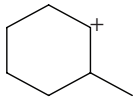
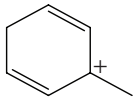
(b) $H_2C=CH-CH_2-\underset{\underset{\delta+}{\overset{\|}{CH_2}}}{C}=\overset{\delta+}{C}H_2$

(c) $H_2\overset{\delta+}{C}=CH-CH_2-\underset{\underset{\delta+}{\overset{\|}{CH_2}}}{C}=\overset{\delta+}{C}H_2$

(d) $H_2C=CH-CH_2-\overset{\delta+}{C}H_2=CH=\overset{\delta+}{C}H_2$

17. Which of the following is the most stable carbocation?

(a)  (b) 

(c)  (d) 

18. Rank the following free radicals in order of decreasing stability

(I) $C_6H_5\dot{C}HC_6H_5$ (II) $C_6H_5-\dot{C}H-CH=CH_2$

(III) $CH_3-\dot{C}H-CH_3$ (IV) $C_6H_5-\dot{C}H-CH_3$

(V) $CH_3CH=CHCH_2\dot{C}H_2$ (VI) $CH_3-CH_2-\underset{\underset{CH_3}{|}}{\dot{C}}-CH_3$

(a) I > II > IV > VI > III > V
(b) VI > V > IV > III > II > I
(c) I > II > III > IV > V > VI
(d) I > IV > VI > V > II > III

19. In the following compound $H-\overset{1}{C}\equiv\overset{2}{C}-\overset{3}{C}H_2-\overset{4}{C}H_3$ the hybridization of C2 and C3 carbons are, respectively,

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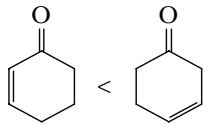
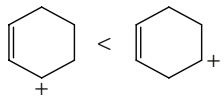
(a) sp^3 and sp^3 (b) sp^2 and sp^3
(c) sp^2 and sp (d) sp^3 and sp

20. Correctly matched option stability of compound in each of the following pairs:

(a) 

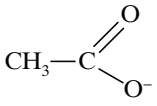
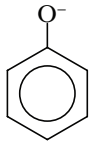
(b) $CH_3CH{=}CH\dot{C}HCH{=}CH_2 < CH_3CH_2CH_2CH_2\dot{C}H{=}CH_2$

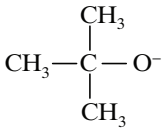
(c) 

(d) $CH_3\overset{+}{C}HCH{=}CHCH_3 > CH_3CH{=}CHCH_2\overset{+}{C}H_2$

21. The hyperconjugative stabilities of *tert*-butyl cation and 2-butene, respectively, are due to
(a) $\sigma \rightarrow p$ (sigma)(empty) and $\sigma \rightarrow \pi^*$ electron delocalization.
(b) $\sigma \rightarrow \sigma^*$ and $\sigma \rightarrow \pi$ electron delocalization.
(c) $\sigma \rightarrow p$ (filled) and $\sigma \rightarrow \pi$ electron delocalization.
(d) p (filled) $\rightarrow \sigma^*$ and $\sigma \rightarrow \pi^*$ electron delocalization.

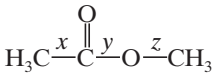
22. Which is the correct stability order of oxy-anions given below?

(I)  (II) 

(III)  (IV) $CH_3{-}CH_2{-}O^-$

(a) (II) > (I) > (IV) > (III) (b) (I) > (II) > (III) > (IV)
(c) (II) > (I) > (III) > (IV) (d) (I) > (II) > (IV) > (III)

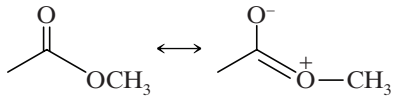
23. In the following there are three carbon-oxygen bonds denoted by x, y and z:

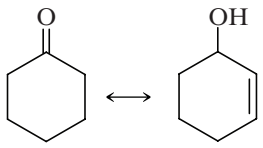


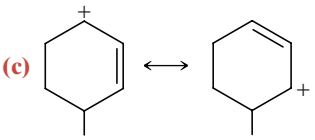
Their lengths are in order
(a) $x = y = z$ (b) $x < y < z$
(c) $x < y < z$ (d) $y < x < z$

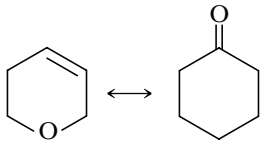
Multiple Correct Choice Type

1. Which of the following is not resonating structure of each other?

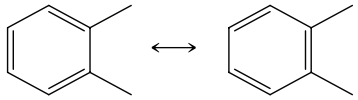
(a) 

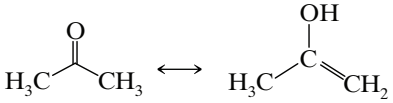
(b) 

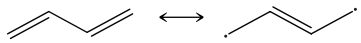
(c) 

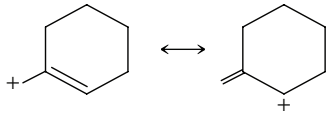
(d) 

2. Which of the following pairs are resonance structures of each other?

(a) 

(b) 

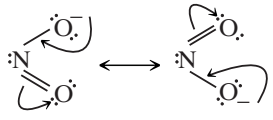
(c) 

(d) 

Linked Comprehension Type

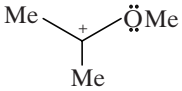
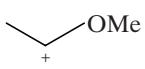
Paragraph for Questions 1 to 2

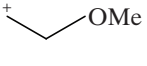
The theory of resonance was developed primarily by Pauling in the 1930s. According to this theory, many molecules and ions are best described by writing two or more Lewis structures and considering the real molecule or ion to be a composite of these structures. Individual Lewis structure are called contributing structures. They are also sometimes referred to as resonance structures or resonance contributors. We show that the real molecule or ion is a resonance hybrid of the various contributing structures by interconnecting them with double headed arrows. Resonance structures are not in equilibrium with each other.



(equivalent contributing structures)

1. Find out the stability order of intermediate.

(I)  (II) 

(III)  (IV) $H_2\overset{+}{C}{-}\ddot{O}Me$

(a) I > II > III > IV (b) I > II > IV > III
(c) IV > I > II > III (d) III > I > II > IV

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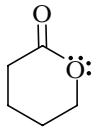
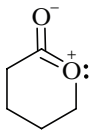
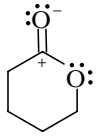
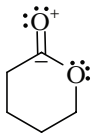
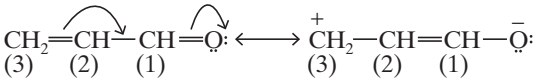
2. Stability order of the following resonating structure will be

(I) 
(II) 
(III) 
(IV) 

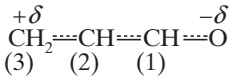
(a) I > II > III > IV **(b)** II > I > III > IV
(c) III > II > I > IV **(d)** I > III > II > IV

Paragraph for Questions 3 to 5

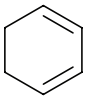
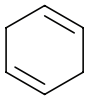
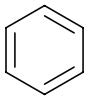
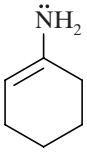
The bond length between C2 and C3 in acryl aldehyde is not equal to the bond length between carbons of ethene because in acryl aldehyde double bond is in conjugation, so it shows resonance which results in an increase in the bond length between C2 and C3 in acryl aldehyde.



Resonance structure (I) Resonance structure (II)

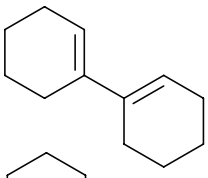
Resonance Hybrid 

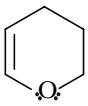
3. Which compound will not show the resonance?

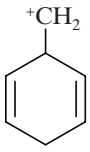
(a)  **(b)**  **(c)**  **(d)** 

4. Which compound does not have the conjugative system to show the resonance?

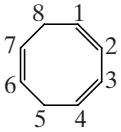
(a) $CH_2=CH-CH=CH-CH_2-CH_3$

(b) 

(c) 

(d) 

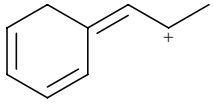
5. Find out the correct statement(s) about the given compound?



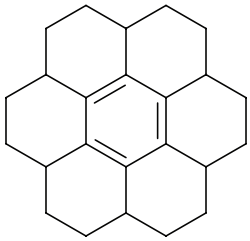
(a) Bond length between C2 and C3 = Bond length between C5 and C6.
(b) Bond length between C1 and C2 = Bond length between C6 and C7.
(c) Bond length between C6 and C7 < Bond length between C3 and C4.
(d) Bond length between C2 and C3 < Bond length between C3 and C4.

Integer Type

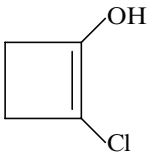
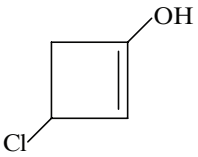
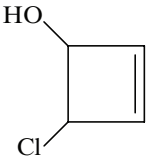
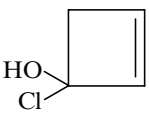
1. Total number of resonating structures in the following compound is



2. Total number of α-hydrogen in the following compound is



Matrix Match Type

Column I	Column II
(a) 	**(p)** Resonance stabilization in the compound
(b) 	**(q)** IUPAC name is 2-chloro-cyclobutenol
(c) 	**(r)** IUPAC name is 3-chlorocyclobutenol
(d) 	**(s)** Resonance is not possible

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ANSWER KEY

Single Correct Choice Type

1. (c)	**2.** (b)	**3.** (a)	**4.** (c)	**5.** (b)
6. (b)	**7.** (c)	**8.** (c)	**9.** (d)	**10.** (d)
11. (d)	**12.** (c)	**13.** (b)	**14.** (d)	**15.** (b)
16. (b)	**17.** (d)	**18.** (a)	**19.** (d)	**20.** (d)
21. (a)	**22.** (d)			

Multiple Correct Choice Type

1. (b), (d) **2.** (a), (d)

Linked Comprehension Type

1. (b)	**2.** (a)	**3.** (b)	**4.** (d)	**5.** (c)

Integer Type

1. (4) **2.** (6)

Matrix Match Type

(a)→(p), (q); (b)→(p); (r); (c)→(s); (d)→(s)

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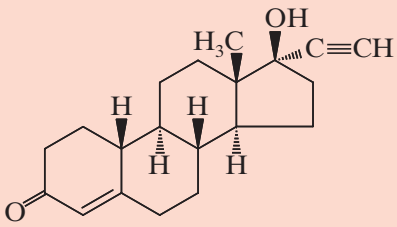
2

Families of Carbon Compounds: Functional Groups and Intermolecular Forces

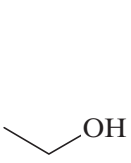


Norethindrone

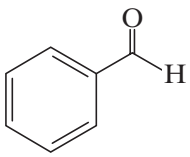
Contents

2.1 | Hydrocarbons: Representative Alkanes, Alkenes, Alkynes, and Aromatic Compounds
2.2 | Polar and Nonpolar Molecules
2.3 | Functional Groups
2.4 | Alkyl Halides or Haloalkanes
2.5 | Alcohols
2.6 | Ethers
2.7 | Amines
2.8 | Aldehydes and Ketones
2.9 | Carboxylic Acids, Esters, and Amides
2.10 | Nitriles
2.11 | Summary of Important Families of Organic Compounds
2.12 | Physical Properties and Molecular Structure
2.13 | Summary of Attractive Electric Forces

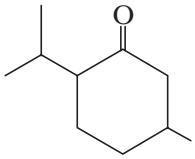
Functional groups are common and specific arrangements of atoms that impart predictable reactivity and properties to a molecule. Even though there are millions of organic compounds, you may be relieved to know that we can readily understand much about whole families of compounds simply by learning about the properties of the common functional groups. For example, all alcohols contain an –OH (hydroxyl) functional group attached to a saturated carbon bearing nothing else but carbon or hydrogen, such as in ethanol. All aldehydes have a –C(=O)– (carbonyl) group with one bond to a hydrogen and the other to one or more carbons, such as in benzaldehyde (from almonds). All ketones include a carbonyl group bonded by its carbon to one or more other carbons on each side, as in the natural oil menthone, found in geraniums and spearmint.



Ethanol



Benzaldehyde



Menthone

Members of each functional group family share common chemical properties and reactivity, and this fact helps greatly in organizing our knowledge of organic chemistry. As you progress in this chapter it will serve you well to learn the arrangements of atoms that define the common functional groups. This knowledge will be invaluable to your study of organic chemistry.

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2.1 | HYDROCARBONS: REPRESENTATIVE ALKANES, ALKENES, ALKYNES, AND AROMATIC COMPOUNDS

Here we introduce the class of compounds that contains only carbon and hydrogen, and we shall see how the -ane, -ene, or -yne ending in a name tells us what kinds of carbon–carbon bonds are present.

Hydrocarbons are compounds that contain only carbon and hydrogen atoms. Methane (CH_4) and ethane (C_2H_6) are hydrocarbons, for example. They also belong to a subgroup of compounds called alkanes.

- **Alkanes** are hydrocarbons that do not have multiple bonds between carbon atoms, and we can indicate this in the family name and in names for specific compounds by the **-ane** ending.

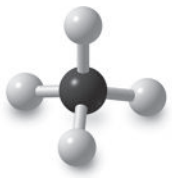
  Other hydrocarbons may contain double or triple bonds between their carbon atoms.
- **Alkenes** contain at least one carbon–carbon double bond, and this is indicated in the family name and in names for specific compounds by an **-ene** ending.
- **Alkynes** contain at least one carbon–carbon triple bond, and this is indicated in the family name and in names for specific compounds by a **-yne** ending.
- **Aromatic compounds** contain a special type of ring, the most common example of which is a benzene ring. There is no special ending for the general family of aromatic compounds.

We shall introduce representative examples of each of these classes of hydrocarbons in the following sections.

Generally speaking, compounds such as the alkanes, whose molecules contain only single bonds, are referred to as **saturated compounds** because these compounds contain the maximum number of hydrogen atoms that the carbon compound can possess. Compounds with multiple bonds, such as alkenes, alkynes, and aromatic hydrocarbons, are called **unsaturated compounds** because they possess fewer than the maximum number of hydrogen atoms, and they are capable of reacting with hydrogen under the proper conditions. We shall have more to say about this in Chapter 7.

2.1A Alkanes

The primary sources of alkanes are natural gas and petroleum. The smaller alkanes (methane through butane) are gases under ambient conditions. Methane is the principal component of natural gas. Higher molecular weight alkanes are obtained largely by refining petroleum. Methane, the simplest alkane, was one major component of the early atmosphere of this planet. Methane is still found in Earth's atmosphere, but no longer in appreciable amounts. It is, however, a major component of the atmospheres of Jupiter, Saturn, Uranus, and Neptune. On Earth, methane is the major component of natural gas. Because the components of natural gas are important in industry, efforts are being made to develop coal gasification processes to provide alternative sources.

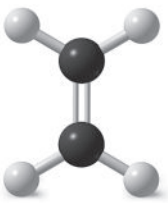


Methane

Some living organisms produce methane from carbon dioxide and hydrogen. These very primitive creatures, called *methanogens*, may be Earth's oldest organisms, and they may represent a separate form of evolutionary development. Methanogens can survive only in an anaerobic (i.e., oxygen-free) environment. They have been found in ocean trenches, in mud, in sewage, and in cows' stomachs.

2.1B Alkenes

Ethene and propene, the two simplest alkenes, are among the most important industrial chemicals. Ethene is used as a starting material for the synthesis of many industrial compounds, including ethanol, ethylene oxide, ethanal, and the polymer polyethylene. Propene is used in making the polymer polypropylene, and, in addition to other uses, propene is the starting material for a synthesis of acetone and cumene.



Ethene

Ethene also occurs in nature as a plant hormone. It is produced naturally by fruits such as tomatoes and bananas and is involved in the ripening process of these fruits. Much use is now made of ethene in the commercial fruit industry to bring about the ripening of tomatoes and bananas picked green because the green fruits are less susceptible to damage during shipping.

There are many naturally occurring alkenes. Two examples are the following:

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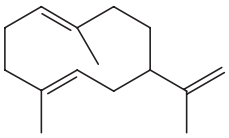
β-Pinene (a component of turpentine)



An aphid alarm pheromone

2.1C Alkynes

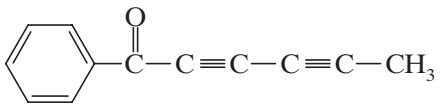
The simplest alkyne is ethyne (also called acetylene). Alkynes occur in nature and can be synthesized in the laboratory. Friedrich Wöhler synthesized ethyne in 1862 by the reaction of calcium carbide and water. Ethyne produced this way was burned in carbide lamps, such as those formerly used on miners' headlamps. Because it burns at a high temperature, ethyne is used in welding torches.

Alkynes whose molecules have multiple triple bonds exist in the atmosphere of the outer planets in our solar system. H. W. Kroto (University of Sussex, England) has identified compounds called cyanopolyynes in intersteller space. (Kroto shared the 1996 Nobel Prize in Chemistry for the discovery of buckminsterfullerenes C.)

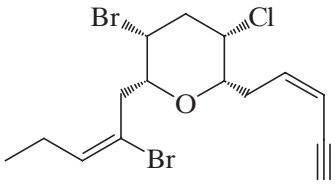
Two examples of alkynes among thousands that have a biosynthetic origin are capillin, an antifungal agent, and dactylyne, a marine natural product that is an inhibitor of pento-barbital metabolism. Ethinyl estradiol is a synthetic alkyne whose estrogen-like properties have found use in oral contraceptives.



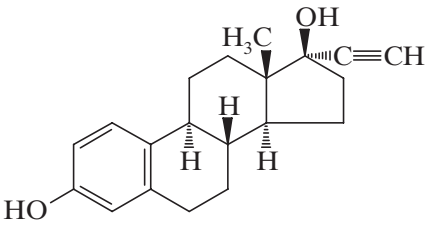
Ethyne



Capillin



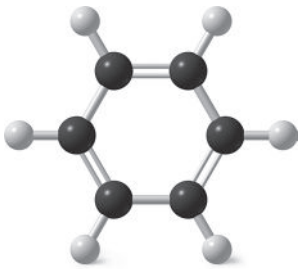
Dactylyne



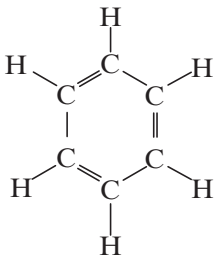
Ethinyl estradiol [17a-ethynyl-1, 3, 5(10)-estratriene-3, 17β-diol]

2.1D Benzene: A Representative Aromatic Hydrocarbon

In Chapter 13 we shall study in detail a group of unsaturated cyclic hydrocarbons known as aromatic compounds. The compound known as **benzene** is the prototypical aromatic compound. Benzene can be written as a six-membered ring with alternating single and double bonds, called a **Kekulé structure** after August Kekulé (Section 1.4), who first conceived of this representation:



Benzene



Kekulé structure for benzene

or



Bond-line representation of Kekulé structure

Even though the Kekulé structure is frequently used for benzene compounds, there is much evidence that this representation is inadequate and incorrect. For example, if benzene had alternating single and double bonds as the Kekulé structure indicates, we would expect the lengths of the carbon–carbon bonds around the ring to be alternately

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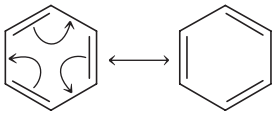
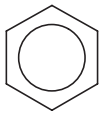
longer and shorter, as we typically find with carbon–carbon single and double bonds. In fact, the carbon–carbon bonds of benzene are all the same length (1.39 Å), a value in between that of a carbon–carbon single bond and a carbon–carbon double bond. There are two ways of dealing with this problem: with resonance theory or with molecular orbital theory.

If we use resonance theory, we visualize benzene as being represented by either of two equivalent Kekulé structures:



Two contributing Kekulé structures for benzene

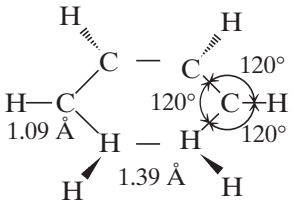


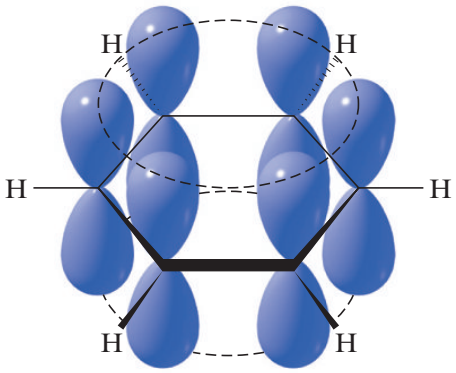
A representation of the resonance hybrid

Based on the principles of resonance theory (Section 1.5) we recognize that benzene cannot be represented adequately by either structure, but that, instead, *it should be visualized as a hybrid of the two structures*. We represent this hybrid by a hexagon with a circle in the middle. Resonance theory, therefore, solves the problem we encountered in understanding how all of the carbon–carbon bonds are the same length. According to resonance theory, the bonds are not alternating single and double bonds, they are a resonance hybrid of the two: Any bond that is a single bond in the first contributor is a double bond in the second, and vice versa.

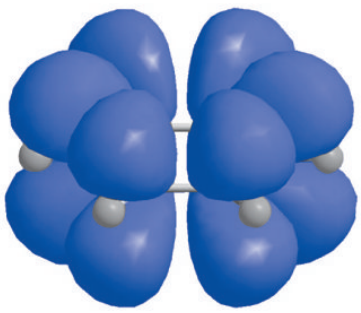
- All of the carbon–carbon bonds in benzene are one and one-half bonds, have a bond length in between that of a single bond and a double bond, and have bond angles of 120°.

In the molecular orbital explanation, which we shall describe in much more depth in Chapter 13, we begin by recognizing that the carbon atoms of the benzene ring are sp^2 hybridized. Therefore, each carbon has a p orbital that has one lobe above the plane of the ring and one lobe below, as shown here in the schematic and calculated p orbital representations.

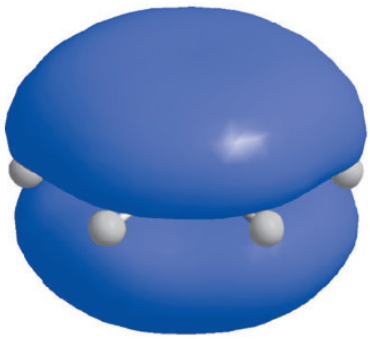




Schematic representation of benzene p orbitals



Calculated p orbital shapes in benzene



Calculated benzene molecular orbital resulting from favorable overlap of p orbitals above and below plane of benzene ring

The lobes of each p orbital above and below the ring overlap with the lobes of p orbitals on the atoms to either side of it. This kind of overlap of p orbitals leads to a set of bonding molecular orbitals that encompass all of the carbon atoms of the ring, as shown in the calculated molecular orbital. Therefore, the six electrons associated with these p orbitals

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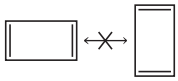
(one electron from each orbital) are **delocalized** about all six carbon atoms of the ring. This delocalization of electrons explains how all the carbon–carbon bonds are equivalent and have the same length.

Practice Problem 2.1

Cyclobutadiene (below) is like benzene in that it has alternating single and double bonds in a ring. However, its bonds are not the same length, the double bonds being shorter than the single bonds; the molecule is rectangular, not square. Explain why it would be incorrect to write resonance structures as shown.



2.2 | POLAR AND NONPOLAR MOLECULES

Until now, we have not considered the possibility that the electrons of a covalent bond might be shared unequally.

If electronegativity differences exist between two bonded atoms, and they are not large, the electrons are not shared equally and a **polar covalent bond** is the result.

Remember: One definition of **electronegativity** is *the ability of an atom to attract electrons that it is sharing in a covalent bond*.

An example of such a polar covalent bond is the one in hydrogen chloride. The chlorine atom, with its greater electronegativity, pulls the bonding electrons closer to it. This makes the hydrogen atom somewhat electron deficient and gives it a *partial* positive charge (Δ+). The chlorine atom becomes somewhat electron rich and bears a *partial* negative charge (Δ–):



Because the hydrogen chloride molecule has a partially positive end and a partially negative end, it is a **dipole**, and it has a **dipole moment**.

The direction of polarity of a polar bond can be symbolized by a vector quantity ⟶ The crossed end of the arrow is the positive end and the arrowhead is the negative end:

The dipole moment is a physical property that can be measured experimentally. It is defined as the product of the magnitude of the charge in electrostatic units (esu) and the distance that separates them in centimeters (cm):

$$\text{Dipole moment} = \text{charge (in esu)} \times \text{distance (in cm)}$$
$$\mu = e \times d$$

The charges are typically on the order of 10^{-10} esu and the distances are on the order of 10^{-18} cm. Dipole moments, therefore, are typically on the order of 10^{-18} esu·cm. For convenience, this unit, 1×10^{-18} esu cm, is defined as one **debye** and is abbreviated D. (The unit is named after Peter J. W. Debye, a chemist born in the Netherlands, who taught at Cornell University from 1936 to 1966. Debye won the Nobel Prize in Chemistry in 1936.) In SI units $1\ \text{D} = 3.336 \times 10^{-30}$ coulomb meter (C · m).

Polar covalent bonds strongly influence the physical properties and reactivity of molecules. In many cases, these polar covalent bonds are part of **functional groups**, which we shall study shortly. Any diatomic molecule in which the two atoms are *different* (and thus have different electronegativities) will, of necessity, have a dipole moment. In general, a molecule with a dipole moment is a **polar molecule**.

Consider a molecule of carbon tetrachloride (CCl_4). Because the electronegativity of chlorine is greater than that of carbon, each of the carbon–chlorine bonds in CCl_4 is polar. Each chlorine atom has a partial negative charge, and the carbon atom is considerably positive. Because a molecule of carbon tetrachloride is tetrahedral (Fig. 2.1), however, *the center of positive charge and the center of negative charge coincide, and the molecule has no net dipole moment*. The chloromethane molecule (CH_3Cl) has a net dipole moment of 1.87 D. Since carbon and hydrogen have electronegativities that are nearly the same, the contribution of three C—H bonds to the net dipole is negligible. The electronegativity difference between carbon and chlorine is large, however, and the highly polar C—Cl bond accounts for most of the dipole moment of CH_3Cl.

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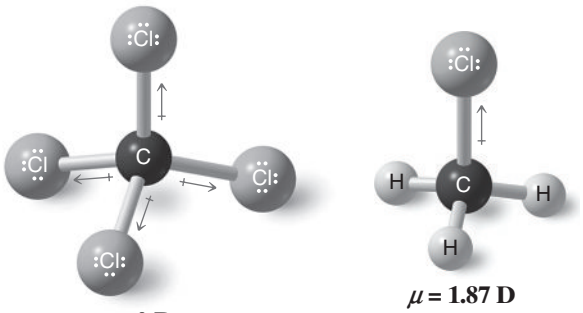


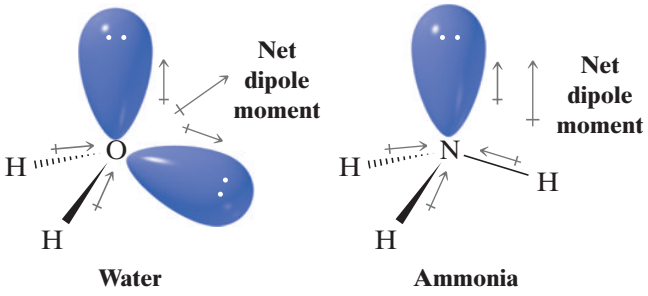
Figure 2.1 Dipole moments in CCl_4 and CH_3Cl.

Solved Problem 2.1

Compare the dipole moments of water and ammonia.

Answer

Unshared pairs of electrons make large contributions to the dipole moments of water and ammonia. Because an unshared pair has no other atom attached to it to partially neutralize its negative charge, an unshared electron pair contributes a large moment directed away from the central atom. (The O—H and N—H moments are also appreciable.)



Practice Problem 2.2

Tetrachloroethene ($CCl_2{=}CCl_2$) does not have a dipole moment. Explain this fact on the basis of the shape of $CCl_2{=}CCl_2$.

Practice Problem 2.3

Using a three-dimensional formula, show the direction of the dipole moment of CH_3OH. Write $\delta+$ and $\delta-$ signs next to the appropriate atoms.

Practice Problem 2.4

Trichloromethane ($CHCl_3$, also called *chloroform*) has a larger dipole moment than $CFCl_3$. Use three-dimensional structures and bond moments to explain this fact.

2.2A Dipole Moments in Alkenes

Cis–trans isomers of alkenes have different physical properties. They have different melting points and boiling points, and often cis–trans isomers differ markedly in the magnitude of their dipole moments. Table 2.1 summarizes some of the physical properties of two pairs of *cis–trans* isomers.

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Table 2.1 Physical Properties of Some *cis–trans* Isomers

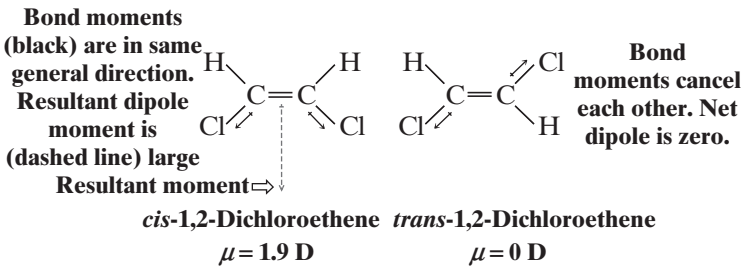
Compound	Melting Point (°C)	Boiling Point (°C)	Dipole Moment (D)
cis-1,2-Dichloroethene	−80	60	1.90
trans-1,2-Dichloroethene	−50	48	0
cis-1,2-Dibromoethene	−53	112.5	1.35
trans-1,2-Dibromoethene	−6	108	0

Solved Problem 2.2

Explain why *cis*-1,2-dichloroethene (Table 2.1) has a large dipole moment whereas *trans*-1,2-dichloroethene has a dipole moment equal to zero.

Answer

If we examine the net dipole moments (shown in dashed line) for the bond moments (black), we see that in *trans*-1,2-dichloroethene the bond moments cancel each other, whereas in *cis*-1,2-dichloroethene they augment each other.



Practice Problem 2.5

Indicate the direction of the important bond moments in each of the following compounds (neglect C—H bonds). You should also give the direction of the net dipole moment for the molecule. If there is no net dipole moment, state that $\mu = 0$ D.

(a) *cis*-CHF=CHF; **(b)** *trans*-CHF=CHF; **(c)** $CH_2=CF_2$; **(d)** $CF_2=CF_2$

Practice Problem 2.6

Write structural formulas for all of the alkenes with **(a)** the formula $C_2H_2Br_2$ and **(b)** the formula $C_2Br_2Cl_2$. In each instance designate compounds that are cis–trans isomers of each other. Predict the dipole moment of each one.

2.3 | FUNCTIONAL GROUPS

A functional group is the part of a molecule where most of its chemical reactions occur. It is the part that effectively determines the compound's chemical properties (and many of its physical properties as well).

- **Functional groups** are common and specific arrangements of atoms that impart predictable reactivity and properties to a molecule.

The functional group of an alkene, for example, is its carbon–carbon double bond. When we study the reactions of alkenes in greater detail in Chapter 8, we shall find that most of the chemical reactions of alkenes are the chemical reactions of the carbon–carbon double bond.

The functional group of an alkyne is its carbon–carbon triple bond. Alkanes do not have a functional group. Their molecules have carbon–carbon single bonds and carbon–hydrogen bonds, but these bonds are present in molecules of almost all organic compounds, and C—C and C—H bonds are, in general, much less reactive than common functional

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groups. Table 2.2 summarizes the most important functional groups. First, however, let us introduce some common **alkyl groups**, which are specific groups of carbon and hydrogen atoms that are not part of functional groups.

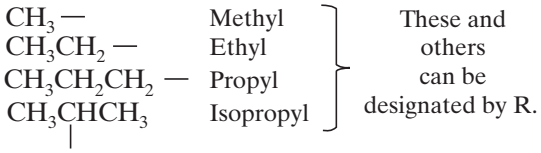
2.3A Alkyl Groups and the Symbol R

Alkyl groups are the groups that we identify for purposes of naming compounds. They are groups that would be obtained by removing a hydrogen atom from an alkane:

Alkane	Alkyl Group	Abberviation
$CH_3—H$	$CH_3—$	Me–
Methane	**Methyl**	
$CH_3CH_2—H$	$CH_3CH_2—$	Et–
Ethane	**Ethyl**	
$CH_3CH_2CH_2—H$	$CH_3CH_2CH_2—$	Pr–
Propane	**Propyl**	
$CH_3CH_2CH_2CH_2—H$	$CH_3CH_2CH_2CH_2—$	Bu–
Butane	**Butyl**	

While only one alkyl group can be derived from methane or ethane (the **methyl** and **ethyl** groups, respectively), two groups can be derived from propane. Removal of a hydrogen from one of the end carbon atoms gives a group that is called the **propyl** group; removal of a hydrogen from the middle carbon atom gives a group that is called the **isopropyl** group. The names and structures of these groups are used so frequently in organic chemistry that you should learn them now. See Section 5.3C for names and structures of branched alkyl groups derived from butane and other hydrocarbons.

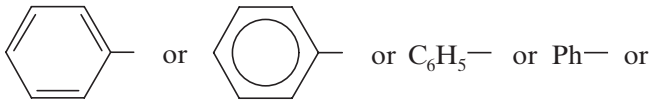
We can simplify much of our future discussion if, at this point, we introduce a symbol that is widely used in designating general structures of organic molecules: the symbol R. R ***is used as a general symbol to represent any alkyl group***. For example, R might be a methyl group, an ethyl group, a propyl group, or an isopropyl group:



Thus, the general formula for an alkane is R—H.

2.3B Phenyl and Benzyl Groups

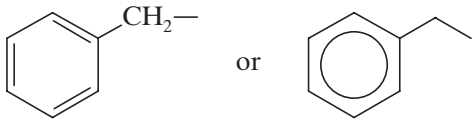
When a benzene ring is attached to some other group of atoms in a molecule, it is called a **phenyl group**, and it is represented in several ways:



ϕ— or Ar— (if ring substituents are present)

Ways of representing a benzyl group

The combination of a phenyl group and a **methylene group** ($—CH_2—$) is called a benzyl group.



or $C_6H_5CH_2—$ or Bn—

Way of representing a benzyl group

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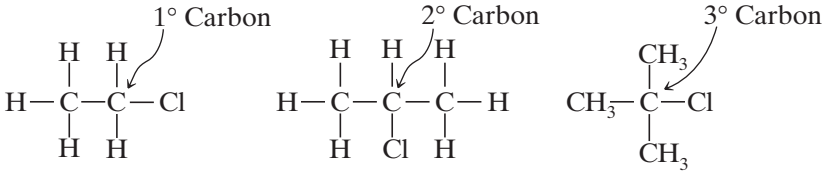
2.4 | ALKYL HALIDES OR HALOALKANES

Alkyl halides are compounds in which a halogen atom (fluorine, chlorine, bromine, or iodine) replaces a hydrogen atom of an alkane. For example, CH_3Cl and CH_3CH_2Br are alkyl halides. Alkyl halides are also called **haloalkanes**. The generic formula for an alkyl halide is R—$\ddot{\underset{\ddot{}}{X}}$: where X = fluorine, chlorine, bromine, or iodine.

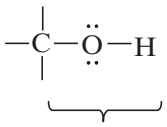
Alkyl halides are classified as being primary (1°), secondary (2°), or tertiary (3°). ***This classification is based on the carbon atom to which the halogen is directly attached***. If the carbon *atom* that bears the halogen is attached to only one other carbon, the carbon atom is said to be a **primary carbon atom** and the alkyl halide is classified as a **primary alkyl halide**. If the carbon that bears the halogen is itself attached to two other carbon atoms, then the carbon is a **secondary carbon** and the alkyl halide is a **secondary alkyl halide**. If the carbon that bears the halogen is attached to three other carbon atoms, then the carbon is a **tertiary carbon** and the alkyl halide is a **tertiary alkyl halide**. Examples of primary, secondary, and tertiary alkyl halides are the following:



A 1° alkyl chloride | **A 2° alkyl chloride** | **A 3° alkyl chloride**

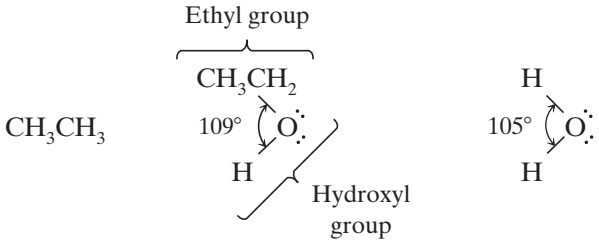
2.5 | ALCOHOLS

Methyl alcohol (also called methanol) has the structural formula CH_3OH and is the simplest member of a family of organic compounds known as **alcohols**. The characteristic functional group of this family is the hydroxyl (—OH) group attached to an sp^{3-} hybridized carbon atom. Another example of an alcohol is ethyl alcohol, CH_3CH_2OH (also called ethanol).



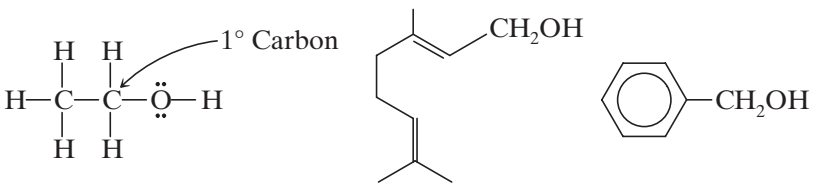
This is the functional group of an alcohol.

Alcohols may be viewed structurally in two ways: (1) as hydroxyl derivatives of alkanes and (2) as alkyl derivatives of water. Ethyl alcohol, for example, can be seen as an ethane molecule in which one hydrogen has been replaced by a hydroxyl group or as a water molecule in which one hydrogen has been replaced by an ethyl group:



Ethane | **Ethyl alcohol (ethanol)** | **Water**

As with alkyl halides, alcohols are classified into three groups: primary (1°), secondary (2°), and tertiary (3°) alcohols. ***This classification is based on the degree of substitution of the carbon to which the hydroxyl group is directly attached***. If the carbon has only one other carbon attached to it, the carbon is said to be a **primary carbon** and the alcohol is a **primary alcohol**:



Ethyl alcohol (a 1° alcohol) | **Geraniol (a 1° alcohol)** | **Benzyl alcohol (a 1° alcohol)**

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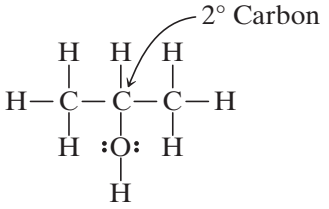
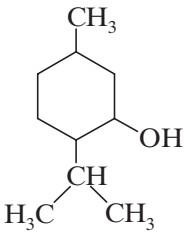
If the carbon atom that bears the hydroxyl group also has two other carbon atoms attached to it, this carbon is called a secondary carbon, and the alcohol is a secondary alcohol:

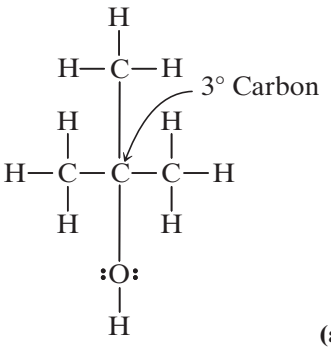


Isopropyl alcohol
(a 2° alcohol)

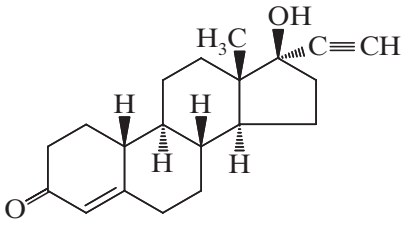


Menthol
(a 2° alcohol found in peppermint oil)

If the carbon atom that bears the hydroxyl group has three other carbons attached to it, this carbon is called a tertiary carbon, and the alcohol is a tertiary alcohol:



***tert*-Butyl alcohol**
(a 3° alcohol)



Norethindrone
(an oral contraceptive that contains a 3° alcohol group as well as a ketone group and carbon–carbon double and triple bonds)

Solved Problem 2.3

Write bond-line structural formulas for **(a)** two primary alcohols, **(b)** a secondary alcohol, and **(c)** a tertiary alcohol—all having the molecular formula $C_4H_{10}O$.

Answer

(a) $CH_3CH_2CH_2CH_2OH$ and CH_3CHCH_2OH (with CH_3 branch)

(b) $CH_3CHCH_2CH_3$ (with OH)

(c) $CH_3C(CH_3)_2OH$

Practice Problem 2.7

One way of naming alcohols is to name the alkyl group that is attached to the —OH and add the word *alcohol*. Write bond-line formulas for **(a)** propyl alcohol and **(b)** isopropyl alcohol.

2.6 | ETHERS

Ethers have the general formula R—O—R or R—O—R′, where R′ may be an alkyl (or phenyl) group different from R. Ethers can be thought of as derivatives of water in which both hydrogen atoms have been replaced by alkyl groups. The bond angle at the oxygen atom of an ether is only slightly larger than that of water:

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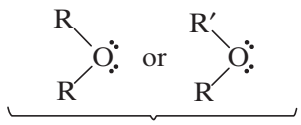
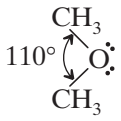
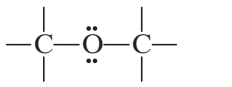


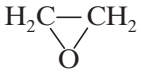
General formula for an ether



Dimethyl ether
(a typical ether)



The functional group of an ether



Ethylene oxide



Tetrahydrofuran (THF)

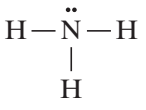
Two cyclic ethers

Practice Problem 2.8

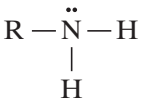
One way of naming ethers is to name the two alkyl groups attached to the oxygen atom in alphabetical order and add the word *ether*. If the two alkyl groups are the same, we use the prefix *di-*, for example, as in *dimethyl ether*. Write bond-line structural formulas for **(a)** diethyl ether, **(b)** ethyl propyl ether, and **(c)** ethyl isopropyl ether. What name would you give to **(d)** $CH_3OCH_2CH_2CH_3$ **(e)** $(CH_3)_2CHOCH(CH_3)_2$ and **(f)** $CH_3OC_6H_5$?

2.7 | AMINES

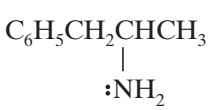
Just as alcohols and ethers may be considered as organic derivatives of water, amines may be considered as organic derivatives of ammonia:



Ammonia



An amine

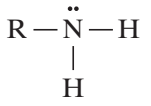


Amphetamine
(a dangerous stimulant)

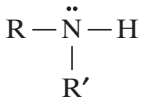


Putrescine
(found in decaying meat)

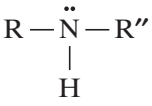
Amines are classified as primary, secondary, or tertiary amines. **This classification is based on *the number of organic groups that are attached to the nitrogen atom***:



A primary (1°) amine

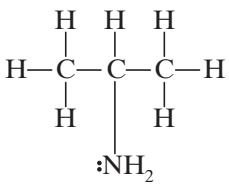


A secondary (2°) amine

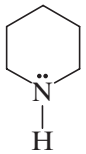


A tertiary (3°) amine

Notice that this is quite different from the way alcohols and alkyl halides are classified. Isopropylamine, for example, is a primary amine even though its $-NH_2$ group is attached to a secondary carbon atom. It is a primary amine because only one organic group is attached to the nitrogen atom:



Isopropylamine
(a 1° amine)



Piperidine
(a cyclic 2° amine)

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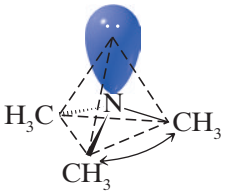
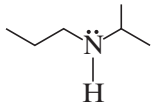


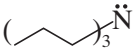
Bond angle 108.7°

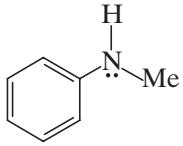
Amines are like ammonia in having a trigonal pyramidal shape. The C—N—C bond angles of trimethylamine are 108.7°, a value very close to the H—C—H bond angles of methane. Thus, for all Practice purposes, the nitrogen atom of an amine can be considered to be sp^3 hybridized with the unshared electron pair occupying one orbital (see right). This means that the unshared pair is relatively exposed, and as we shall see this is important because it is involved in almost all of the reactions of amines.

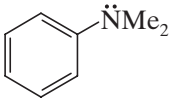
Solved Problem 2.4

One way of naming amines is to name in alphabetical order the alkyl groups attached to the nitrogen atom, using the prefixes *di-* and *tri-* if the groups are the same. An example is *isopropylamine* whose formula is shown above. What are names for **(a)**, **(b)**, **(c)**, and **(d)**?

(a) 

(b) 

(c) 

(d) 

Answer

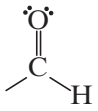
(a) Butylisopropylamine; **(b)** tripropylamine;
(c) *N*-methylbenzene; **(d)** *N*,*N*-dimethylbenzene.

Practice Problem 2.9

Which amines in the above solved problem are primary amines, secondary amines, and tertiary amines?

2.8 | ALDEHYDES AND KETONES

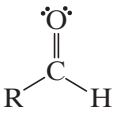
Aldehydes and ketones both contain the **carbonyl group**—a group in which a carbon atom has a double bond to oxygen:



The carbonyl group

The carbonyl group of an aldehyde is bonded to one hydrogen atom and one carbon atom (except for formaldehyde, which is the only aldehyde bearing two hydrogen atoms). The carbonyl group of a ketone is bonded to two carbon atoms. Using R, we can designate the general formulas for aldehydes and ketones as follows:

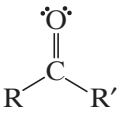
Aldehydes



or RCHO

R═H in formaldehyde

Ketones

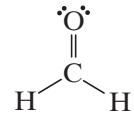


or RCOR′

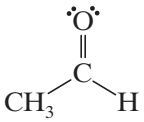
(where R′ is an alkyl group that may be the same or different from R)

Some specific examples of aldehydes and ketones are the following:

Aldehydes

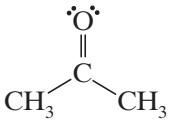


Formaldehyde

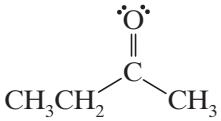


Acetaldehyde

Ketones



Acetone



Ethyl methyl ketone

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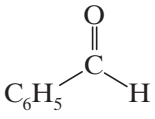
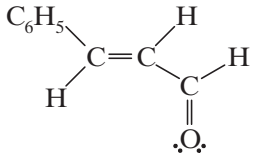
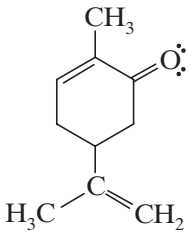


Benzaldehyde

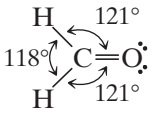


***trans*-Cinnamaldehyde (present in cinnamon)**

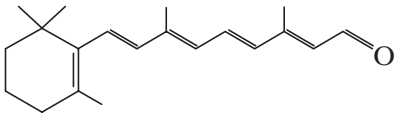


Carvone (from spearmint)

Aldehydes and ketones have a trigonal planar arrangement of groups around the carbonyl carbon atom. The carbon atom is sp^2 hybridized. In formaldehyde, for example, the bond angles are as follows:



Helpful Hint: Retinal (below) is an aldehyde made from vitamin A that plays a vital role in vision.



Retinal

Practice Problem 2.10

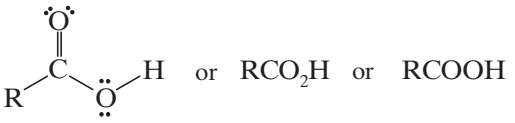
Write bond-line formulas for **(a)** four aldehydes and **(b)** three ketones that have the formula $C_5H_{10}O$.

2.9 | CARBOXYLIC ACIDS, ESTERS, AND AMIDES

Carboxylic acids, esters, and amides all contain a carbonyl group that is bonded to an oxygen or nitrogen atom. As we shall learn in later chapters, all of these functional groups are interconvertible by appropriately chosen reactions.

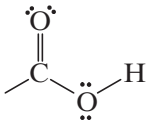
2.9A Carboxylic Acids

Carboxylic acids have a carbonyl group bonded to a hydroxyl group, and they have the general formula R–COOH. The functional group, –COOH, is called the **carboxyl group** (**carbo**nyl + hydro**xyl**):



or RCO_2H or RCOOH

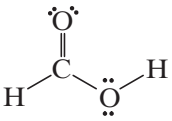
A carboxylic acid



or $—CO_2H$ or —COOH

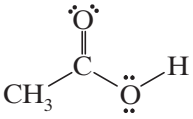
The carboxyl group

Examples of carboxylic acids are formic acid, acetic acid, and benzoic acid:



or HCO_2H or HCOOH

Formic acid



or CH_3CO_2H or CH_3COOH

Acetic acid

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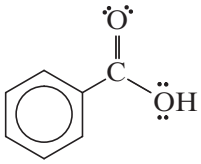


or $C_6H_5CO_2H$ or C_6H_5COOH

Benzoic acid

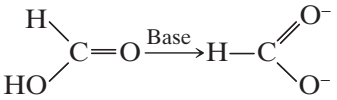
Formic acid is an irritating liquid produced by ants. (The sting of the ant is caused, in part, by formic acid being injected under the skin. *Formic* is the Latin word for ant.) Acetic acid, the substance responsible for the sour taste of vinegar, is produced when certain bacteria act on the ethyl alcohol of wine and cause the ethyl alcohol to be oxidized by air.

Solved Problem 2.5

When formic acid donates the proton from its oxygen to a base, a formate ion is the result. Write another resonance structure for formic acid and for the formate ion. Which species, formic acid or the formate ion, would be most stabilized by resonance?

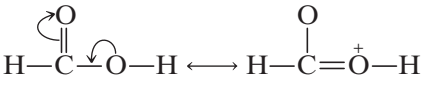
Answer

The reaction is

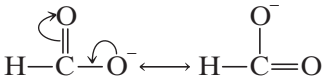


Formic acid **Formate ion**

The resonance structures of formic acid and formate ion are as follows. Out of these the resonance structure of formate ion is more stable as in formic acid structure positive charge on electronegative O atom destabilizes the structure.



Formic acid



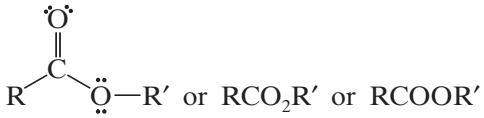
Formate ion

Practice Problem 2.11

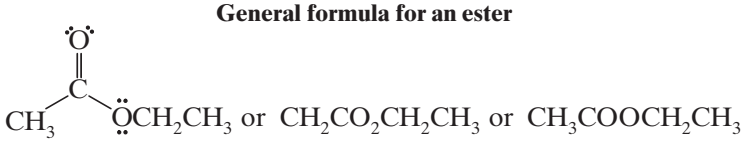
Write formulas for four carboxylic acids with the formula $C_5H_{10}O_2$.

2.9B Esters

Esters have the general formula RCO_2R' (or RCOOR'), where a carbonyl group is bonded to an alkoxyl (—OR) group. The ester pentyl butanoate has the odor of apricots and pears



General formula for an ester



Ethyl acetate is an important solvent

Practice Problem 2.12

Write formulas for three esters with the formula $C_5H_{10}O_2$.

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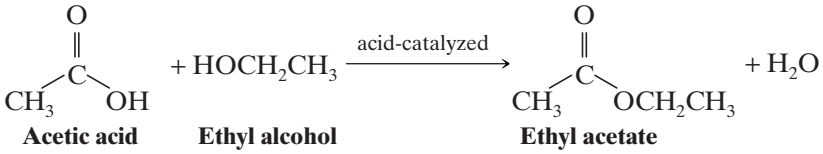
Esters can be made from a carboxylic acid and an alcohol through the acid-catalyzed loss of a molecule of water. For example:



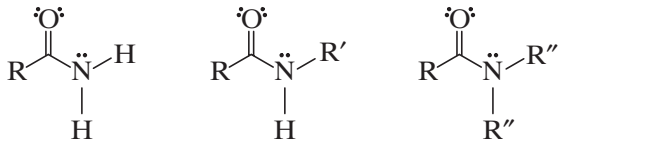
Acetic acid **Ethyl alcohol** **Ethyl acetate**

Helpful Hint: Your body makes esters from long-chain carboxylic acids called "fatty acids" by combining them with glycerol.

2.9C Amides

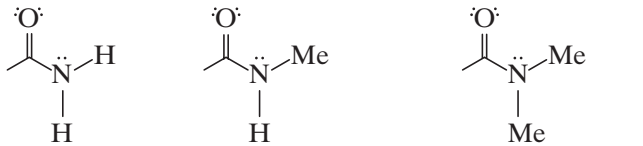
Amides have the formulas $RCONH_2$, $RCONHR'$, or $RCONR'R''$ where a carbonyl group is bonded to a nitrogen atom bearing hydrogen and/or alkyl groups. General formulas and some specific examples are shown below.

Helpful Hint: Nylon is a polymer comprised of regularly repeating amide groups.



An unsubstituted amide **An *N*-Substituted amide** **An *N*, *N*-Disubstituted amide**

General formulas for amides



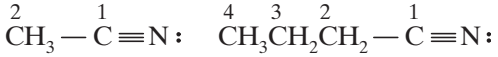
Acetamide ***N*-Methylacetamide** ***N*, *N*-Dimethylacetamide**

Specific examples of amides

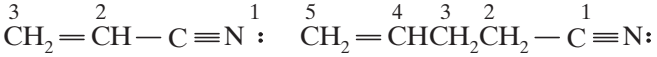
Helpful Hint: *N*- and *N,N*-indicate that the substituents are attached to the nitrogen atom.

2.10 | NITRILES

A nitrile has the formula R—C≡N: (or R—CN). The carbon and the nitrogen of a nitrile are *sp* hybridized. In IUPAC systematic nomenclature, acyclic nitriles are named by adding the suffix *-nitrile* to the name of the corresponding hydrocarbon. The carbon atom of the —C≡N group is assigned number 1. The name acetonitrile is an acceptable common name for CH_3CN, and acrylonitrile is an acceptable common name for $CH_2{=}CHCN$:



Ethanenitrile (acetonitrile) **Butanenitrile**



Propenenitrile (acrylonitrile) **4-Pentenenitrile**

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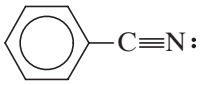
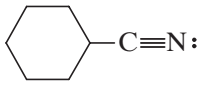
Cyclic nitriles are named by adding the suffix *-carbonitrile* to the name of the ring system to which the —CN group is attached. Benzonitrile is an acceptable common name for C_6H_5CN:



Benzenecarbonitrile (benzonitrile)

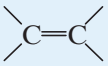
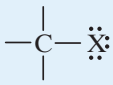
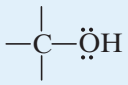
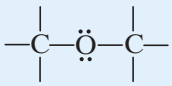


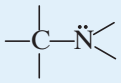
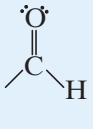
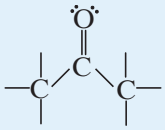
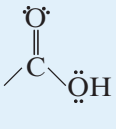
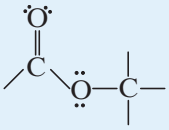
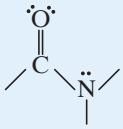
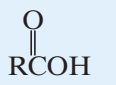
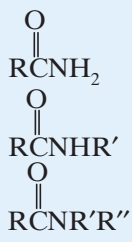
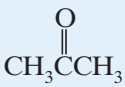
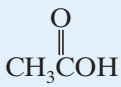
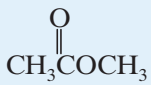
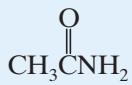
Cyclohexanecarbonitrile

2.11 | SUMMARY OF IMPORTANT FAMILIES OF ORGANIC COMPOUNDS

A summary of the important families of organic compounds is given in Table 2.2. You should learn to identify these common functional groups as they appear in other, more complicated molecules.

Table 2.2 Important Families of Organic Compounds

	Family						
	Alkane	Alkene	Alkyne	Aromatic	Haloalkane	Alcohol	Ether
Functional group	C—H and C—C bonds		—C≡C—	Aromatic ring			
General formula	RH	$RCH{=}CH_2$ RCH=CHR R_2H =CHR R_2H =CR_2	RC≡CH RC≡CR	ArH	RX	ROH	ROR
Specific example	CH_3CH_3	$CH_2{=}CH_2$	HC≡CH		CH_3CH_2Cl	CH_3CH_2OH	CH_3OCH_3
IUPAC name	Ethane	Ethene	Ethyne	Benzene	Chloroethane	Ethanol	Methoxymethane
Common name[a]	Ethane	Ethylene	Acetylene	Benzene	Ethyl chloride	Ethyl alcohol	Dimethyl ether

	Family					
Amine	Aldehyde	Ketone	Carboxylic acid	Ester	Amide	Nitrile
						—C≡N:
RNH_2 R_2NH R_3N						RCN
CH_3NH_2						$CH_3C{\equiv}N$

(Continued)

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Table 2.2 Continued

Family						
Amine	Aldehyde	Ketone	Carboxylic acid	Ester	Amide	Nitrile
Methanamine	Ethanal	Propanone	Ethanoic acid	Methyl ethanoate	Ethanamide	Ethanenitrile
Methylamine	Acetaldehyde	Acetone	Acetic acid	Methyl acetate	Acetamide	Acetonitrile

[a]These names are also accepted by the IUPAC.

2.12 | PHYSICAL PROPERTIES AND MOLECULAR STRUCTURE

So far, we have said little about one of the most obvious characteristics of organic compounds, that is, *their physical state or phase*. Whether a particular substance is a solid, or a liquid, or a gas would certainly be one of the first observations that we would note in any experimental work. The temperatures at which transitions occur between phases, that is, melting points (mp) and boiling points (bp), are also among the more easily measured **physical properties**. Melting points and boiling points are also useful in identifying and isolating organic compounds.

Suppose, for example, we have just carried out the synthesis of an organic compound that is known to be a liquid at room temperature and 1 atm pressure. If we know the boiling point of our desired product and the boiling points of by-products and solvents that may be present in the reaction mixture, we can decide whether or not simple distillation will be a feasible method for isolating our product.

In another instance our product might be a solid. In this case, in order to isolate the substance by crystallization, we need to know its melting point and its solubility in different solvents.

The physical constants of known organic substances are easily found in handbooks and other reference books. Table 2.3 lists the melting and boiling points of some of the compounds that we have discussed in this chapter.

Table 2.3 Physical Properties of Representative Compounds

Compound	Structure	mp (°C)	bp (°C) (1 atm)
Methane	CH_4	–182.6	–162
Ethane	CH_3CH_3	–172	–88.2
Ethene	$CH_2{=}CH_2$	–169	–102
Ethyne	$HC{\equiv}CH$	–82	–84 subl
Chloromethane	CH_3Cl	–97	–23.7
Chloroethane	CH_3CH_2Cl	–138.7	13.1
Ethyl alcohol	CH_3CH_2OH	–114	78.5
Acetaldehyde	CH_3CHO	–121	20
Acetic acid	CH_3CO_2H	16.6	118
Sodium acetate	CH_3CO_2Na	324	dec
Ethylamine	$CH_3CH_2NH_2$	–80	17
Diethyl ether	$(CH_3CH_2)_2O$	–116	34.6
Ethyl acetate	$CH_3CO_2CH_2CH_3$	–84	77

Often in the course of research, however, the product of a synthesis is a new compound—one that has never been described before. In these instances, success in isolating the new compound depends on making reasonably accurate estimates of its melting point, boiling point, and solubilities. Estimations of these macroscopic physical properties are based on the most likely structure of the substance and on the forces that act between molecules and ions. The temperatures at which phase changes occur are an indication of the strength of these intermolecular forces.

Helpful Hint: Understanding how molecular structure influences physical properties is very useful in practical organic chemistry.

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2.12A Ionic Compounds: Ion–Ion Forces

The **melting point** of a substance is the temperature at which an equilibrium exists between the well-ordered crystalline state and the more random liquid state. If the substance is an ionic compound, such as sodium acetate (Table 2.3), the **ion–ion forces** that hold the ions together in the crystalline state are the strong electrostatic lattice forces that act between the positive and negative ions in the orderly crystalline structure. In Fig. 2.2 each sodium ion is surrounded by negatively charged acetate ions, and each acetate ion is surrounded by positive sodium ions. A large amount of thermal energy is required to break up the orderly structure of the crystal into the disorderly open structure of a liquid. As a result, the temperature at which sodium acetate melts is quite high, 324°C. The **boiling points** of ionic compounds are higher still, so high that most ionic organic compounds decompose (are changed by undesirable chemical reactions) before they boil. Sodium acetate shows this behavior.

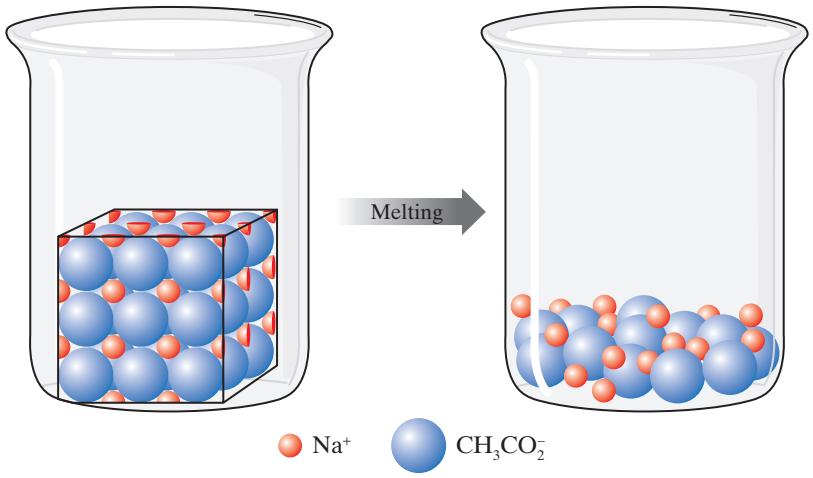

Figure 2.2 The melting of sodium acetate.

2.12B Intermolecular Forces (van der Waals Forces)

The forces that act between molecules are not as strong as those between ions, but they account for the fact that even completely nonpolar molecules can exist in liquid and solid states. These intermolecular forces, collectively called **van der Waals forces**, are all electrical in nature. We will focus our attention on three types:

1. Dipole–dipole forces
2. Hydrogen bonds
3. Dispersion forces

Dipole–Dipole Forces

Most organic molecules are not fully ionic but have instead a *permanent dipole moment* resulting from a nonuniform distribution of the bonding electrons. Acetone and acetaldehyde are examples of molecules with permanent dipoles because the carbonyl group that they contain is highly polarized. In these compounds, the attractive forces between molecules are much easier to visualize. In the liquid or solid state, **dipole–dipole** attractions cause the molecules to orient themselves so that the positive end of one molecule is directed toward the negative end of another.

Hydrogen Bonds

Very strong dipole–dipole attractions occur between hydrogen atoms bonded to small, strongly electronegative atoms (O, N, or F) and nonbonding electron pairs on other such electronegative atoms. This type of intermolecular force is called a **hydrogen bond**.

Hydrogen bonds (bond dissociation energies of about 4–38 kJ mol^{-1}) are weaker than ordinary covalent bonds but much stronger than the dipole–dipole interactions that occur above, for example, in acetone.

Hydrogen bonding explains why water, ammonia, and hydrogen fluoride all have far higher boiling points than methane (bp –161.6°C), even though all four compounds have similar molecular weights.

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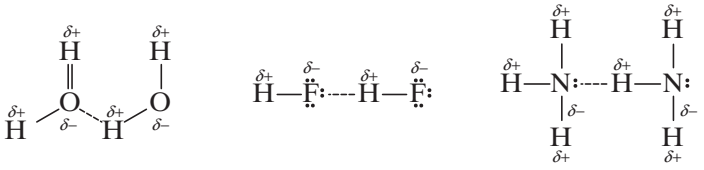
Helpful Hint: Water molecules associated by attraction of opposite partial charges.

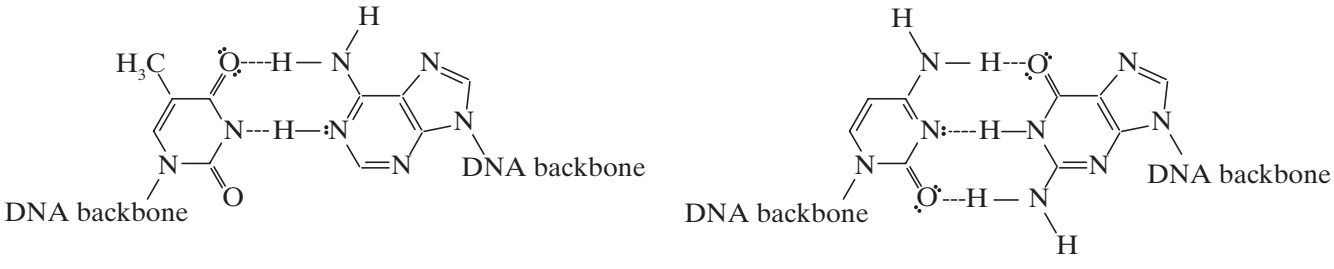


bp 100°C **bp 19.5°C** **bp –33.4°C**

Hydrogen bonds are shown by the dashed lines

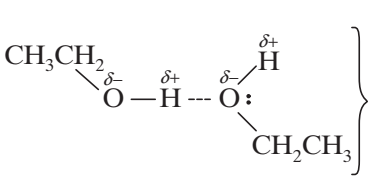
One of the most important consequences of hydrogen bonding is that it causes water to be a liquid rather than a gas at 25°C. Calculations indicate that in the absence of hydrogen bonding, water would have a boiling point near –80°C and would not exist as a liquid unless the temperature were lower than that temperature. Had this been the case, it is highly unlikely that life, as we know it, could have developed on the planet Earth.

Hydrogen bonds hold the base pairs of double-stranded DNA together. Thymine hydrogen bonds with adenine. Cytosine hydrogen bonds with guanine.



Thymine **Adenine** **Cytosine** **Guanine**

Hydrogen bonding accounts for the fact that ethyl alcohol has a much higher boiling point (+78.5°C) than dimethyl ether (–24.9°C) even though the two compounds have the same molecular weight. Molecules of ethyl alcohol, because they have a hydrogen atom covalently bonded to an oxygen atom, can form strong hydrogen bonds to each other.



The dashed line represent a hydrogen bond. Strong hydrogen bonding is limited to molecules having a hydrogen atom attached to an O, N, or F atom.

Molecules of dimethyl ether, because they lack a hydrogen atom attached to a strongly electronegative atom, cannot form strong hydrogen bonds to each other. In dimethyl ether the intermolecular forces are weaker dipole–dipole interactions.

Practice Problem 2.13

The compounds in each part below have the same (or similar) molecular weights. Which compound in each part would you expect to have the higher boiling point? Explain your answers. **(a)** $CH_3CH_2CH_2CH_2OH$ or $CH_3CH_2OCH_2CH_3$, **(b)** $(CH_3)_3N$ or $CH_3CH_2NHCH_3$, **(c)** $CH_3CH_2CH_2CH_2OH$ or $HOCH_2CH_2CH_2OH$.

A factor (in addition to polarity and hydrogen bonding) that affects the *melting point* of many organic compounds is the compactness and rigidity of their individual molecules.

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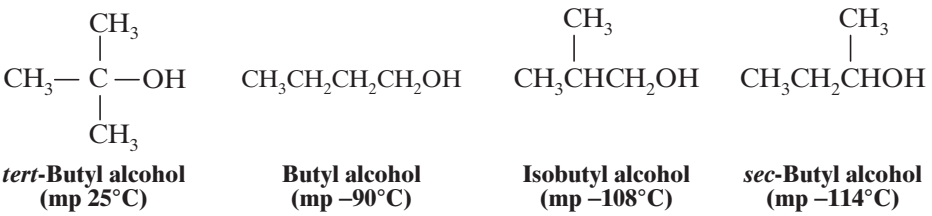
- Molecules that are symmetrical generally have abnormally high melting points. *tert*-Butyl alcohol, for example, has a much higher melting point than the other isomeric alcohols shown here:



***tert*-Butyl alcohol (mp 25°C)** | **Butyl alcohol (mp –90°C)** | **Isobutyl alcohol (mp –108°C)** | ***sec*-Butyl alcohol (mp –114°C)**

Practice Problem 2.14

Which compound would you expect to have the higher melting point, propane or cyclopropane? Explain your answer.

Dispersion Forces

If we consider a substance like methane where the particles are non-polar molecules, we find that the melting point and boiling point are very low: –182.6°C and –162°C, respectively. Instead of asking, "Why does methane melt and boil at low temperatures?" a more appropriate question might be "Why does methane, a nonionic, nonpolar substance, become a liquid or a solid at all?" The answer to this question can be given in terms of attractive intermolecular forces called **dispersion forces** or London forces.

An accurate account of the nature of dispersion forces requires the use of quantum mechanics. We can, however, visualize the origin of these forces in the following way. The average distribution of charge in a nonpolar molecule (such as methane) over a period of time is uniform. At any given instant, however, *because electrons move*, the electrons and therefore the charge may not be uniformly distributed. Electrons may, in one instant, be slightly accumulated on one part of the molecule, and, as a consequence, *a small temporary dipole will occur* (Fig. 2.3). This temporary dipole in one molecule can induce opposite (attractive) dipoles in surrounding molecules. It does this because the negative (or positive) charge in a portion of one molecule will distort the electron cloud of an adjacent portion of another molecule, causing an opposite charge to develop there. These temporary dipoles change constantly, but the net result of their existence is to produce attractive forces between nonpolar molecules and thus make possible the existence of their liquid and solid states.

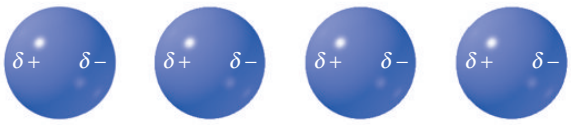


Figure 2.3 Temporary dipoles and induced dipoles in nonpolar molecules resulting from an uneven distribution of electrons at a given instant.

Two important factors determine the magnitude of dispersion forces.

1. **The relative polarizability of electrons of the atoms involved**. *By polarizability we mean how easily the electrons respond to a changing electric field*. The electrons of large atoms such as iodine are loosely held and are easily polarized, while the electrons of small atoms such as fluorine are more tightly held and are much less polarizable. Atoms with unshared pairs are more easily polarized than atoms with only bonding pairs. The order of polarizability for halogens is F < Cl < Br < I. Table 2.4 gives the relative magnitudes of dispersion forces and dipole–dipole interactions for several simple compounds. Notice with HI the dispersion forces are far more important than dipole–dipole forces, whereas with H_2O, dipole–dipole forces (of the kind we call hydrogen bonds) are more important.

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Table 2.4 Attractive Energies in Simple Covalent Compounds

		Attractive Energies (kJ mol^{-1})			
Molecule	Dipole Moment (D)	Dipole–Dipole	Dispersion	Melting Point (°C)	Boiling Point (°C) at 1 atm
H_2O	1.85	36	8.8	0	100
NH_3	1.47	14	15	–78	–33
HCl	1.08	3	17	–115	–85
HBr	0.80	0.8	22	–88	–67
HI	0.42	0.03	28	–51	–35

CF_4 and CI_4 are both nonpolar molecules. But if we were to consider the intermolecular forces between two CI_4 molecules, which contain polarizable iodine atoms, we would find that the dispersion forces are much larger than between two CF_4 molecules, which contains fluorine atoms that are not very polarizable.

2. **The relative surface area of the molecules involved.** The larger the surface area, the larger is the overall attraction between molecules caused by dispersion forces. Molecules that are generally longer, flatter, or cylindrical have a greater surface area available for intermolecular interactions than more spherical molecules, and consequently have greater attractive forces between them than the tangential interactions between branched molecules. This is evident when comparing pentane, the unbranched C_5H_{12} hydrocarbon, with neopentane, the most highly branched C_5H_{12} isomer (in which one carbon bears four methyl groups). Pentane has a boiling point of 36.1°C. Neopentane has a boiling point of 9.5°C. The difference in their boiling points indicate that the attractive forces between pentane molecules are stronger than between neopentane molecules.

   For large molecules, the cumulative effect of these small and rapidly changing dispersion forces can lead to a large net attraction.

Helpful Hint: Dispersion forces are what provides a gecko's grip to smooth surfaces.

2.12C Boiling Points

The *boiling point* of a liquid is the temperature at which the vapor pressure of the liquid equals the pressure of the atmosphere above it. For this reason, the boiling points of liquids are *pressure dependent*, and boiling points are always reported as occurring at a particular pressure, at 1 atm (or at 760 torr), for example. A substance that boils at 150°C at 1 atm pressure will boil at a substantially lower temperature if the pressure is reduced to, for example, 0.01 torr (a pressure easily obtained with a vacuum pump). The normal boiling point given for a liquid is its boiling point at 1 atm.

In passing from a liquid to a gaseous state, the individual molecules (or ions) of the substance must separate. Because of this, we can understand why ionic organic compounds often decompose before they boil. The thermal energy required to completely separate (volatilize) the ions is so great that chemical reactions (decompositions) occur first.

Nonpolar compounds, where the intermolecular forces are very weak, usually boil at low temperatures even at 1 atm pressure. This is not always true, however, because of other factors that we have not yet mentioned: the effects of molecular weight and molecular shape and surface area. Heavier molecules require greater thermal energy in order to acquire velocities sufficiently great to escape the liquid phase, and because the surface areas of larger molecules can be much greater, intermolecular dispersion attractions can also be much larger. These factors explain why nonpolar ethane (bp –88.2°C) boils higher than methane (bp –162°C) at a pressure of 1 atm. It also explains why, at 1 atm, the even heavier and larger nonpolar molecule decane ($C_{10}H_{22}$) boils at +174°C. The relationship between dispersion forces and surface area helps us understand why neopentane (2, 2-dimethylpropane) has a lower boiling point (9.5°C) than pentane (36.1°C), even though they have the same molecular weight. The branched structure of neopentane allows less surface interaction between neopentane molecules, hence lower dispersion forces, than does the linear structure of pentane.

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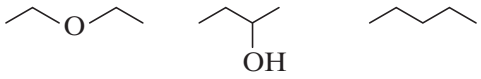
Solved Problem 2.6

Arrange the following compounds according to their expected boiling points, with the lowest boiling point first, and explain your answer. Notice that the compounds have similar molecular weights.



Diethyl ether **sec-Butyl alcohol** **Pentane**

Answer

The order of increasing boiling points is:

Pentane < diethyl ether < *sec*-butyl alcohol

Pentane has no polar groups and has only dispersion forces holding its molecules together. It would have the lowest boiling point. Diethyl ether has the polar ether group that provides dipole–dipole forces which are greater than dispersion forces, meaning it would have a higher boiling point than pentane. *sec*-Butyl alcohol has an —OH group that can form strong hydrogen bonds; therefore, it would have the highest boiling point.

Practice Problem 2.15

Arrange the following compounds in order of increasing boiling point. Explain your answer in terms of the intermolecular forces in each compound.



2.12D Solubilities

Intermolecular forces are of primary importance in explaining the **solubilities** of substances. Dissolution of a solid in a liquid is, in many respects, like the melting of a solid. The orderly crystal structure of the solid is destroyed, and the result is the formation of the more disorderly arrangement of the molecules (or ions) in solution. In the process of dissolving, too, the molecules or ions must be separated from each other, and energy must be supplied for both changes. The energy required to overcome lattice energies and intermolecular or interionic attractions comes from the formation of new attractive forces between solute and solvent.

Consider the dissolution of an ionic substance as an example. Here both the lattice energy and interionic attractions are large. We find that water and only a few other very polar solvents are capable of dissolving ionic compounds. These solvents dissolve ionic compounds by **hydrating** or **solvating** the ions (Fig. 2.4).

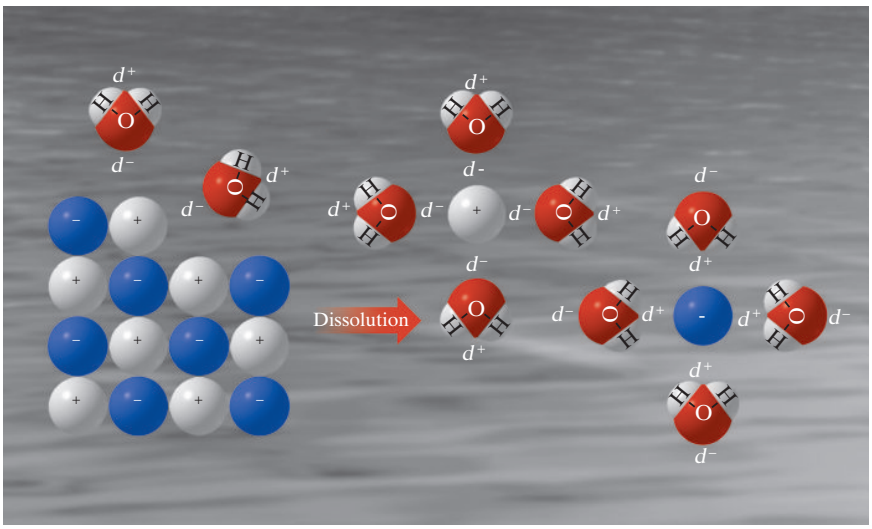


Figure 2.4 The dissolution of an ionic solid in water, showing the hydration of positive and negative ions by the very polar water molecules. The ions become surrounded by water molecules in all three dimensions, not just the two shown here.

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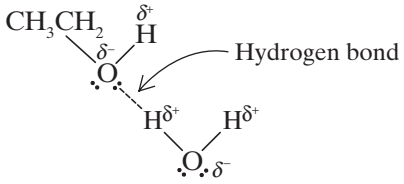
Water molecules, by virtue of their great polarity as well as their very small, compact shape, can very effectively surround the individual ions as they are free from the crystal surface. Positive ions are surrounded by water molecules with the negative end of the water dipole pointed toward the positive ion; negative ions are solvated in exactly the opposite way. Because water is highly polar, and because water is capable of forming strong hydrogen bonds, the **ion–dipole forces** of attraction are also large. The energy supplied by the formation of these forces is great enough to overcome both the lattice energy and interionic attractions of the crystal.

A general rule for solubility is that "like dissolves like" in terms of comparable polarities.

1. Polar and ionic solids are usually soluble in polar solvents.
2. Polar liquids are usually miscible.
3. Nonpolar solids are usually soluble in nonpolar solvents.
4. Nonpolar liquids are usually miscible.
5. Polar and nonpolar liquids, like oil and water, are usually not soluble to large extents.

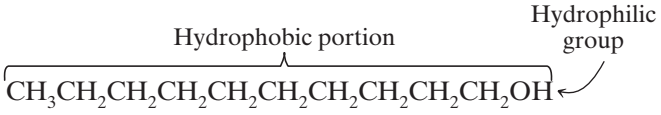
Methanol and water are miscible in all proportions; so too are mixtures of ethanol and water and mixtures of both propyl alcohols and water. In these cases the alkyl groups of the alcohols are relatively small, and the molecules therefore resemble water more than they do an alkane. Another factor in understanding their solubility is that the molecules are capable of forming strong hydrogen bonds to each other:



We often describe molecules or parts of molecules as being hydrophilic or hydrophobic. The alkyl groups of methanol, ethanol, and propanol are hydrophobic. Their hydroxyl groups are hydrophilic.

1. **Hydrophobic** means incompatible with water (*hydro*, water; *phobic*, fearing or avoiding).
2. **Hydrophilic** means compatible with water (*philic*, loving or seeking).

Decyl alcohol, with a chain of 10 carbon atoms, is a compound whose hydrophobic alkyl group overshadows its hydrophilic hydroxyl group in terms of water solubility.



Decyl alcohol

An explanation for why nonpolar groups such as long alkane chains avoid an aqueous environment, that is, for the so-called **hydrophobic effect**, is complex. The most important factor seems to involve an **unfavorable entropy change** in the water. Entropy changes (Section 3.10) have to do with changes from a relatively ordered state to a more disordered one or the reverse. Changes from order to disorder are favorable, whereas changes from disorder to order are unfavorable. For a nonpolar hydrocarbon chain to be accommodated by water, the water molecules have to form a more ordered structure around the chain, and for this, the entropy change is unfavorable.

The presence of a hydrophobic group and a hydrophilic group are essential components of soaps and detergents. The hydrophobic long carbon chains of a soap or detergent embed themselves in the oily layer that typically surrounds the thing we want to wash away. The hydrophilic ionic groups at the ends of the chains are then left exposed on the surface and make the surface one that water molecules find attractive. Oil and water don't mix, but now the oily layer looks like something ionic and the water can take it "right down the drain."

Helpful Hint: Organic chemists usually define a compound as water soluble if at least 3 g of the organic compound dissolves in 100 mL of water. We find that for compounds containing one hydrophilic group—and thus capable of forming strong hydrogen bonds—the following approximate guidelines hold: Compounds with one to three carbon atoms are water soluble, compounds with four or five carbon atoms are borderline, and compounds with six carbon atoms or more are insoluble.

When a compound contains more than one hydrophilic group, these guidelines do not apply. Polysaccharides, proteins, and nucleic acids all contain thousands of carbon atoms *and many are water soluble*. They dissolve in water because they also contain thousands of hydrophilic groups.

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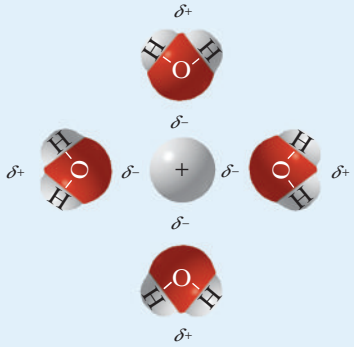
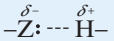
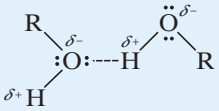
2.13 | SUMMARY OF ATTRACTIVE ELECTRIC FORCES

The attractive forces occurring between molecules and ions that we have studied so far are summarized in Table 2.5.

Table 2.5 Attractive Electric Forces

Electric Force	Relative Strength	Type	Example
Cation–anion (in a crystal)	Very strong		Sodium chloride crystal lattice
Covalent bonds	Strong (140–523 kJ mol^{-1})	Shared electron pairs	H—H (436 kJ mol^{-1}) CH_3—CH_3 (378 kJ mol^{-1}) I—I (151 kJ mol^{-1})
Ion–dipole	Moderate		Na^+ in water (see Fig. 2.4)
Hydrogen bonds	Moderate to weak (4–38 kJ mol^{-1})		
Dipole–dipole	Weak		
Dispersion	Variable	Transient dipole	Interactions between methane molecules

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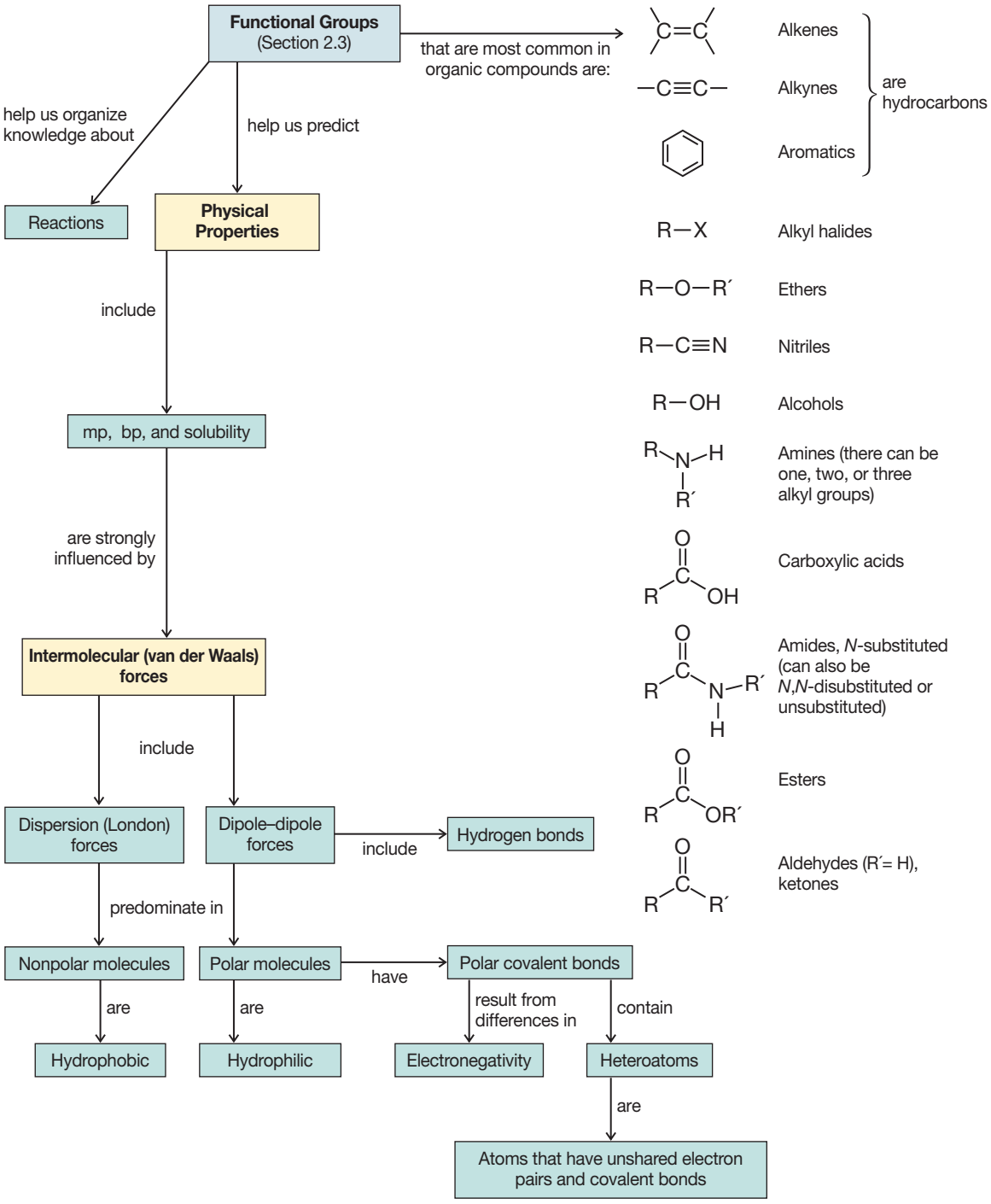
CONCEPT MAP



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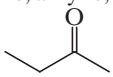
REVIEW PROBLEMS

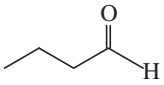
Functional Groups and Structural Formulas

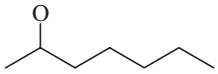
2.16 Classify each of the following compounds as an alkane, alkene, alkyne, alcohol, aldehyde, amine, and so forth.

(a) 

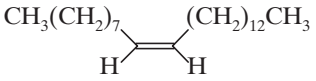
(b) $CH_3—C\equiv CH$

(c) 

(d) 

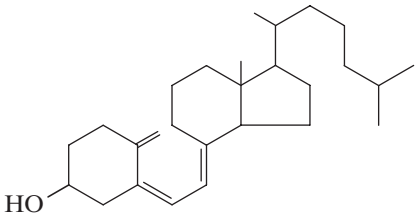
(e) 

(obtained from oil of cloves)

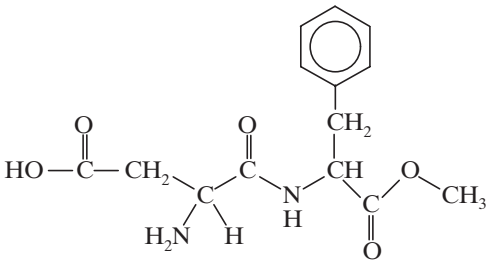
(f) 

(sex attractant of common housefly)

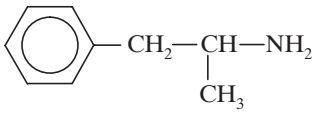
2.17 Identify all of the functional groups in each of the following compounds:

(a) 

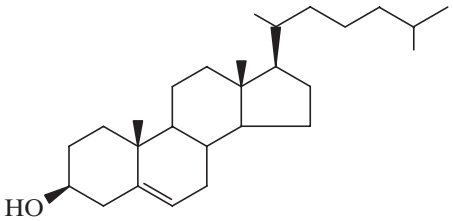
Vitamin D_3

(b) 

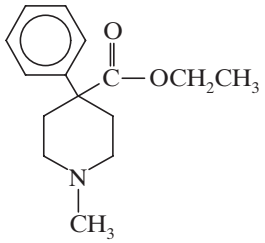
Aspartame

(c) 

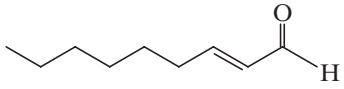
Amphetamine

(d) 

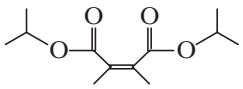
Cholesterol

(e) 

Demerol

(f) 

A cockroach repellent found in cucumbers

(g) 

A synthetic cockroach repellent

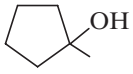
2.18 There are four alkyl bromides with the formula C_4H_9Br. Write their structural formulas and classify each as to whether it is a primary, secondary, or tertiary alkyl bromide.

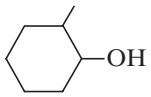
2.19 There are seven isomeric compounds with the formula $C_4H_{10}O$. Write their structures and classify each compound according to its functional group.

2.20 Write structural formulas for four compounds with the formula C_3H_6O and classify each according to its functional group.

2.21 Classify the following alcohols as primary, secondary, or tertiary:

(a) $(CH_3)_3CCH_2OH$ **(b)** $CH_3CH(OH)CH(CH_3)_2$

(c) $(CH_3)_2C(OH)CH_2CH_3$ **(d)** 

(e) 

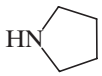
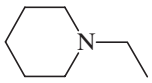
2.22 Classify the following amines as primary, secondary, or tertiary:

(a) $CH_3NHCH(CH_3)_2$

(b) $CH_3CH_2CH(CH_3)CH_2NH_2$

(c) $(CH_3CH_2)_3N$

(d) $(C_6H_5)_2CHCH_2NHCH_3$

(e)  **(f)** 

2.23 Write structural formulas for each of the following:

(a) Three ethers with the formula $C_4H_{10}O$.

(b) Three primary alcohols with the formula C_4H_8O.

(c) A secondary alcohol with the formula C_3H_6O.

(d) A tertiary alcohol with the formula C_4H_8O.

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(e) Two esters with the formula $C_3H_6O_2$.

(f) Four primary alkyl halides with the formula $C_5H_{11}Br$.

(g) Three secondary alkyl halides with the formula $C_5H_{11}Br$.

(h) A tertiary alkyl halide with the formula $C_5H_{11}Br$.

(i) Three aldehydes with the formula $C_5H_{10}O$.

(j) Three ketones with the formula $C_5H_{10}O$.

(k) Two primary amines with the formula C_3H_9N.

(l) A secondary amine with the formula C_3H_9N.

(m) A tertiary amine with the formula C_3H_9N.

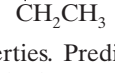
(n) Two amides with the formula C_2H_5NO.

Physical Properties

2.24 Hydrogen fluoride has a dipole moment of 1.82 D; its boiling point is 19.34°C. Ethyl fluoride (CH_3CH_2F) has an almost identical dipole moment and has a larger molecular weight, yet its boiling point is –37.7°C. Explain.

2.25 Why does one expect the cis isomer of an alkene to have a higher boiling point than the trans isomer?

2.26 Cetylethyldimethylammonium bromide is the common name for $(CH_3)_2N^+(CH_2)_{15}CH_3Br^-$ a compound with



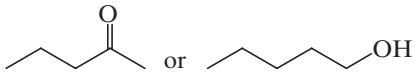
antiseptic properties. Predict its solubility behavior in water and diethyl ether.

2.27 Which compound in each of the following pairs would have the higher boiling point? Explain your answers.

(a) $CH_3CH_2CH_2OH$ or $CH_3CH_2OCH_3$

(b) $CH_3CH_2CH_2OH$ or $HOCH_2CH_2OH$

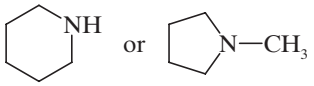
(c)



(d)



(e)



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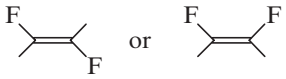
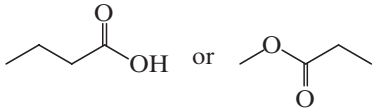
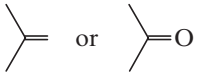


(g)



(h) Hexane $CH_3(CH_2)_4CH_3$ or nonane $CH_3(CH_2)_7CH_3$

(i)



2.28 Which of the following solvents should be capable of dissolving ionic compounds?

(a) Liquid SO_2 **(b)** Liquid NH_3

(c) Benzene **(d)** CCl_4

2.29 Write a three-dimensional formula for each of the following molecules using the wedge–dashed wedge–line formalism. If the molecule has a net dipole moment, indicate its direction with an arrow, →. If the molecule has no net dipole moment, you should so state. (You may ignore the small polarity of CH bonds in working this and similar problems.)

(a) CH_3F **(b)** CH_2F_2 **(c)** CHF_3

(d) CF_4 **(e)** CH_2FCl **(f)** BCl_3

(g) BeF_2 **(h)** CH_3OCH_3

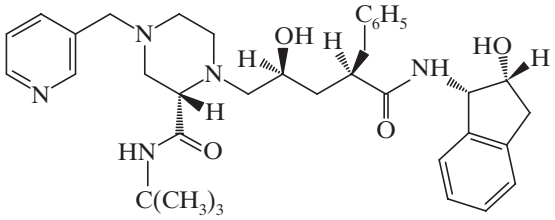
(i) CH_3OH **(j)** CH_2O

2.30 Consider each of the following molecules in turn: (**a**) dimethyl ether, $(CH_3)_2O$; (**b**) trimethylamine, $(CH_3)_3N$; (**c**) trimethylboron, $(CH_3)_3B$; and (**d**) dimethylberyllium, $(CH_3)_2Be$. Describe the hybridization state of the central atom (i.e., O, N, B, or Be) of each molecule, tell what bond angles you would expect at the central atom, and state whether the molecule would have a dipole moment.

2.31 Alkenes can interact with metal ions such as Ag^+. What is the nature of this interaction?

2.32 Analyze the statement: For a molecule to be polar, the presence of polar bonds is necessary, but it is not a sufficient requirement.

2.33 Identify all of the functional groups in Crixivan, an important drug in the treatment of AIDS.

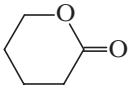


Crixivan (an HIV protease inhibitor)

Multiconcept Problems

2.34 There are four amides with the formula C_3H_7NO. **(a)** Write their structures. **(b)** One of these amides has a melting and a boiling point that are substantially lower than those of the other three. Which amide is this? Explain your answer.

2.35 Cyclic compounds of the general type shown here are called lactones. What functional group does a lactone contain?



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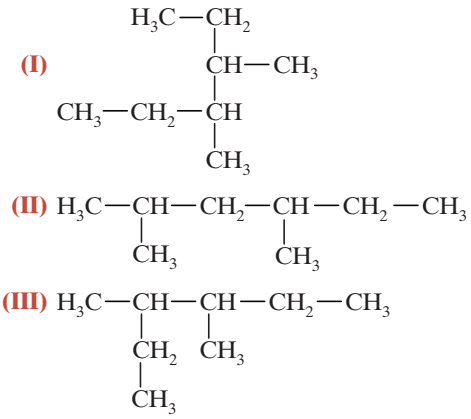
ADDITIONAL OBJECTIVE QUESTIONS

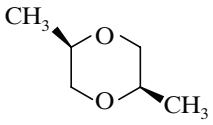
Single Correct Choice Type

1. Which of the following structures represent the same compound?



(a) (I) and (II) **(b)** (II) and (III)
(c) (I) and (III) **(d)** All are same

2. How many types of functional groups are present in the given compound?

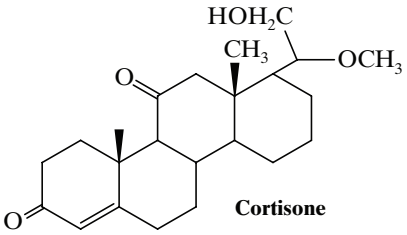


(a) 6 **(b)** 5 **(c)** 4 **(d)** 7

3. The correct order of the solubility of the different alcohols in water is

(a) *n*-propyl alcohol > ethyl alcohol > *n*-butyl alcohol.
(b) Ethyl alcohol > *n*-butyl alcohol > *n*-propyl alcohol.
(c) *n*-butyl alcohol > *n*-propyl alcohol > ethyl alcohol.
(d) Ethanol > *n*-propanol > *n*-butyl alcohol.

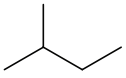
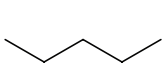
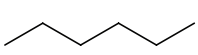
4. The functional groups in cortisone are



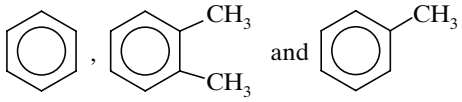
Cortisone

(a) ether, alkene and alcohol.
(b) alcohol, ketone, alkene and ether.
(c) alcohol, ketone and amine.
(d) Ether, amine and ketone.

5. Which of the following alkanes will have the lowest boiling point?

(a) 
(b) 
(c) 
(d) 

6. Number of secondary carbon atoms present in the given compounds is respectively:

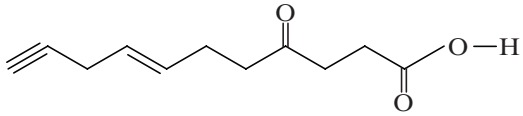


(a) 6, 4, 5 **(b)** 4, 5, 6 **(c)** 5, 4, 5 **(d)** 6, 2, 1

7. Which of the following has the greatest dipole moment?

(a) Methyl fluoride **(b)** Methyl iodide
(c) Methyl chloride **(d)** Methyl bromide

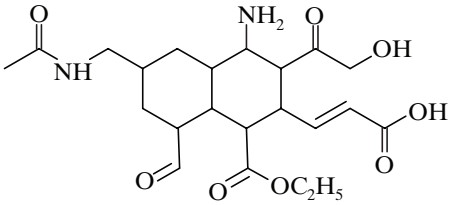
8. Number of functional groups in the given compound is



(a) 3 **(b)** 4 **(c)** 5 **(d)** 6

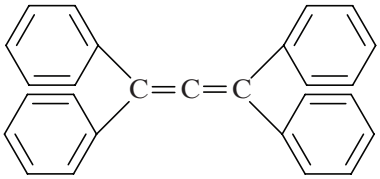
Integer Type

1.



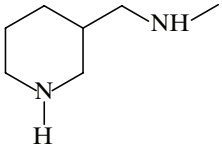
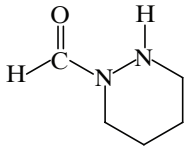
Sum of total number of functional groups present in the given compound is

2. How many 2° carbon are present in the following compound?



Matrix Match Type

1.

Column I (Compound)	Column II (Type)
(a) 	**(p)** 1° Amine
(b) 	**(q)** 2° Amine

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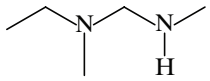
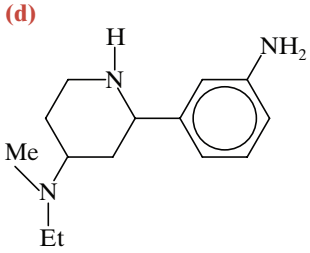
(c) 

(r) 3° Amine

(d) 

(s) 1° Carbon

(t) 2° Carbon

2.

Column-I	Column-II
(a) $H_3C—CH=CH—CH_3$	**(p)** Dipole (*cis* > *trans*)
(b) $H_3C—CH=CH—CN$	**(q)** Dipole (*trans* > *cis*)
(c) $H_3C—CH=CH—Cl$	**(r)** Melting point (*trans* > *cis*)
(d) $Cl—CH=CH—Cl$	**(s)** Boiling point (*cis* > *trans*)

ANSWER KEY

Single Correct Choice Type

1. (c) **2.** (b) **3.** (d) **4.** (b) **5.** (c)
6. (a) **7.** (a) **8.** (b)

Integer Type

1. (8) **2.** (21)

Matrix Match Type

1. a→(q),(s),(t); b→(p),(q),(s),(t); c→(q),(r),(s); d→(p),(q),(r),(s),(t)
2. a→(p),(r),(s); b→(q),(r); c→(q),(r); d→(p),(r),(s)

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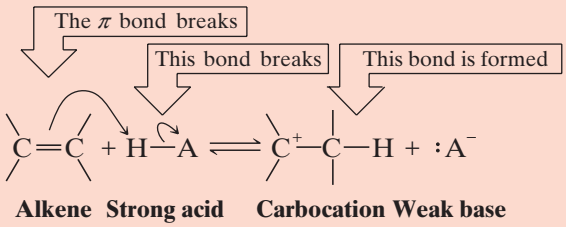
3

An Introduction to Organic Reactions and Their Mechanisms: Acids and Bases



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3.8 | Relationships between Structure and Acidity
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3.10 | The Relationship between the Equilibrium Constant and the Standard Free-Energy Change, $\Delta G°$
3.11 | The Acidity of Carboxylic Acids versus Alcohols
3.12 | The Effect of the Solvent on Acidity
3.13 | Organic Compounds as Bases
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3.15 | Acid–Base Reactions and the Synthesis of Deuterium-and Tritium-Labeled Compounds
3.16 | Reactions of $NaHCO_3$ as a Base
3.17 | Steric Inhibition of Resonance (SIR) Effect
3.18 | Ortho and Para Effects

A **reaction mechanism** is **a description of the events that take place on a molecular level as reactants become products**. If, as is often the case, the reaction takes place in more than one step, we will want to know what chemical species, called **intermediates**, intervene between each step along the way. Any mechanism we propose must be consistent with what we know about the reaction and with what we know about the reactivity of organic compounds generally. We cannot actually see the molecular events because molecules are too small, but from solid evidence and from good chemical intuition, we can propose reasonable mechanisms. If at some later time a valid experiment gives results that contradict our proposed mechanism, then we change it, because in the final analysis our mechanism must be consistent with all our experimental observations.

One of the most important things about approaching organic chemistry mechanistically is this: It helps us organize what otherwise might be an overwhelmingly complex body of knowledge into a form that makes it understandable. There are millions of organic compounds now known, and there are millions of reactions that these compounds undergo. If we had to learn them all by rote memorization, then we would soon give up. But, we don't have to do this. In the same way that functional groups help us organize compounds in a comprehensible way, mechanisms help us organize reactions. Fortunately, too, there is a relatively small number of basic mechanisms.

3.1 | REACTIONS AND THEIR MECHANISMS

Virtually all organic reactions fall into one of four categories: *substitutions, additions, eliminations*, or *rearrangements*.

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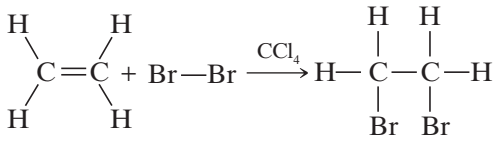
Substitutions are the characteristic reactions of saturated compounds such as alkanes and alkyl halides and of aromatic compounds (even though they are unsaturated). In a substitution, *one group replaces another*. For example, chloromethane reacts with sodium hydroxide to produce methyl alcohol and sodium chloride:



A substitution reaction

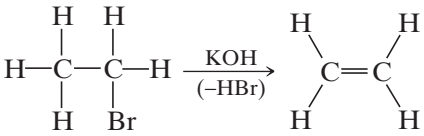
In this reaction a hydroxide ion from sodium hydroxide replaces the chlorine of methyl chloride. We shall study this reaction in detail in Chapter 6.

Additions are characteristic of compounds with multiple bonds. Ethene, for example, reacts with bromine by an addition. In an addition *all parts of the adding reagent appear in the product; two molecules become one*:



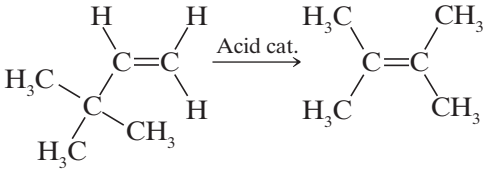
An addition reaction

Eliminations are the opposite of additions. *In an elimination one molecule loses the elements of another small molecule*. Elimination reactions give us a method for preparing compounds with double and triple bonds. In Chapter 7, for example, we shall study an important elimination called *dehydrohalogenation*, a reaction that is used to prepare alkenes. In dehydrohalogenation, as the word suggests, the elements of a hydrogen halide are eliminated. An alkyl halide becomes an alkene:



An elimination reaction

In a **rearrangement** *a molecule undergoes a reorganization of its constituent parts*. For example, heating the following alkene with a strong acid causes the formation of another isomeric alkene:



A rearrangement

In this rearrangement not only have the positions of the double bond and a hydrogen atom changed, but a methyl group has moved from one carbon to another.

In the following sections we shall begin to learn some of the principles that explain how these kinds of reactions take place.

3.1A Homolysis and Heterolysis of Covalent Bonds

Reactions of organic compounds always involve the making and breaking of covalent bonds. A covalent bond may break in two fundamentally different ways.

- When a bond breaks such that one fragment takes away both electrons of the bond, leaving the other fragment with an empty orbital, this kind of cleavage is called **heterolysis** (Greek *dhetero*, different, + *lysis*, loosening or cleavage). Heterolysis produces charged fragments or **ions** and is termed an **ionic reaction**. The broken bond is said to have cleaved *heterolytically*:



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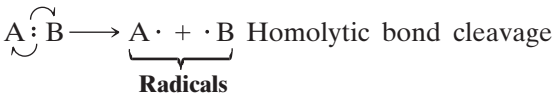
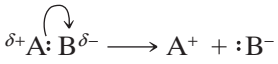
- When a bond breaks so that each fragment takes away one of the electrons of the bond, this process is called **homolysis** (Greek: *homo*, the same, +*lysis*). Homolysis produces fragments with unpaired electrons called **radicals**.



Homolytic bond cleavage

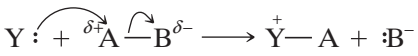
Helpful Hint: Notice in these illustrations that we have used curved arrows to show the movement of electrons. We will have more to say about this convention in Section 3.5, but for the moment notice that we use a double-barbed curved arrow to show the movement of a pair of electrons and a single-barbed curved arrow to show the movement of a single electron.

Heterolysis of a bond normally requires that the bond be polarized:



Polarization of a bond usually results from differing electronegativities of the atoms joined by the bond. The greater the difference in electronegativity, the greater is the polarization. In the instance just given, atom B is more electronegative than A.

Even with a highly polarized bond, heterolysis rarely occurs without assistance. The reason: *Heterolysis requires separation of oppositely charged ions*. Because oppositely charged ions attract each other, their separation requires considerable energy. Often, heterolysis is assisted by a molecule with an unshared pair that can form a bond to one of the atoms:



Formation of the new bond furnishes some of the energy required for the heterolysis.

3.2 | ACID–BASE REACTIONS

We begin our study of chemical reactions by examining some of the basic principles of acid–base chemistry. There are several reasons for doing this:

- Many of the reactions that occur in organic chemistry are either acid–base reactions themselves or they involve an acid–base reaction at some stage.
- Acid–base reactions are simple fundamental reactions that will enable you to see how chemists use curved arrows to represent mechanisms of reactions and how they depict the processes of bond breaking and bond making that occur as molecules react.

Acid–base reactions also allow us to examine important ideas about the relationship between the structures of molecules and their reactivity and to see how certain thermodynamic parameters can be used to predict how much of the product will be formed when a reaction reaches equilibrium. Acid–base reactions also provide an illustration of the important role solvents play in chemical reactions. They even give us a brief introduction to organic synthesis. Finally, acid–base chemistry is something that you will find familiar because of your studies in general chemistry. We begin, therefore, with a brief review.

3.2A Brønsted–Lowry Acids and Bases

Two classes of acid–base reactions are fundamental in organic chemistry: Brønsted–Lowry and Lewis acid–base reactions. We start our discussion with Brønsted–Lowry acid–base reactions.

- Brønsted–Lowry acid–base reactions involve the transfer of protons.
- A **Brønsted–Lowry acid** is a substance that can donate (or lose) a proton.
- A **Brønsted–Lowry base** is a substance that can accept (or remove) a proton.

Let us consider some examples.

Hydrogen chloride (HCl), in its pure form, is a gas. When HCl gas is bubbled into water, the following reaction occurs.

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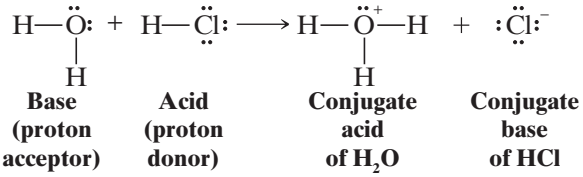


In this reaction hydrogen chloride donates a proton; therefore it acts as a Brønsted–Lowry acid. Water accepts a proton from hydrogen chloride; thus water serves as a Brønsted–Lowry base. The products are a hydronium ion (H_3O^+) and chloride ion (Cl^-).

Just as we classified the reactants as either an acid or a base, we also classify the products in a specific way.

- The molecule or ion that forms when an acid loses its proton is called the **conjugate base** of that acid. In the above example, chloride ion is the conjugate base.
- The molecule or ion that forms when a base accepts a proton is called the **conjugate acid**. Hydronium ion is the conjugate acid of water.

Hydrogen chloride is considered a strong acid because transfer of its proton in water proceeds essentially to completion. Other strong acids that completely transfer a proton when dissolved in water are hydrogen iodide, hydrogen bromide, and sulfuric acid.

$$HI + H_2O \longrightarrow H_3O^+ + I^-$$

$$HBr + H_2O \longrightarrow H_3O^+ + Br^-$$

$$H_2SO_4 + H_2O \longrightarrow H_3O^+ + HSO_4^-$$

$$H_2SO_4^- + H_2O \rightleftharpoons H_3O^+ + SO_4^{2-}$$

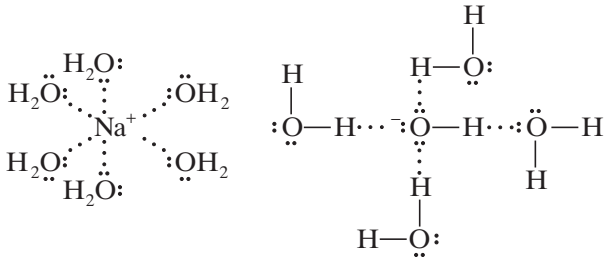
Helpful Hint: The extent to which an acid transfers protons to a base, such as water, is a measure of its strength as an acid. Acid strength is therefore a measure of the percentage of ionization and not of concentration.

Sulfuric acid is called a diprotic acid because it can transfer two protons. Transfer of the first proton occurs completely, while the second is transferred only to the extent of about 10% (hence the equilibrium arrows in the equation for the second proton transfer).

3.2B Acids and Bases in Water

- Hydronium ion is the strongest acid that can exist in water to any significant extent: Any stronger acid will simply transfer its proton to a water molecule to form hydronium ions.
- Hydroxide ion is the strongest base that can exist in water to any significant extent: Any base stronger than hydroxide will remove a proton from water to form hydroxide ions.

When an ionic compound dissolves in water the ions are solvated. With sodium hydroxide, for example, the positive sodium ions are stabilized by interaction with unshared electron pairs of water molecules, and the hydroxide ions are stabilized by hydrogen bonding of their unshared electron pairs with the partially positive hydrogens of water molecules.



Solvated sodium ion **Solvated hydroxide ion**

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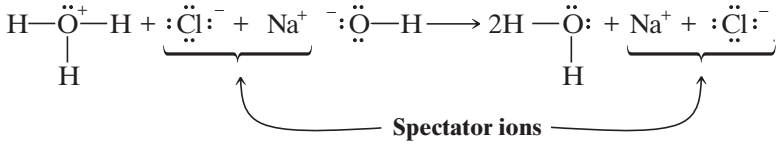
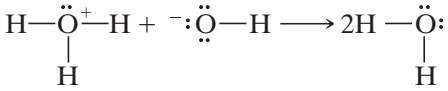
When an aqueous solution of sodium hydroxide is mixed with an aqueous solution of hydrogen chloride (hydrochloric acid), the reaction that occurs is between hydronium and hydroxide ions. The sodium and chloride ions are called **spectator ions** because they play no part in the acid–base reaction:

Total Ionic Reaction



Net Reaction



What we have just said about hydrochloric acid and aqueous sodium hydroxide is true when solutions of all aqueous strong acids and bases are mixed. The net ionic reaction is simply

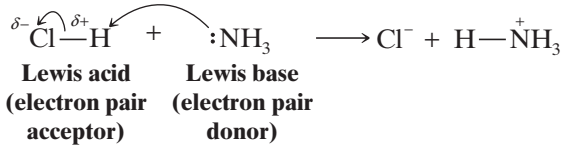
$$H_3O^+ + OH^- \longrightarrow 2H_2O$$

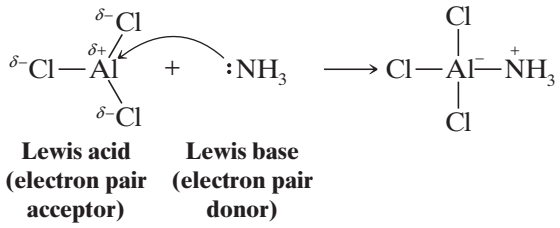
3.3 | LEWIS ACIDS AND BASES

In 1923 G. N. Lewis proposed a theory that significantly broadened the understanding of acids and bases. As we go along we shall find that an understanding of **Lewis acid–base theory** is exceedingly helpful to understanding a variety of organic reactions. Lewis proposed the following definitions for acids and bases.

- Acids are electron pair acceptors.
- Bases are electron pair donors.

In Lewis acid–base theory, proton donors are not the only acids; many other species are acids as well. Aluminum chloride, for example, reacts with ammonia in the same way that a proton donor does. Using curved arrows to show the donation of the electron pair of ammonia (the Lewis base), we have the following examples:





In the reaction with hydrogen chloride above, notice that the electron pair acceptor (the proton) must also lose an electron pair as the new bond is formed with nitrogen. This is necessary because the hydrogen atom had a full valence shell of electrons at the start. On the other hand, because the valence shell of the aluminum atom in aluminum chloride was not full at the beginning (it had only a sextet of valence electrons), it can accept an electron pair without breaking any bonds. The aluminum atom actually achieves an octet by accepting the pair from nitrogen, although it gains a formal negative charge. When it accepts the electron pair, aluminum chloride is, in the Lewis definition, *acting as an acid*.

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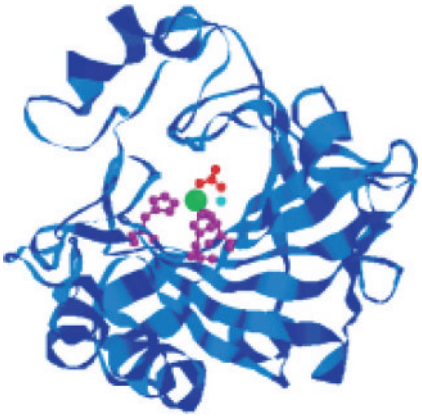
Bases are much the same in the Lewis theory and in the Brønsted–Lowry theory, because in the Brønsted–Lowry theory a base must donate a pair of electrons in order to accept a proton.

- The Lewis theory, by virtue of its broader definition of acids, allows acid–base theory to include all of the Brønsted–Lowry reactions and, as we shall see, a great many others. Most of the reactions we shall study in organic chemistry involve Lewis acid–base interactions, and a sound understanding of Lewis acid–base chemistry will help greatly.

Any *electron-deficient atom* can act as a Lewis acid. Many compounds containing group IIIA elements such as boron and aluminum are Lewis acids because group IIIA atoms have only a sextet of electrons in their outer shell. Many other compounds that have atoms with vacant orbitals also act as Lewis acids. Zinc and iron(III) halides (ferric halides) are frequently used as Lewis acids in organic reactions (Fig. 3.1).



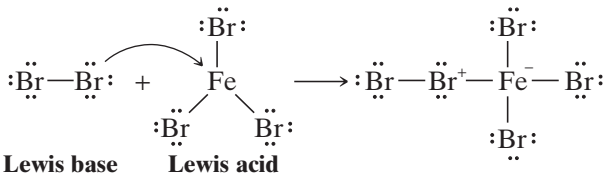
Carbonic anhydrase

Figure 3.1 A zinc ion acts as a Lewis acid in the mechanism of the enzyme carbonic anhydrase.

Solved Problem 3.1

Write an equation that shows the Lewis acid and Lewis base in the reaction of bromine (Br_2) with ferric bromide ($FeBr_3$).

Answer



3.3A Opposite Charges Attract

- In Lewis acid–base theory, as in many organic reactions, the attraction of oppositely charged species is fundamental to reactivity.

As one further example, we consider boron trifluoride, an even more powerful Lewis acid than aluminum chloride, and its reaction with ammonia. For example, consider boron trifluoride (BF_3) has substantial positive charge centered on the boron atom and negative charge located on the three fluorines. On the other hand, in ammonia, substantial negative charge is localized in the region of ammonia's nonbonding electron pair. Thus, the electrostatic properties of these two molecules are perfectly suited for a Lewis acid–base reaction. When the expected reaction occurs between them, the nonbonding electron pair of ammonia attacks the boron atom of boron trifluoride, filling boron's valence shell. The boron now carries a formal negative charge and the nitrogen carries a formal positive charge. We can see that substantial negative charge resides in the BF_3 part of the molecule, and substantial positive charge is localized near the nitrogen.

Practice Problem 3.1

Write equations showing the Lewis acid–base reaction that takes place when:

(a) Methanol (CH_3OH) reacts with BF_3.

(b) Chloromethane (CH_3Cl) reacts with $AlCl_3$.

(c) Dimethyl ether (CH_3OCH_3) reacts with BF_3.

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Practice Problem 3.2

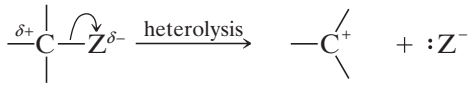
Which of the following are potential Lewis acids and which are potential Lewis bases?

(a) $CH_3CH_2-\ddot{N}(CH_3)-CH_3$ **(b)** $H_3C-C^+(CH_3)_2$ **(c)** $(C_6H_5)_3P:$ **(d)** $\ddot{B}r:^-$

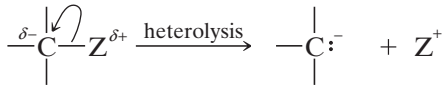
(e) $(CH_3)_3B$ **(f)** $H:^-$

3.4 | HETEROLYSIS OF BONDS TO CARBON: CARBOCATIONS AND CARBANIONS

Heterolysis of a bond to a carbon atom can lead to either of two ions: either to an ion with a positive charge on the carbon atom, called a **carbocation**, or to an ion with a negatively charged carbon atom, called a **carbanion**:



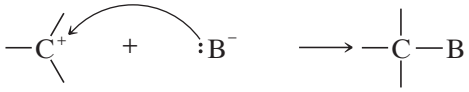
Carbocation



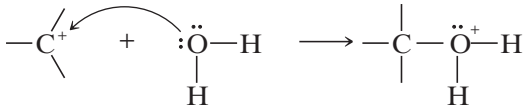
Carbanion

- Carbocations are electron deficient. They have only six electrons in their valence shell, and because of this, carbocations are Lewis acids.

In this way they are like BF_3 and $AlCl_3$. Most carbocations are also short-lived and highly reactive. They occur as intermediates in some organic reactions. Carbocations react rapidly with Lewis bases—with molecules or ions that can donate the electron pair that they need to achieve a stable octet of electrons (i.e., the electronic configuration of a noble gas):

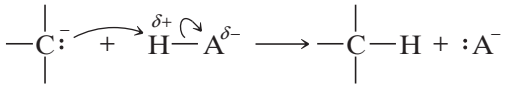


Carbocation (a Lewis acid) **Anion (a Lewis base)**

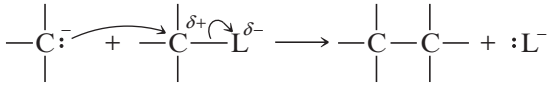


Carbocation (a Lewis acid) **Water (a Lewis base)**

- **Carbanions** are electron rich. They are anions and have an unshared electron pair. Carbanions, therefore, are **Lewis bases and react accordingly**



Carbanion **Lewis acid**



Carbanion **Lewis acid**

3.4A Electrophiles and Nucleophiles

Because carbocations are electron-seeking reagents chemists call them **electrophiles** (meaning electron-loving).

- **Electrophiles are reagents that seek electrons so as to achieve a stable shell of electrons like that of a noble gas.**

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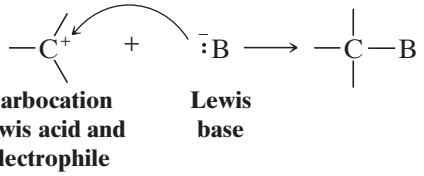
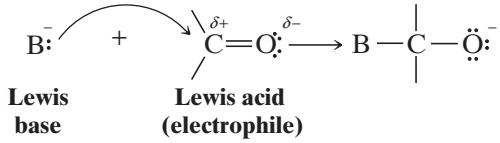
- **All Lewis acids are electrophiles**. By accepting an electron pair from a Lewis base, a carbocation fills its valence shell.



- **Carbon atoms that are electron poor because of bond polarity, but are not carbocations, can also be electrophiles**. They can react with the electron-rich centers of Lewis bases in reactions such as the following:

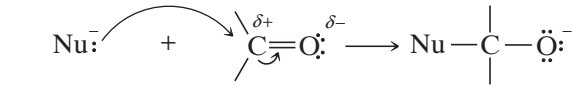


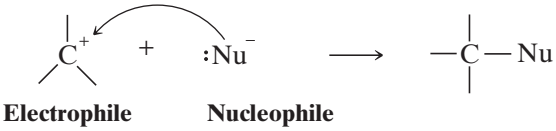
Carbanions are Lewis bases. Carbanions seek a proton or some other positive center to which they can donate their electron pair and thereby neutralize their negative charge.

When a Lewis base *seeks a positive center other than a proton, especially that of a carbon atom*, chemists call it a **nucleophile** (meaning nucleus loving; the *nucleo-* part of the name comes from *nucleus*, the positive center of an atom).

A nucleophile is a Lewis base that seeks a positive center such as a positively charged carbon atom.

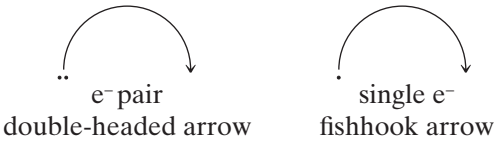
Since electrophiles are also Lewis acids (electron pair acceptors) and nucleophiles are Lewis bases (electron pair donors), why do chemists have two terms for them? The answer is that *Lewis acid* and *Lewis base* are terms that are used generally, but when one or the other reacts to form a bond to a carbon atom, we usually call it an *electrophile* or a *nucleophile*.





3.5 | HOW TO USE CURVED ARROWS IN ILLUSTRATING REACTIONS

Up to this point we have not indicated how bonding changes occur in the reactions we have presented, but this can easily be done using curved-arrow notation. Change in electronic configuration can be represented using *curved arrow notation*. This notation shows *movement* of electrons (flow of electrons). The electrons must move from a *source* to a *sink* as shown below.





One-barb fishhook represents one electron transfer



Two-barb fishhook represents two electron (i.e., electron pair) transfer

Redistribution of electrons [i.e., change in configuration is the origin of reactivity (chemical change)].

The main characteristics of curved arrow notation are as follows:

1. It is a graphical way to depict changes in electronic configurationln during a reaction.
2. It shows how electronic configurations can be rearranged in order to generate an alternative bonding representation of the same structure (e.g., a resonance structure).

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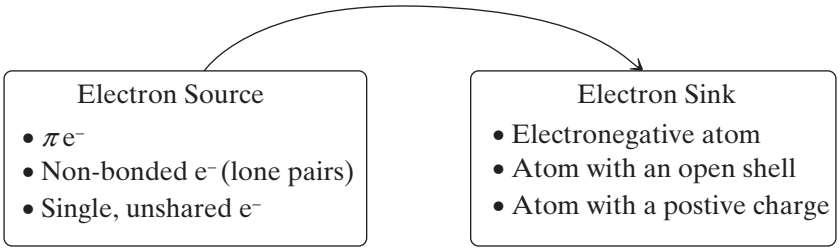
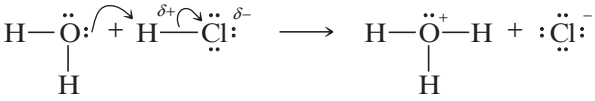
3. It shows the direction of electron flow in a reaction mechanism.
4. It points from the source of an electron pair to the atom receiving the pair. (Curved arrows can also show the movement of single electrons. We shall discuss reactions of this type in a later chapter.)
5. It always show the flow of electrons from a site of higher electron density to a site of lower electron density.
6. It **never** shows the movement of atoms. Atoms are assumed to follow the flow of the electrons.



The following examples illustrate the use of curved arrow.

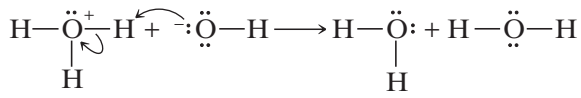


A water molecule uses one of the nonbonding electron pairs to form a bond to a proton of HCl. The bond between the hydrogen and chlorine breaks, and the electron pair goes to the chlorine atom.

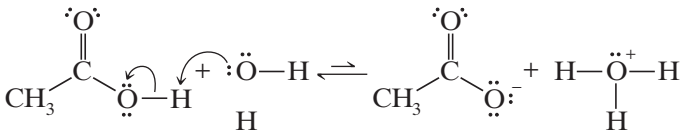
This leads to the formation of a hydronium ion and a chloride ion.

We see here that as the water molecule collides with a hydrogen chloride molecule, it uses one of its unshared electron pairs (shown in blue) to form a bond to the proton of HCl. This bond forms because the negatively charged electrons of the oxygen atom are attracted to the positively charged proton. As the bond between the oxygen and the proton forms, the hydrogen–chlorine bond of HCl breaks, and the chlorine of HCl departs with the electron pair that formerly bonded it to the proton. (If this did not happen, the proton would end up forming two covalent bonds, which, of course, a proton cannot do.) We, therefore, use a curved arrow to show the bond cleavage as well. By pointing from the bond to the chlorine, the arrow indicates that the bond breaks and the electron pair leaves with the chloride ion.

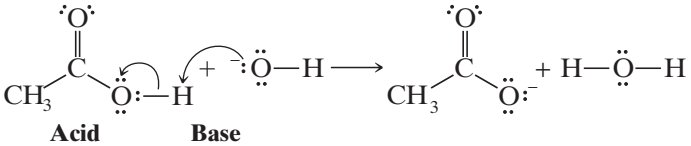
Helpful Hint: The curved arrow begins with a covalent bond or unshared electron pair (a site of higher electron density) and points toward a site of electron deficiency



Acid **Base**



Acid **Base**



Acid **Base**

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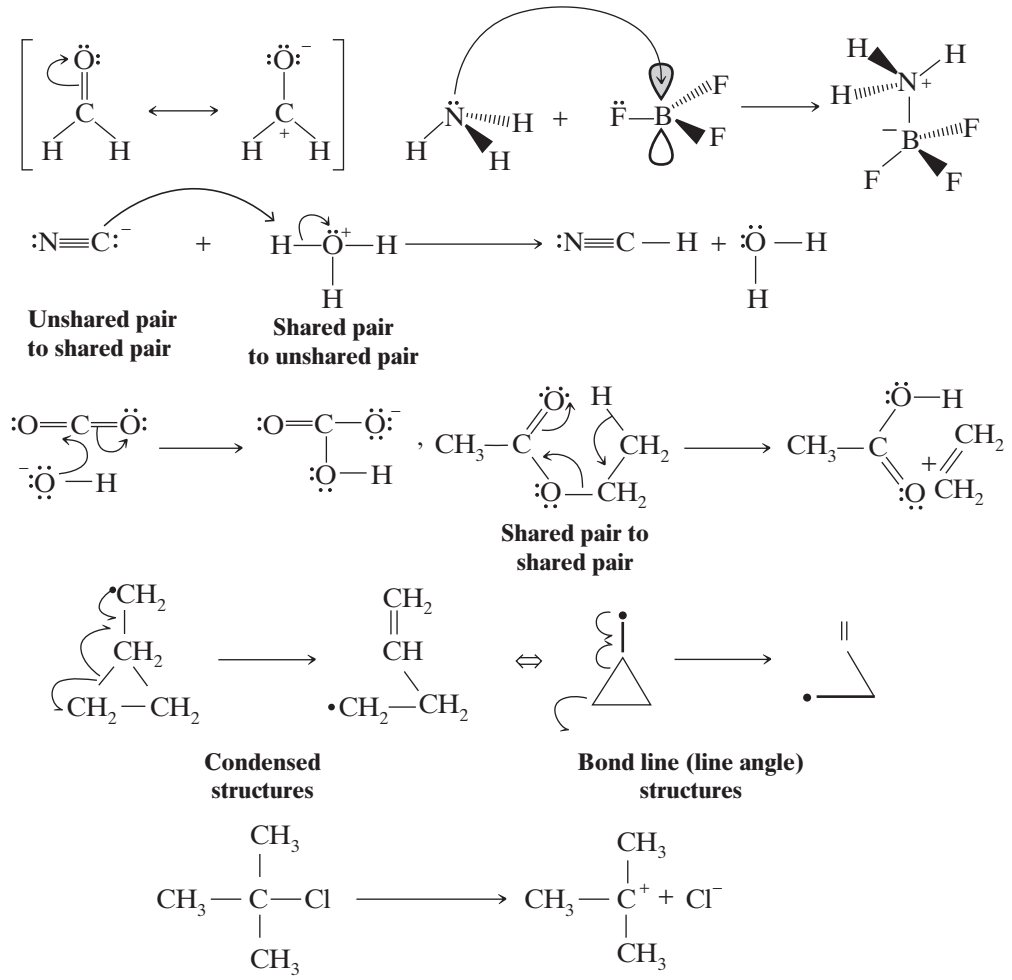
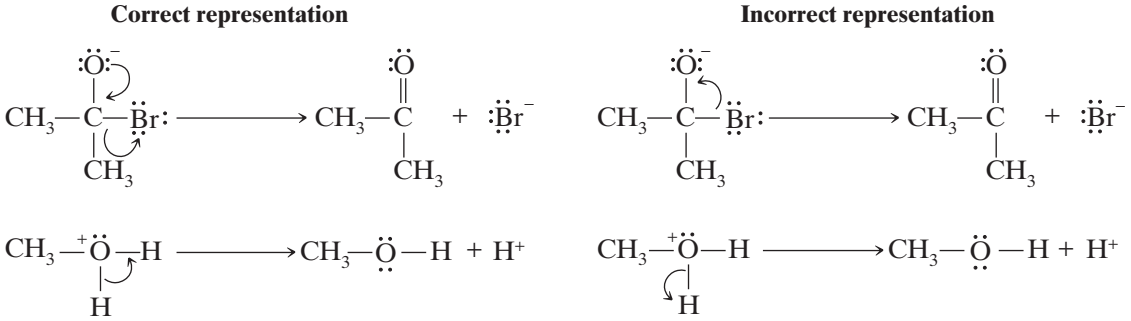
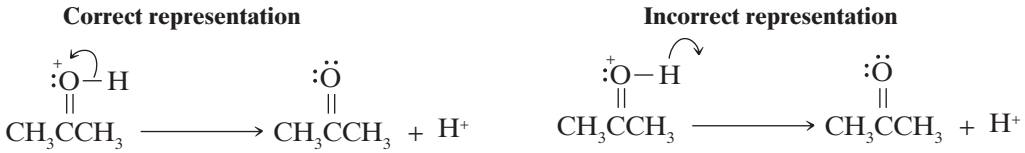


Some important points to be noted for using curved arrow notation are as follows:

1. Ensure that the arrows are drawn always in the direction of the electron flow and never against the flow. This means that an arrow will always be drawn away from a negative charge and/or toward a positive charge. For example,



2. The curved arrows are drawn to indicate the movement of electrons only. They should never be used to indicate the movement of an atom (e.g., the movement of a proton, as shown below).



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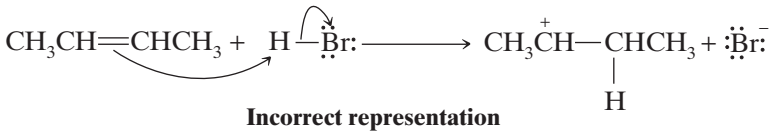
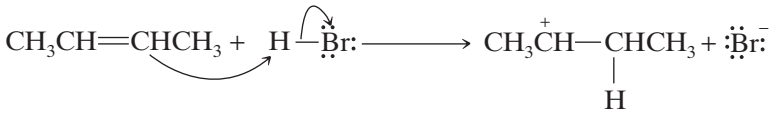
3. The arrow starts from the electron source and not from an atom.

Correct representation



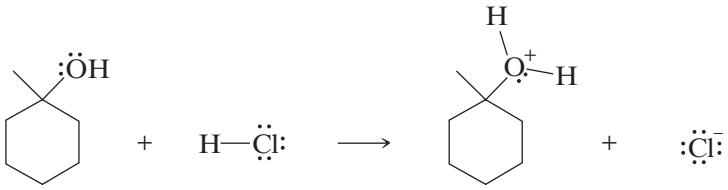
Incorrect representation



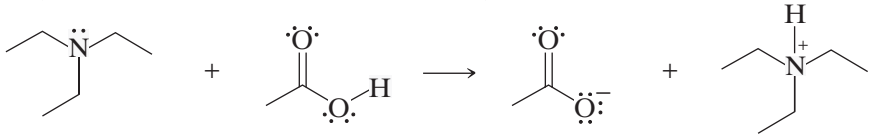
Solved Problem 3.2

Add curved arrows to the following reactions to indicate the flow of electrons for all of the bond-forming and bond-breaking steps.

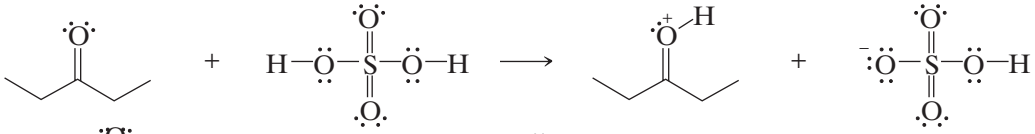
(a)



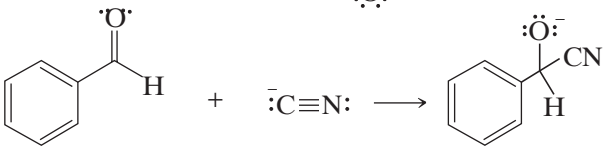
(b)



(c)



(d)

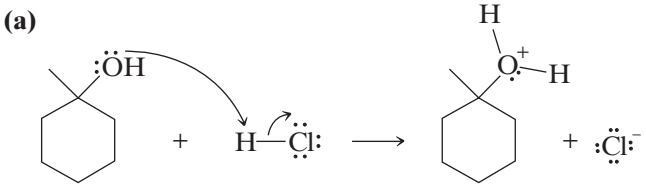


Answer

Curved arrows point from the source of an electron pair to the atom receiving the pair, and always point from a site of higher electron density to a site of lower electron density. We must also not exceed two electrons for a hydrogen atom, or an octet of electrons for any elements in the second row of the periodic table. We must also account for the formal charges on atoms and write equations whose charges are balanced.

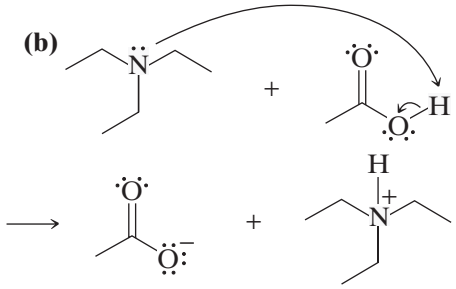
In **(a)**, the hydrogen atom of HCl is partially positive (electrophilic) due to the electronegativity of the chlorine atom. The alcohol oxygen is a source of electrons (a Lewis base) that can be given to this partially positive proton. The proton must lose a pair of electrons as it gains a pair, however, and thus the chloride ion accepts a pair of electrons from the bond it had with the hydrogen atom as the hydrogen becomes bonded to the alcohol oxygen.

(a)



In **(b)**, the carboxylic acid hydrogen is partially positive and therefore electrophilic, and the amine provides an unshared pair of electrons that forms a bond with the carboxylic acid hydrogen, causing departure of a carboxylate anion.

(b)



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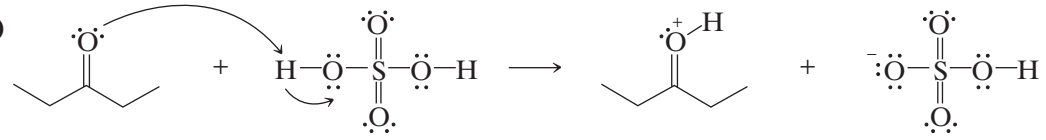
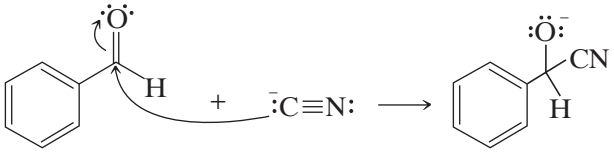
The circumstances in **(c)** are quite similar to **(a)** and **(b)**. In this case the electrophile is a proton of sulfuric acid.

(c)



(d)



In **(d),** the aldehyde carbon is electrophilic due to the electronegativity of the carbonyl oxygen. The cyanide anion acts as a Lewis base, donating an electron pair to the carbonyl carbon, and causing an electron pair to shift to the oxygen so that no atom has more than an octet of electrons.

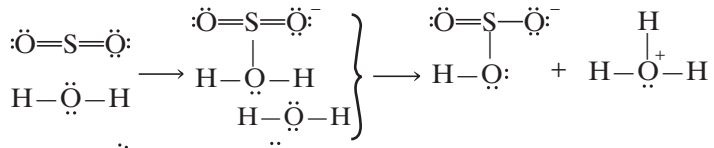
Practice Problem 3.3

Use the curved-arrow notation to write the reaction that would take place between dimethylamine $(CH_3)_2NH$ and boron trifluoride. Identify the Lewis acid and Lewis base and assign appropriate formal charges.

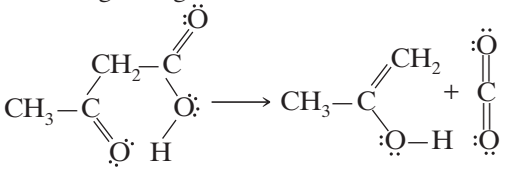
Practice Problem 3.4

Represent the movement of electrons using *curved arrow notation* in the following changes.

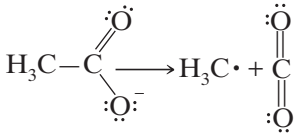
(a)



(b)

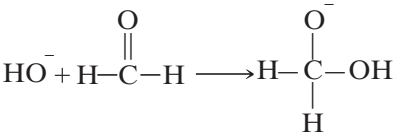


(c)

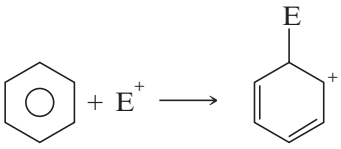


(d) $HO^- + H^+ \longrightarrow H_2O$

(e)



(f)



Practice Problem 3.5

Indicate which of the following are electrophiles and which are nucleophiles.

$$H^-,\ AlCl_3,\ CH_3O^-,\ CH_3C{\equiv}CH,\ CH_3\overset{+}{C}HCH_3,\ NH_3$$

Practice Problem 3.6

Use curved arrows to show the movement of electrons in each of the following reactions:

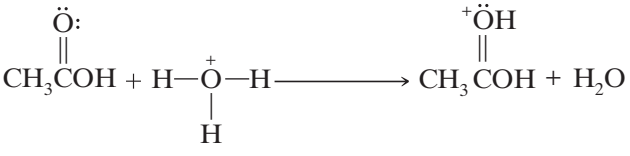
(a)



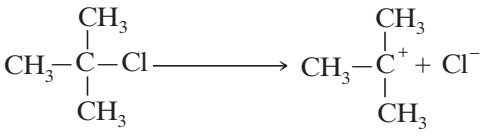
(b)



(c)



(d)



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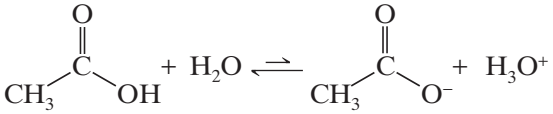
3.6 | THE STRENGTH OF BRØNSTED–LOWRY ACIDS AND BASES: K_a AND pK_a

In contrast to the strong acids, such as HCl and H_2SO_4, acetic acid is a much weaker acid. When acetic acid dissolves in water, the following reaction does not proceed to completion:



Experiments show that in a 0.1 M solution of acetic acid at 25°C only about 1% of the acetic acid molecules ionize by transferring their protons to water. Therefore, acetic acid is a weak acid. As we shall see next, **acid strength** is characterized in terms of acidity constant (K_a) or pK_a values.

3.6A The Acidity Constant, K_a

Because the reaction that occurs in an aqueous solution of acetic acid is an equilibrium, we can describe it with an expression for the **equilibrium constant (K_{eq})**:

$$K_{eq} = \frac{[H_3O^+]\,[CH_3CO_2^-]}{[CH_3CO_2H][H_2O]}$$

For dilute aqueous solutions, the concentration of water is essentially constant (~55.5 M), so we can rewrite the expression for the equilibrium constant in terms of a new constant **(K_a)** called the **acidity constant**:

$$K_a = K_{eq}[H_2O] = \frac{[H_3O^+]\,[CH_3CO_2^-]}{[CH_3CO_2H]}$$

At 25°C, the acidity constant for acetic acid is 1.76×10^{-5}.

We can write similar expressions for any weak acid dissolved in water. Using a generalized hypothetical acid (HA), the reaction in water is

$$HA + H_2O \rightleftharpoons H_3O^+ + A^-$$

and the expression for the acidity constant is

$$K_a = \frac{[H_3O^+] + [A^-]}{[HA]}$$

Because the concentrations of the products of the reaction are written in the numerator and the concentration of the undissociated acid in the denominator, **a large value of K_a means the acid is a strong acid and a small value of K_a means the acid is a weak acid**. If the K_a is greater than 10, the acid will be, for all practical purposes, completely dissociated in water at concentrations less than 0.01 M.

Practice Problem 3.7

Formic acid (HCO_2H) has $K_a = 1.77 \times 10^{-4}$. **(a)** What are the molar concentrations of the hydronium ion and formate ion (HCO_2^-) in a 0.1M aqueous solution of formic acid? **(b)** What percentage of the formic acid is ionized?

3.6B Acidity and pK_a

Chemists usually express the acidity constant, K_a, as its negative logarithm, **pK_a**:

$$pK_a = -\log K_a$$

This is analogous to expressing the hydronium ion concentration as pH:

$$pH = -\log[H_3O^+]$$

For acetic acid the pK_a is 4.75:

$$pK_a = -\log(1.76 \times 10^{-5}) = -(-4.75) = 4.75$$

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Helpful Hint: K_a and pK_a are indicators of acid strength.

Notice that there is an inverse relationship between the magnitude of the pK_a and the strength of the acid.

- **The larger the value of the pK_a, the weaker is the acid.**

For example, acetic acid with $pK_a = 4.75$ is a weaker acid than trifluoroacetic acid with $pK_a = 0$ ($K_a = 1$). Hydrochloric acid with $pK_a = -7$ ($K_a = 10^7$) is a far stronger acid than trifluoroacetic acid. (It is understood that a positive pK_a is larger than a negative pK_a.)

$$\underset{pK_a = 4.75}{\underset{\textbf{Weak acid}}{CH_3CO_2H}} \; < \; \underset{pK_a = 0}{\underset{\textbf{Very strong acid}}{CF_3CO_2H}} \; < \; \underset{pK_a = -7}{HCl}$$

Increasing acid strength

Table 3.1 lists pK_a values for a selection of acids relative to water as the base. The values in the middle pK_a range of the table are the most accurate because they can be measured in aqueous solution. Special methods must be used to estimate the pK_a values for the very strong acids at the top of the table and for the very weak acids at the bottom. The pK_a values for these very strong and weak acids are therefore approximate. All of the acids that we shall consider in this book will have strengths in between that of ethane (an extremely weak acid) and that of $HSbF_6$ (an acid that is so strong that it is called a "superacid"). As you examine Table 3.1, take care not to lose sight of the vast range of acidities that it represents (a factor of 10^{62}).

Table 3.1 Relative strength of selected acids and their conjugate bases

	Acid	Approximate pK_a	Conjugate Base	
Strongest acid	$HSbF_6$	<–12	SbF_6^-	Weakest base
	HI	–10	I^-	
	H_2SO_4	–9	HSO_4^-	
	HBr	–9	Br^-	
	HCl	–7	Cl^-	
	$C_6H_5SO_3H$	–6.5	$C_6H_5SO_3^-$	
	$(CH_3)_2\overset{+}{O}H$	–3.8	$(CH_3)_2O$	
	$(CH_3)_2C{=}\overset{+}{O}H$	–2.9	$(CH_3)_2C{-}O$	
	$CH_3\overset{+}{O}H_2$	–2.5	CH_3OH	
	H_3O^+	–1.74	H_2O	
	HNO_3	–1.4	NO_3^-	
	CF_3CO_2H	0.18	$CF_3CO_2^-$	
	HF	3.2	F^-	
	$C_6H_5CO_2H$	4.21	$C_6H_5CO_2^-$	
	$C_6H_5NH_3^+$	4.63	$C_6H_5NH_2$	
	CH_3CO_2H	4.75	$CH_3CO_2^-$	
	H_2CO_3	6.35	HCO_3^-	
	$CH_3COCH_2COCH_3$	9.0	$CH_3COHCOCH_3$	
	NH_4^+	9.2	NH_3	
	C_6H_5OH	9.9	$C_6H_5O^-$	
	HCO_3^-	10.2	CO_3^{2-}	
	$CH_3NH_3^+$	10.6	CH_3NH_2	
	H_2O	15.7	OH^-	
	CH_3CH_2OH	16	$CH_3CH_2O^-$	

Increasing acid strength

Increasing base strength

(Continued)

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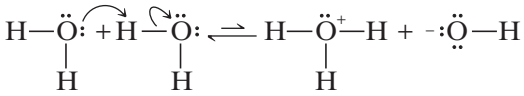
Table 3.1 Continued

	Acid	Approximate pK_a	Conjugate Base	
	$(CH_3)_3COH$	18	$(CH_3)_3CO^-$	
	CH_3COCH_3	19.2	$^-CH_2COCH_3$	
	$HC{\equiv}CH$	25	$HC{=}C^-$	
	H_2	35	H^-	
	NH_3	38	NH_2^-	
	$CH_2{=}CH_2$	44	$CH_2{=}CH^-$	
Weakest acid	CH_3CH_3	50	$CH_3CH_2^-$	Strongest base

Water, itself, is a very weak acid and undergoes self-ionization even in the absence of acids and bases:



In pure water at 25°C, the concentrations of hydronium and hydroxide ions are equal to 10^{-7} M. Since the concentration of water in pure water is 55.5 M, we can calculate the K_a for water.

$$K_a = \frac{[H_3O^+][OH^-]}{[H_2O]} \qquad K_a = \frac{(10^{-7})(10^{-7})}{55.5} = 1.8\times10^{-16} \qquad pK_a = 15.7$$

Practice Problem 3.8

(a) An acid (HA) has $K_a = 10^{-7}$. What is its pK_a? **(b)** Another acid (HB) has $K_a = 5$; what is its pK_a? **(c)** Which is the stronger acid?

Practice Problem 3.9

Show calculations proving that the pK_a of the hydronium ion (H_3O^+) is –1.74 as given in Table 3.1.

3.6C Predicting the Strength of Bases

In our discussion so far we have dealt only with the strengths of acids. Arising as a natural corollary to this is a principle that allows us to estimate the **strengths of bases**. Simply stated, the principle is this:

- **The stronger the acid, the weaker will be its conjugate base.**
  We can, therefore, **relate the strength of a base to the pK_a of its conjugate acid.**
- **The larger the pK_a of the conjugate acid, the stronger is the base.**
  Consider the following as examples:

Increasing base strength

Cl^-	$CH_3CO_2^-$	OH^-
Very weak base	**Weak base**	**Strong base**
pK_a of conjugate acid (HCl) = –7	**pK_a of conjugate acid (CH_3CO_2H) = 4.75**	**pK_a of conjugate acid (H_2O) = 15.7**

We see that the hydroxide ion is the strongest in this series of three bases because its conjugate acid, water, is the weakest acid. (We know that water is the weakest acid because it has the largest pK_a.)

Amines are like ammonia in that they are weak bases. Dissolving ammonia in water brings about the following equilibrium:

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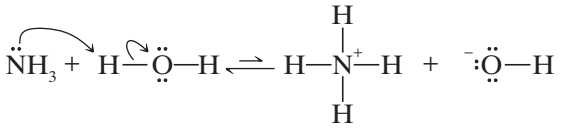
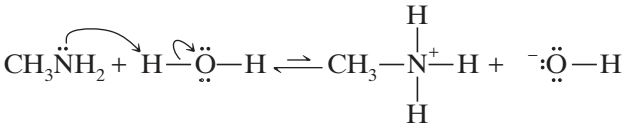


Dissolving methylamine in water causes the establishment of a similar equilibrium.



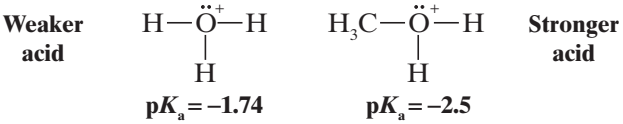
Again we can relate the basicity of these substances to the strength of their conjugate acids. The conjugate acid of ammonia is the ammonium ion, NH_4^+. The pK_a of the ammonium ion is 9.2. The conjugate acid of methylamine is the $CH_3NH_3^+$ ion. This ion, called the methylaminium ion, has pK_a = 10.6. Since the conjugate acid of methylamine is a weaker acid than the conjugate acid of ammonia, we can conclude that methylamine is a stronger base than ammonia.

Solved Problem 3.3

Using the pK_a values in Table 3.1 decide which is the stronger base, CH_3OH or H_2O.

Answer

From Table 3.1, we find the pK_a values of the conjugate acids of water and methanol.

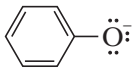


Because water is the conjugate base of the weaker acid, it is the stronger base.



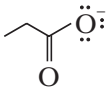
Practice Problem 3.10

Using the pK_a values of analogous compounds in Table 3.1 predict which would be the stronger base.

(a) (i)  or (ii) 

(b) (i) $(CH_3)_3CO^-$ or (ii)

(c) (i)  or (ii) 

(d) (i)  or (ii) 

Practice Problem 3.11

The pK_a of the anilinium ion ($C_6H_5\overset{+}{N}H_3$) is 4.63. On the basis of this fact, decide whether aniline ($C_6H_5NH_2$) is a stronger or weaker base than methylamine.

3.7 | HOW TO PREDICT THE OUTCOME OF ACID–BASE REACTIONS

Table 3.1 gives the approximate pK_a values for a range of representative compounds. While you probably will not be expected to memorize all of the pK_a values in Table 3.1, it is a good idea to begin to learn the general order of acidity

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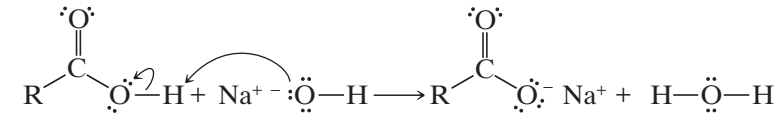
and basicity for some of the common acids and bases. The examples given in Table 3.1 are representative of their class or functional group. For example, acetic acid has a $pK_a = 4.75$, and carboxylic acids generally have pK_a values near this value (in the range $pK_a = 3–5$). Ethyl alcohol is given as an example of an alcohol, and alcohols generally have pK_a values near that of ethyl alcohol (in the pK_a range 15–18), and so on. (There are exceptions, of course, and we shall learn what these exceptions are as we go on.)

By learning the relative scale of acidity of common acids now, you will be able to predict whether or not an acid–base reaction will occur as written.

- The general principle to apply is this: **Acid–base reactions always favor the formation of the weaker acid and the weaker base**.

The reason for this is that the outcome of an acid–base reaction is determined by the position of an equilibrium. Acid–base reactions are said, therefore, to be **under equilibrium control**, and reactions under equilibrium control always favor the formation of the most stable (lowest potential energy) species. The weaker acid and weaker base are more stable (lower in potential energy) than the stronger acid and stronger base.

Using this principle, we can predict that a carboxylic acid (RCO_2H) will react with aqueous NaOH in the following way because the reaction will lead to the formation of the weaker acid (H_2O) and weaker base (RCO_2^-):



Stronger acid $pK_a = 3–5$ | **Stronger base** | **Weaker base** | **Weaker acid** $pK_a = 15.7$

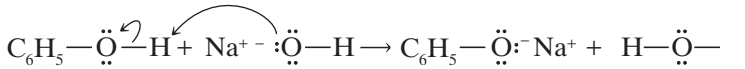
Because there is a large difference in the value of the pK_a of the two acids, the position of equilibrium will greatly favor the formation of the products. In instances like these we commonly show the reaction with a one-way arrow even though the reaction is an equilibrium.

Solved Problem 3.4

Consider the mixing of an aqueous solution of phenol, C_6H_5OH (see Table 3.1), and NaOH. What acid–base reaction, if any, would take place?

Answer

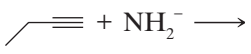
Consider the relative acidities of the reactant (phenol) and of the acid that might be formed (water) by a proton transfer to the base (the hydroxide ion). The following reaction would take place because it would lead to the formation of a weaker acid (water) from the stronger acid (phenol). It would also lead to the formation of a weaker base, C_6H_5ONa, from the stronger base, NaOH.



Stronger acid $pK_a = 9.9$ | **Stronger base** | **Weaker base** | **Weaker acid** $pK_a = 15$

Practice Problem 3.12

Predict the outcome of the following reaction.



3.7A Water Solubility as the Result of Salt Formation

Although acetic acid and other carboxylic acids containing fewer than five carbon atoms are soluble in water, many other carboxylic acids of higher molecular weight are not appreciably soluble in water. Because of their acidity, however, *water-insoluble carboxylic acids dissolve in aqueous sodium hydroxide*; they do so by reacting to form water-soluble sodium salts:

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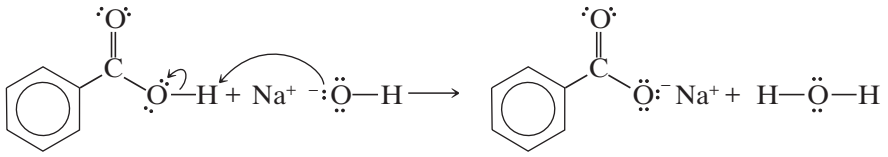
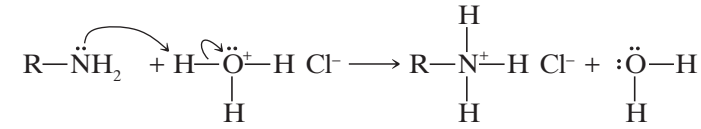


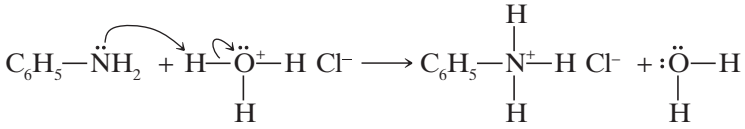
Insoluble in water **Soluble in water (due to its polarity as a salt)**

We can also predict that an amine will react with aqueous hydrochloric acid in the following way:



Stronger base **Stronger acid** $pK_a = -1.74$ **Weaker acid** $pK_a = 9–10$ **Weaker base**

While methylamine and most amines of low molecular weight are very soluble in water, amines with higher molecular weights, such as aniline ($C_6H_5NH_2$), have limited water solubility. However, these *water-insoluble amines dissolve readily in hydrochloric acid* because the acid–base reactions convert them into soluble salts:



Water insoluble **Water-soluble salt**

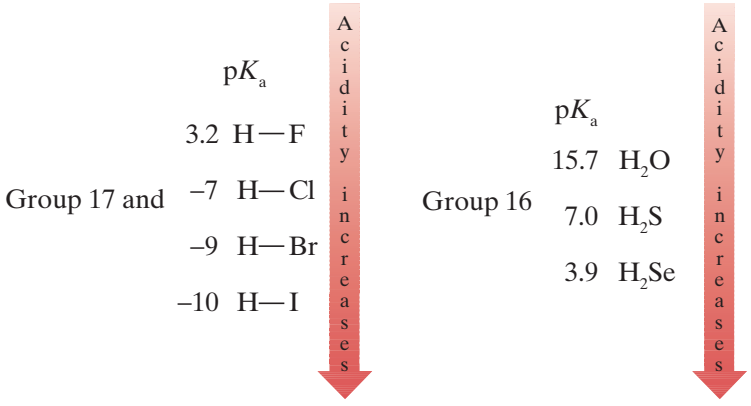
3.8 | RELATIONSHIPS BETWEEN STRUCTURE AND ACIDITY

The strength of a Brønsted–Lowry acid depends on the extent to which a proton can be separated from it and transferred to a base. Removing the proton involves breaking a bond to the proton, and it involves making the conjugate base more electrically negative.

When we compare compounds in a single column of the periodic table, the strength of the bond to the proton is the dominating effect.

- Bond strength to the proton decreases as we move down the column, increasing its acidity.

This phenomenon is mainly due to decreasing effectiveness of orbital overlap between the hydrogen 1*s* orbital and the orbitals of successively larger elements in the column. The less effective the orbital overlap, the weaker is the bond, and the stronger is the acid. The acidities of the hydrogen halides furnish an example (Group 17). The same trend of acidities and basicities holds true in other columns of the periodic table. Consider, for example, the column headed by oxygen (Group 16):



Helpful Hint: Proton acidity increases as we descend a column in the periodic table due to decreasing bond strength to the proton. Proton acidity increases from left to right in a given row of the periodic table due to increasing stability of the conjugate base.

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Comparing the hydrogen halides with each other, H—F is the weakest acid and H—I is the strongest. This follows from the fact that the H—F bond is by far the strongest and the H—I bond is the weakest.

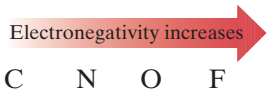
Because HI, HBr, and HCl are strong acids, their conjugate bases (I^-, Br^-, Cl^-) are all weak bases. HF, however, which is less acidic than the other hydrogen halides by 10–13 orders of magnitude (compare their pK_a values), has a conjugate base that is correspondingly more basic than the other halide anions. The fluoride anion is still not nearly as basic as other species we commonly think of as bases, such as the hydroxide anion, however. A comparison of the pK_a values for HF (3.2) and H_2O (15.7) illustrates this point.

Here the strongest bond is the O—H bond and H_2O is the weakest acid; the weakest bond is the Se—H bond and H_2Se is the strongest acid.

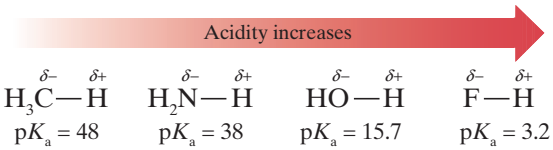
- Acidity increases from left to right when we compare compounds in a given row of the periodic table.

Bond strengths vary somewhat, but the predominant factor becomes the electronegativity of the atom bonded to the hydrogen. The electronegativity of the atom in question affects acidity in two related ways. It affects the polarity of the bond to the proton and it affects the relative stability of the anion (conjugate base) that forms when the proton is lost.

We can see an example of this effect when we compare the acidities of the compounds CH_4, NH_3, H_2O, and HF. These compounds are all hydrides of first-row elements, and electronegativity increases across a row of the periodic table from left to right (see Table 1.2):

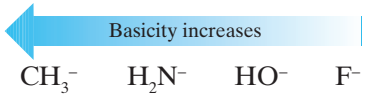


Because fluorine is the most electronegative, the bond in H—F is most polarized, and the proton in H—F is the most positive. Therefore, H—F loses a proton most readily and is the most acidic in this series:



Based on electronegativity and increasing polarization of the bonds to hydrogen, we see that almost no positive charge is evident at the hydrogens of methane. Very little positive charge is present at the hydrogens of ammonia. This is consistent with the weak electronegativity of both carbon and nitrogen and hence with the behavior of methane and ammonia as exceedingly weak acids (pK_a values of 48 and 38, respectively). Water shows significant positive charge at its hydrogens (pK_a more than 20 units lower than ammonia), and hydrogen fluoride clearly has the highest amount of positive charge at its hydrogen (pK_a of 3.2), resulting in strong acidity.

Because H—F is the strongest acid in this series, its conjugate base, the fluoride ion (F^-), will be the weakest base. Fluorine is the most electronegative atom and it accommodates the negative charge most readily:

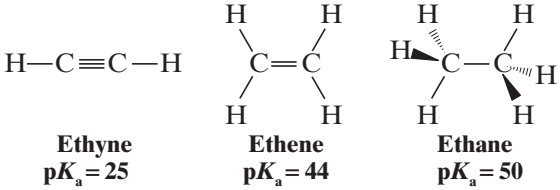


The methanide ion (CH_3^-) is the least stable anion of the four, because carbon being the least electronegative element is least able to accept the negative charge. The methanide ion, therefore, is the strongest base in this series. [The methanide ion, a **carbanion**, and the amide ion (NH_2^-) are exceedingly strong bases because they are the conjugate bases of extremely weak acids.]

Trends in acidity within the periodic table are summarized in Fig. 3.2.

3.8A The Effect of Hybridization

The protons of ethyne are more acidic than those of ethene, which in turn are more acidic than those of ethane:



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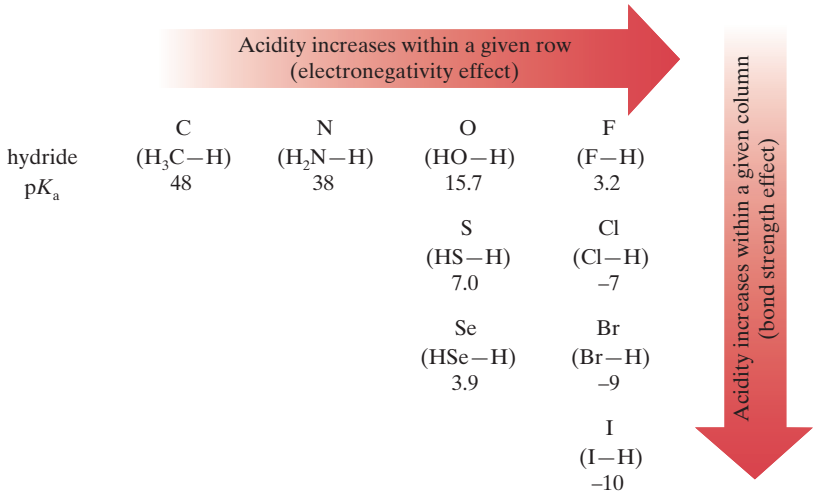

Figure 3.2 A summary of periodic trends in relative acidity. Acidity increases from left to right across a given row (electronegativity effect) and from top to bottom in a given column (bond strength effect) of the periodic table.

We can explain this order of acidities on the basis of the hybridization state of carbon in each compound. Electrons of 2*s* orbitals have lower energy than those of 2*p* orbitals because *electrons in 2s orbitals tend, on the average, to be much closer to the nucleus than electrons in 2p orbitals*. (Consider the shapes of the orbitals: 2*s* orbitals are spherical and centered on the nucleus; 2*p* orbitals have lobes on either side of the nucleus and are extended into space.)

With hybrid orbitals, **having more *s* character means that the electrons of the anion will, on the average, be lower in energy, and the anion will be more stable**.

The *sp* orbitals of the C—H bonds of ethyne have 50% *s* character (because they arise from the combination of one *s* orbital and one *p* orbital), those of the sp^2 orbitals of ethene have 33.3% *s* character, while those of the sp^3 orbitals of ethane have only 25% *s* character. This means, in effect, that the *sp* carbon atoms of ethyne act as if they were more electronegative than the sp^2carbon atoms of ethene and the sp^3 carbon atoms of ethane. (Remember: Electronegativity measures an atom's ability to hold bonding electrons close to its nucleus, and having electrons closer to the nucleus makes it more stable.)

The effect of hybridization on acidity can be seen in ethyne, ethene, and ethane. Some positive charge is present on the hydrogens of ethyne (pK_a = 25), but almost no positive charge is present on the hydrogens of ethene and ethane (both having pK_a values more than 20 units greater than ethyne). This is consistent with the effectively greater electronegativity of the *sp* orbitals in ethyne, which have more *s* character than the sp^2 and sp^3 orbitals in ethene and ethane. [Also the negative charge resulting from electron density in the π bonds of ethyne and ethene.]

Now we can see how the order of relative acidities of ethyne, ethene, and ethane parallels the effective electronegativity of the carbon atom in each compound:

Relative Acidity of the Hydrocarbons

$$HC{\equiv}CH > H_2C{=}CH_2 > H_3C{-}CH_3$$

Being the most electronegative, the *sp*-hybridized carbon atom of ethyne polarizes its C—H bonds to the greatest extent, causing its hydrogens to be most positive. Therefore, ethyne donates a proton to a base more readily. And, in the same way, the ethynide ion is the weakest base because the more electronegative carbon of ethyne is best able to stabilize the negative charge.

Relative Basicity of the Carbanions

$$H_3C{-}CH_2{:}^- > H_2C{=}CH{:}^- > HC{\equiv}C{:}^-$$

Notice that the explanation given here involves electronegativity, just as that given earlier to account for the relative acidities of HF, H_2O, NH_3, and CH_4.

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3.8B Inductive Effects

The carbon–carbon bond of ethane is completely nonpolar because at each end of the bond there are two equivalent methyl groups: CH_3–CH_3 (the C–C bond is non-polar). This is not the case with the carbon–carbon bond of ethyl fluoride, however: $\overset{\delta+}{\underset{2}{CH_3}} \rightarrow \overset{\delta+}{\underset{1}{CH_2}} \rightarrow \overset{\delta-}{F}$

One end of the bond, the one nearer the fluorine atom, is more negative than the other. This polarization of the carbon–carbon bond results from an intrinsic electron-attracting ability of the fluorine (because of its electronegativity) that is transmitted *through space* and *through the bonds of the molecule*. Chemists call this kind of effect an **inductive effect**.

- **Inductive effects** are electronic effects transmitted through bonds. The inductive effect of a group can be **electron donating** or **electron withdrawing**. Inductive effects weaken as the distance from the group increases.

In the case of ethyl fluoride, the positive charge that the fluorine imparts to C**1** is greater than that imparted to C**2** because the fluorine is closer to C**1**.

Inductive Effect (I Effect) of Groups

Electron donating groups show positive inductive effect (+I). For example,

$$-T > -D > -H$$

$$-\bar{N}-R > -\bar{O}$$

$$-\bar{S}e > -\bar{S}$$

$$-C(CH_3)_3 > -CH(CH_3)_2 > -CH_2-CH_3 > -CH_3$$

$$-O > -\overset{\overset{O}{\|}}{C}-O^-$$

Electron withdrawing groups show negative inductive effect (–I). For example,

$$-\overset{+}{O}R_2 > -\overset{+}{N}R_2$$

$$-\overset{+}{N}HCH_3 > -\overset{+}{P}H-CH_3 > -\overset{+}{A}s-CH_3 > -\overset{+}{S}b-CH_3$$

$$-\overset{+}{O}\begin{matrix}R\\R\end{matrix} > -\overset{+}{S}R_2 > -\overset{+}{S}eR_2 > -\overset{+}{T}eR_2$$

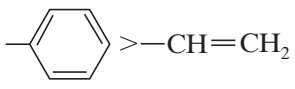
$$-\overset{+}{O}R_2 > -OR$$

$$-\overset{+}{S}R_2 > -SR$$

$$-C\equiv N > -CH=NH_2 > -CH_2-NH_2$$

$$-CH=O > -CH=NH > -CH=CH_2$$

$$-C\equiv CH > \quad CH=CH_2$$



$$> -CH=CH_2$$

$$-F > -OR > -NR_2 > CR_3$$

$$-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-R > -\overset{\overset{O}{\|}}{S}-R > -S-R$$

$$-SiR_3 > -GeR_3$$

$$-C\equiv \overset{+}{N}H > -CH=\overset{+}{N}H_2 > -CH_2-\overset{+}{N}H_3$$

$$-\overset{+}{N}H_3 > -NH_2$$

$$-OCH_3 > -S-CH_3 > -Se-CH_3$$

$$-F > -CI > -Br > -I$$

$$-CH=O > -CH_2-O-CH_3$$

Electron redistributions take place in unsaturated and conjugated systems by the π-orbitals to generate centres of high-and low-electron densities. This phenomena is known as mesomeric (M) or resonance (R) effect.

3.8C Mesomeric Effect (M) Groups

Electron donating groups show positive mesomeric effect (+M). for example,

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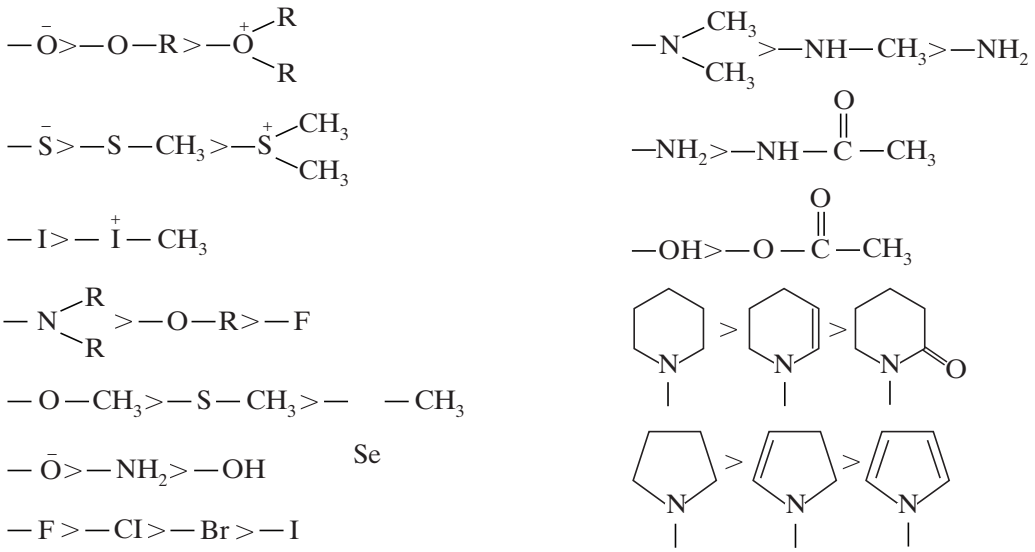

Electron withdrawing groups show negative mesomeric effect. For example,

$$-CH{=}O > -CH{=}NH_2 > -CH{=}CH_2$$
$$-CH{=}S > -CH{=}O$$
$$-C{\equiv}N > -C{\equiv}CH$$
$$-C{\equiv}\overset{+}{N}-CH_3 > C{\equiv}N$$

3.9 | ENERGY CHANGES

Chemical energy is a form of potential energy. It exists because attractive and repulsive electrical forces exist between different pieces of the molecules. Nuclei attract electrons, nuclei repel each other, and electrons repel each other.

It is usually impractical (and often impossible) to describe the *absolute* amount of potential energy contained by a substance. Thus we usually think in terms of its *relative potential energy*. We say that one system has *more* or *less* potential energy than another.

Another term that chemists frequently use in this context is the term **stability** or **relative stability**. *The relative stability of a system is inversely related to its relative potential energy*.

- **The *more* potential energy an object has, the *less stable* it is.**

Consider, as an example, the relative potential energy and the relative stability of snow when it lies high on a mountainside and when it lies serenely in the valley below. Because of the attractive force of gravity, the snow high on the mountain *has greater potential energy and is much less stable* than the snow in the valley. This greater potential energy of the snow on the mountainside can become converted into the enormous kinetic energy of an avalanche. By contrast, the snow in the valley, with its lower potential energy and with its greater stability, is incapable of releasing such energy.

3.9A Potential Energy and Covalent Bonds

Atoms and molecules possess potential energy—often called chemical energy—that can be released as heat when they react. Because heat is associated with molecular motion, this release of heat results from a change from potential energy to kinetic energy.

From the standpoint of covalent bonds, the state of greatest potential energy is the state of free atoms, the state in which the atoms are not bonded to each other at all. This is true because the formation of a chemical bond is always accompanied by the lowering of the potential energy of the atoms. For example, the free energy changes are shown in Fig. 3.3*a* for the ionization of acetic acid and ethanol. We can see that ethanol has a larger positive free-energy change and is a weaker acid because its ionization is more unfavorable. Also, consider as an example the formation of hydrogen molecules from hydrogen atoms. The potential energy of the atoms decreases by 436 kJ mol^{-1} as the covalent bond forms (Fig. 3.3*b*).

A convenient way to represent the relative potential energies of molecules is in terms of their relative **enthalpies**, or **heat contents**, *H*. (*Enthalpy* comes from *en* + *thalpein*, Greek: to heat.) The difference in relative enthalpies of

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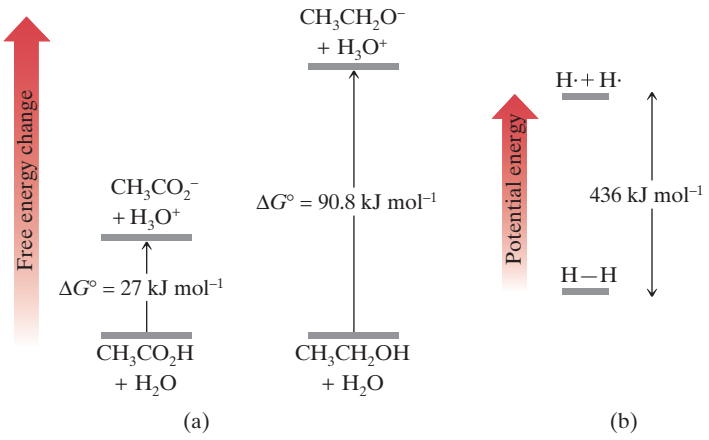

Figure 3.3 (a) Free-energy changes that accompany ionization of acetic acid and ethanol. (b) Relative potential energies of hydrogen atoms and a hydrogen molecule.

reactants and products in a chemical change is called the **enthalpy change** and is symbolized by $\Delta H°$. [The Δ (delta) in front of a quantity usually means the difference, or change, in the quantity. The superscript° indicates that the measurement is made under standard conditions.]

By convention, the sign of $\Delta H°$ for **exothermic** reactions (those evolving heat) is negative. **Endothermic** reactions (those that absorb heat) have a positive $\Delta H°$. The heat of reaction, $\Delta H°$, measures the change in enthalpy of the atoms of the reactants as they are converted to products. For an exothermic reaction, the atoms have a smaller enthalpy as products than they do as reactants. For endothermic reactions, the reverse is true.

3.10 | THE RELATIONSHIP BETWEEN THE EQUILIBRIUM CONSTANT AND THE STANDARD FREE-ENERGY CHANGE, $\Delta G°$

An important **relationship exists between the equilibrium constant (K_{eq}) and the standard free-energy change ($\Delta G°$)** for a reaction.

$$\Delta G° = -RT \ln k_{eq}$$

where R is the gas constant and equals 8.314 J K^{-} mol^{-1} and T is the absolute temperature in kelvins (K).

This equation tells us the following:

- **For a reaction to favor the formation of products when equilibrium is reached it must have a negative value for $\Delta G°$.** Free energy must be *lost* as the reactants become products; that is, the reaction must go down an energy hill. For such a reaction the equilibrium constant will be greater than one. If $G°$ is more negative than 13 kJ mol^{-1} the equilibrium constant will be large enough for the reaction to *go to completion*, meaning that more than 99% of the reactants will be converted to products when equilibrium is reached.
- **For reactions with a positive $\Delta G°$, the formation of products at equilibrium is unfavorable**. The equilibrium constant for these reactions will be less than one.

The free-energy change ($\Delta G°$) has two components, the **enthalpy change ($\Delta H°$)** and the **entropy change ($\Delta S°$)**. The relationship between these three thermodynamic quantities is

$$\Delta G° = \Delta H° - T\Delta S°$$

We have seen that $\Delta H°$ is associated with changes in bonding that occur in a reaction. If, collectively, stronger bonds are formed in the products than existed in the starting materials, then $\Delta H°$ will be negative (i.e., the reaction is *exothermic*). If the reverse is true, then $\Delta H°$ will be positive (the reaction is *endothermic*). **A negative value for $\Delta H°$, therefore, will contribute to making $\Delta G°$ negative and will consequently favor the formation of products**. For the ionization of an acid, the less positive or more negative the value of $\Delta H°$, the stronger the acid will be.

Entropy changes have to do with *changes in the relative order of a system*. **The more random a system is, the greater is its entropy**. Therefore, a positive entropy change ($+\Delta S°$) is always associated with a change from a more ordered system to a less ordered one. A negative entropy change ($-\Delta S°$) accompanies the reverse process. In the equation $\Delta G° = \Delta H° - T\Delta S°$, the entropy change (multiplied by T) is preceded by a negative sign; this means that **a positive**

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entropy change (from order to disorder) makes a negative contribution to ΔG° and is energetically favorable for the formation of products.

For many reactions in which the number of molecules of products equals the number of molecules of reactants (e.g., when two molecules react to produce two molecules), the entropy change will be small. This means that except at high temperatures (where the term $T\Delta S^\circ$ becomes large even if ΔS° is small) the value of ΔH° will largely determine whether or not the formation of products will be favored. If ΔH° is large and negative (if the reaction is exothermic), then the reaction will favor the formation of products at equilibrium. If ΔH° is positive (if the reaction is endothermic), then the formation of products will be unfavorable.

Practice Problem 3.13

State whether you would expect the entropy change, ΔS°, to be positive, negative, or approximately zero for each of the following reactions. (Assume the reactions take place in the gas phase.)

(a) $A + B \longrightarrow C$ **(b)** $A + B \longrightarrow C + D$ **(c)** $A \longrightarrow B + C$

Practice Problem 3.14

(a) What is the value of ΔG° for a reaction where $K_{eq} = 1$? (The change in ΔG° required to produce a 10-fold increase in the equilibrium constant is a useful term to remember.) **(b)** Assuming that the entropy change for this reaction is negligible (or zero), what change in ΔH° is required to produce a 10-fold increase in the equilibrium constant?

3.11 | THE ACIDITY OF CARBOXYLIC ACIDS VERSUS ALCOHOLS

Both carboxylic acids and alcohols are weak acids. However, *carboxylic acids are much more acidic than the corresponding alcohols*. Unsubstituted carboxylic acids have pK_a in the range of 3–5; alcohols have pK as in the range of 15–18. Consider as examples two compounds of about the same molecular proportions but with very different acidities, acetic acid and ethanol.

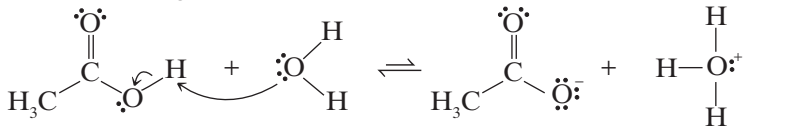


Acetic acid pK_a = 4.75 **Ethanol pK_a = 16**
ΔG° = 27 kJ mol^{-1} **ΔG° = 90.8 kJ mol^{-1}**
(ΔG° values are for OH proton ionization.)

Using the pK_a for acetic acid (4.75), one can calculate that the free-energy change (ΔG°) for ionization of the carboxyl proton of acetic acid is +27 kJ mol^{-1}, a moderately endergonic (unfavorable) process, since the ΔG° value is positive. Using the pK_a of ethanol (16), one can calculate that the corresponding free-energy change for ionization of the hydroxyl proton of ethanol is +90.8 kJ mol^{-1}, a much more endergonic (and hence even less favorable) process. These calculations reflect the fact that ethanol is much less acidic than acetic acid. Figure 3.3 depicts the magnitude of these energy changes in a relative sense.

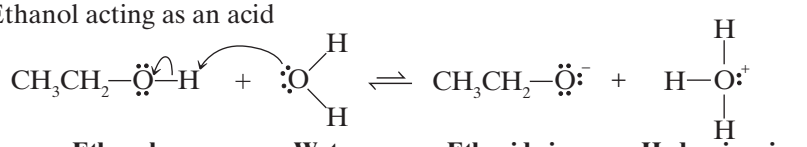
How do we explain the much greater acidity of carboxylic acids than alcohols? Consider first the structural changes that occur if both acetic acid and ethanol act as acids by donating a proton to water.

Acetic acid acting as an acid



Acetic acid **Water** **Acetate ion** **Hydronium ion**

Ethanol acting as an acid



Ethanol **Water** **Ethoxide ion** **Hydronium ion**

What we need to focus on is the relative stability of the conjugate bases derived from a carboxylic acid and an alcohol. This is because the smaller free-energy change for ionization of a carboxylic acid (e.g., acetic acid) as compared to an

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alcohol (e.g., ethanol) has been attributed to greater stabilization of the negative charge in the carboxylate ion as compared to an alkoxide ion. Greater stabilization of the carboxylate ion appears to arise from two factors: (a) **Resonance effects** or delocalization of charge (as depicted by resonance structures for the carboxylate ion), and (b) **Inductive electron-withdrawing effect**. Although both effects make a contribution to the greater acidity of carboxylic acids, the question as to which effect is more important, as we shall see, has not been resolved.

3.11A The Resonance Effect

For many years, the greater acidity of carboxylic acids was attributed primarily to **resonance stabilization of the carboxylate ion**. This explanation invokes a principle of resonance theory that states that molecules and ions *are stabilized by resonance* especially *when the molecule or ion can be represented by two or more* **equivalent** *resonance structures (i.e., by resonance structures of equal stability).*

Two resonance structures can be written for a carboxylic acid and two for its anion (Fig. 3.4), and it can be assumed that *resonance stabilization of the anion is greater* because the resonance structures for the anion are equivalent and because no separation of opposite charges occurs in them. Separation of opposite charges requires energy, and resonance structures that have separated charges are assumed to be less important in providing stability than those that do not. The greater stabilization of the anion of a carboxylic acid (relative to the acid itself) lowers the free energy of the anion and thereby decreases the positive free-energy change required for the ionization.

Helpful Hint: *Any factor that makes the free-energy change for the ionization of an acid less positive (or more negative) makes the acid stronger.*

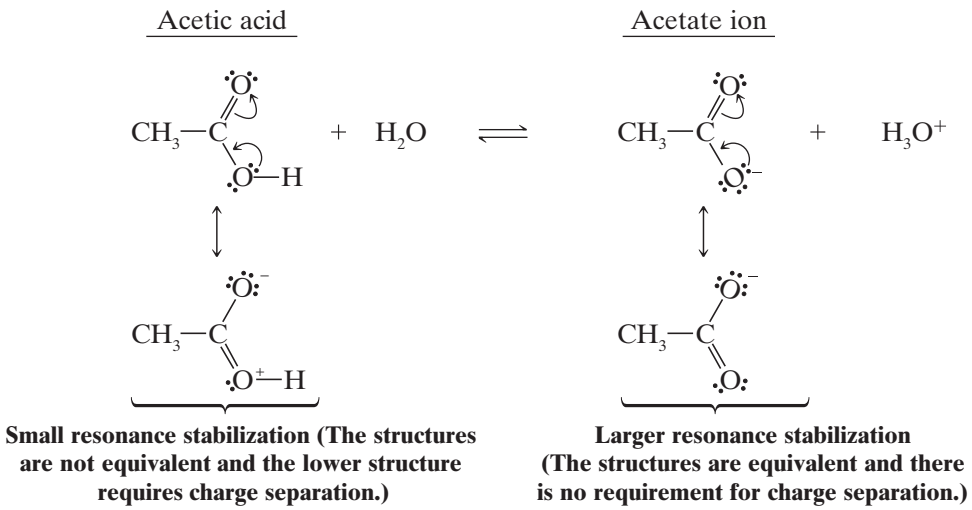

Figure 3.4 Resonance structures of carboxylic acid and carboxylate ion.

No stabilizing resonance structures are possible for an alcohol or its anion:

$$CH_3-CH_2-\ddot{O}-H \quad + H_2O \rightleftharpoons CH_3-CH_2-\ddot{O}:^- \quad + H_3O^+$$

No resonance stabilization **No resonance stabilization**

Hence, **charge delocalization is always a stabilizing factor**, and because of charge stabilization, the energy difference for formation of a carboxylate ion from a carboxylic acid is less than the energy difference for formation of an alkoxide ion from an alcohol. Since the energy difference for ionization of a carboxylic acid is less than for an alcohol, the carboxylic acid is a stronger acid.

3.11B The Inductive Effect

We have already shown how the negative charge in a carboxylate ion can be delocalized over two oxygen atoms by resonance. However, the electronegativity of these oxygen atoms further helps to stabilize the charge, by what is called an **inductive electron-withdrawing effect**. Consider the following two compounds:

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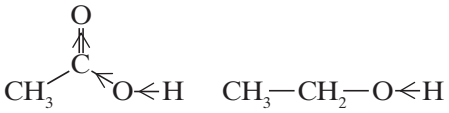
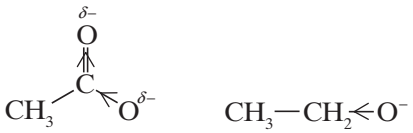


Acetic acid (stronger acid) **Ethanol (weaker acid)**

In both compounds the O–H bond is highly polarized by the greater electronegativity of the oxygen atom. The key to the much greater acidity of acetic acid, in this explanation, is the powerful electron-attracting inductive effect of its carbonyl group (C=O group) when compared with the CH_2 group in the corresponding position of ethanol. The carbonyl group is highly polarized. The carbonyl carbon of acetic acid has a significant positive change as compared to the CH_2 carbon of ethanol. Because the carbon atom of the carbonyl group of acetic acid bears a large positive charge, it adds its electron-attracting inductive effect to that of the oxygen atom of the hydroxyl group attached to it; *these combined effects make the carboxylic acid proton more positive than the proton of the alcohol.* This greater positive charge on the proton of the carboxylic acid helps explain why the proton separates more readily.

Further explanation of the acidity of carboxylic acids relates to the relative stability of the conjugate bases of carboxylic acids and alcohols. The electron-attracting inductive effect of the carbonyl group stabilizes the acetate ion that forms from acetic acid, and therefore the acetate ion is a weaker base than the ethoxide ion.



Acetate anion Weaker base **Ethoxide anion Stronger base**

The ability of acetate to stabilize the negative charge better than ethoxide. The negative charge in the acetate anion is evenly distributed over the two oxygens, as compared to ethoxide, where the negative charge is localized on its oxygen. The ability to better stabilize the negative charge is what makes acetate a weaker base than ethoxide (and hence its conjugate acid stronger than ethanol).

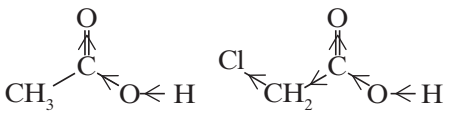
Helpful Hint: The greater acidity of a carboxylic acid is predominantly due to the ability of its conjugate base (a carboxylate ion) to stabilize a negative charge better than an alkoxide ion, the conjugate base of an alcohol.

Practice Problem 3.15

Draw contributing resonance structures and a hybrid resonance structure that explain two related facts: The carbon–oxygen bond distances in the acetate ion are the same, and the oxygens of the acetate ion bear equal negative charges.

3.11C Inductive Effects of Other Groups

The acid-strengthening effect of other electron-attracting groups (other than the carbonyl group) can be shown by comparing the acidities of acetic acid and chloroacetic acid:



$pK_a = 4.75$ **$pK_a = 2.86$**

This is an example of a **substituent effect**. The greater acidity of chloroacetic acid can be attributed, in part, to the extra electron-attracting inductive effect of the electronegative chlorine atom. By adding its inductive effect to that of the carbonyl group and the oxygen, it makes the hydroxyl proton of chloroacetic acid even more positive than that

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of acetic acid. It also stabilizes the chloroacetate ion that is formed when the proton is lost *by dispersing its negative charge* (Fig. 3.5):

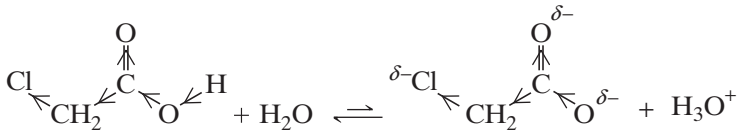
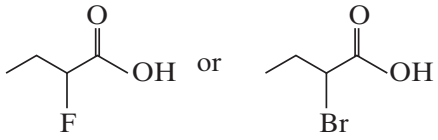


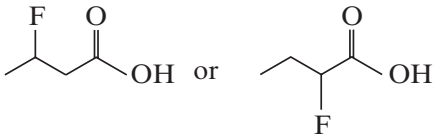
Figure 3.5 Stability of chloroacetate ions due to dispersal of negative charge.

Dispersal of charge always makes a species more stable, and, as we have seen now in several instances, **any factor that stabilizes the conjugate base of an acid increases the strength of the acid**. (In a later section, we shall see that entropy changes in the solvent are also important in explaining the increased acidity of chloroacetic acid.)

Solved Problem 3.5

Which compound in each pair would be most acidic?

(a) 

(b) 

Answer

(a) The difference is the halogen substituent on carbon 2. In the first example it is fluorine; in the second it is bromine. Fluorine is much more electronegative (electron-attracting) than bromine; therefore it will be able to disperse the negative charge of the anion formed when the proton is lost. Thus the first compound will be the stronger acid.

(b) The difference is the position of the fluorine substituents. In the second compound the fluorine is closer to the carboxyl group where it will be better able to disperse the negative charge in the anion formed when the proton is lost. The second compound will be the stronger acid.

Practice Problem 3.16

Which would you expect to be the stronger acid? Explain your reasoning in each instance.

(a) CH_2ClCO_2H or $CHCl_2CO_2H$

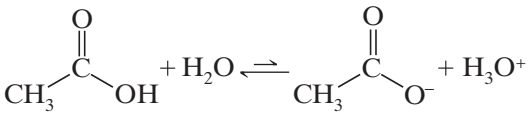
(b) CCl_3CO_2H or $CHCl_2CO_2H$

(c) CH_2FCO_2H or CH_2BrCO_2H

(d) CH_2FCO_2H or $CH_2FCH_2CO_2H$

3.12 | THE EFFECT OF THE SOLVENT ON ACIDITY

In the absence of a solvent (i.e., in the gas phase), most acids are far weaker than they are in solution. In the gas phase, for example, acetic acid is estimated to have a pK_a of about 130 ($K_a \sim 10^{-130}$)! The reason is this: When an acetic acid molecule donates a proton to a water molecule in the gas phase, the ions that are formed are oppositely charged particles and the particles must become separated:



In the absence of a solvent, separation is difficult. In solution, solvent molecules surround the ions, insulating them from one another, stabilizing them, and making it far easier to separate them than in the gas phase.

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In a solvent such as water, called a protic solvent, solvation by hydrogen bonding is important.

- A **protic solvent** is one that has a hydrogen atom attached to a strongly electronegative element such as oxygen or nitrogen.

Molecules of a protic solvent, therefore, can form hydrogen bonds to the unshared electron pairs of oxygen (or nitrogen) atoms of an acid and its conjugate base, but they may not stabilize both equally.

Consider, for example, the ionization of acetic acid in aqueous solution. Water molecules solvate both the undissociated acid (CH_3CO_2H) and its anion ($CH_3CO_2^-$) by forming hydrogen bonds to them. However, hydrogen bonding to $CH_3CO_2^-$ is much stronger than to CH_3CO_2H because the water molecules are more attracted by the negative charge. This differential solvation, moreover, has important consequences for the entropy change that accompanies the ionization. **Solvation of any species decreases the entropy of the solvent because the solvent molecules become much more ordered as they surround molecules of the solute**. Because solvation of $CH_3CO_2^-$ is stronger, the solvent molecules become more orderly around it. The entropy change ($\Delta S°$) for the ionization of acetic acid, therefore, is negative. This means that the $T\Delta S°$ term in the equation $\Delta G° = \Delta H° - T\Delta S°$ makes an acid-weakening positive contribution to $\Delta G°$. In fact, as Table 3.2 shows, the $T\Delta S°$ term contributes more to the value of $\Delta G°$ than does $\Delta H°$, and accounts for the fact that the free-energy change for the ionization of acetic acid is positive (unfavorable).

Table 3.2 Thermodynamic values for the dissociation of acetic and chloroacetic acids in H_2O at 25°C

Acid	pK_a	$\Delta G°$ (kJ mol^{-1})	=	$H°$ (kJ mol^{-1})	–	$T\Delta S°$ (kJ mol^{-1})
CH_3CO_2H	4.75	+27		–0.4		28
$ClCH_2CO_2H$	2.86	+16		–4.6		21

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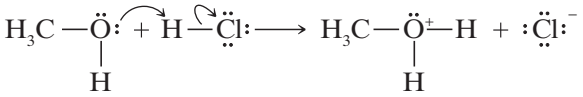
In a previous section, we discussed that chloroacetic acid is a stronger acid than acetic acid, and we attributed this increased acidity to the presence of the electron-withdrawing chlorine atom. Table 3.2 shows us that both $\Delta H°$ and $T\Delta S°$ are more favorable for the ionization of chloroacetic acid ($\Delta H°$ is more negative by 4.2 kJ mol^{-1}, and $T\Delta S°$ is less negative by 7 kJ mol^{-1}). The larger contribution is clearly in the entropy term. Apparently, by stabilizing the chloroacetate anion, the chlorine atom makes the chloroacetate ion less prone to cause an ordering of the solvent because it requires less stabilization through solvation.

3.13 | ORGANIC COMPOUNDS AS BASES

If an organic compound contains an atom with an unshared electron pair, it is a potential base. We saw in a previous section that compounds with an unshared electron pair on a nitrogen atom (i.e., amines) act as bases. Let us now consider several examples in which organic compounds having an unshared electron pair on an oxygen atom act in the same way.

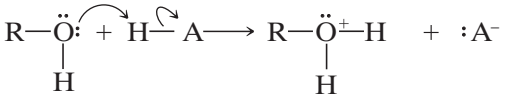
Dissolving gaseous HCl in methanol brings about an acid–base reaction much like the one that occurs with water:



Methanol — **Methyloxonium ion (a protonated alcohol)**

The conjugate acid of the alcohol is often called a **protonated alcohol**, although more formally it is called an **alkyloxonium ion** or simply an **oxonium ion**.

Alcohols, in general, undergo this same reaction when they are treated with solutions of strong acids such as HCl, HBr, HI, and H_2SO_4:



Alcohol — **Strong acid** — **Alkyloxonium ion** — **Weak base**

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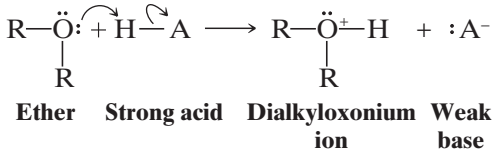
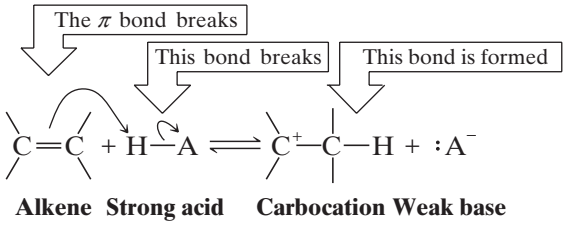
So, too, do ethers:



Compounds containing a carbonyl group also act as bases in the presence of a strong acid:

Proton transfer reactions like these are often the first step in many reactions that alcohols, ethers, aldehydes, ketones, esters, amides, and carboxylic acids undergo. The pK_a values for some of these protonated intermediates are given in Table 3.1.

An atom with an unshared electron pair is not the only locus that confers basicity on an organic compound. The π bond of an alkene can have the same effect. Later we shall study many reactions in which, as a first step, alkenes react with a strong acid by accepting a proton in the following way:



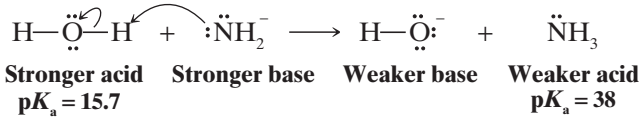
In this reaction the electron pair of the π bond of the alkene is used to form a bond between one carbon of the alkene and the proton donated by the strong acid. Notice that two bonds are broken in this process: the π bond of the double bond and the bond between the proton of the acid and its conjugate base. One new bond is formed: a bond between a carbon of the alkene and the proton. This process leaves the other carbon of the alkene trivalent, electron deficient, and with a formal positive charge. A compound containing a carbon of this type is called a **carbocation**. As we shall see in later chapters, carbocations are unstable intermediates that react further to produce stable molecules.

Practice Problem 3.17

It is a general rule that any organic compound containing oxygen, nitrogen, or a multiple bond will dissolve in concentrated sulfuric acid. Explain the basis of this rule in terms of acid–base reactions and intermolecular forces.

3.14 | ACIDS AND BASES IN NONAQUEOUS SOLUTIONS

If you were to add sodium amide ($NaNH_2$) to water in an attempt to carry out a reaction using the amide ion (NH_2^-) as a very powerful base, the following reaction would take place immediately:



The amide ion would react with water to produce a solution containing hydroxide ion (a much weaker base) and ammonia. This example illustrates what is called the **leveling effect** of the solvent. *Water*, the solvent here, *donates a proton to any base stronger than a hydroxide ion*. Therefore, *it is not possible to use a base stronger than hydroxide ion in aqueous solution*.

We can use bases stronger than hydroxide ion, however, if we choose solvents that are weaker acids than water. We can use amide ion (e.g., from $NaNH_2$) in a solvent such as hexane, diethyl ether, or liquid NH_3 (the liquified gas, bp –33°C, not the aqueous solution that you may have used in your general chemistry laboratory). All of these solvents are very weak acids (we generally don't think of them as acids), and therefore they will not donate a proton even to the strong base NH_2^-.

We can, for example, convert ethyne to its conjugate base, a carbanion, by treating it with sodium amide in liquid ammonia:

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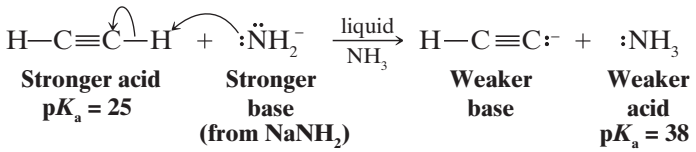
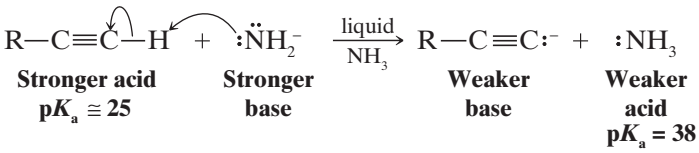
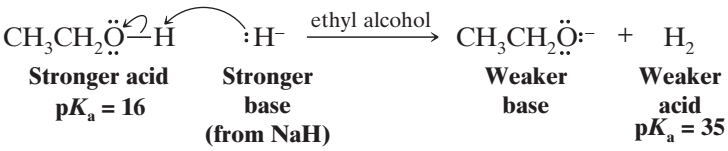


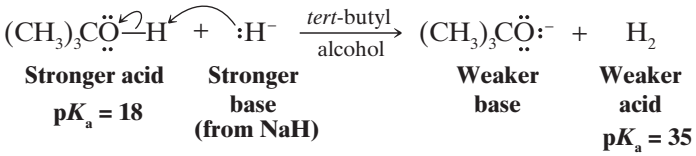
Most **terminal alkynes** (alkynes with a proton attached to a triply bonded carbon) have pK_a values of about 25; therefore, all react with sodium amide in liquid ammonia in the same way that ethyne does. The general reaction is



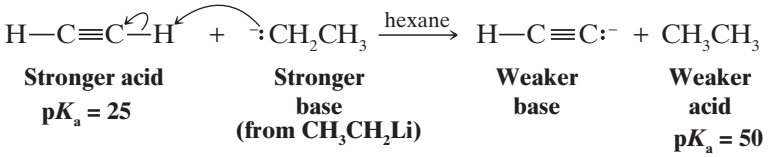
Alcohols are often used as solvents for organic reactions because, being somewhat less polar than water, they dissolve less polar organic compounds. Using alcohols as solvents also offers the advantage of using RO^- ions (called **alkoxide ions**) as bases. Alkoxide ions are somewhat stronger bases than hydroxide ions because alcohols are weaker acids than water. For example, we can create a solution of sodium ethoxide (CH_3CH_2ONa) in ethyl alcohol by adding sodium hydride (NaH) to ethyl alcohol. We use a large excess of ethyl alcohol because we want it to be the solvent. Being a very strong base, the hydride ion reacts readily with ethyl alcohol:



The *tert*-butoxide ion, $(CH_3)_3CO^-$, in *tert*-butyl alcohol, $(CH_3)_3COH$, is a stronger base than the ethoxide ion in ethyl alcohol, and it can be prepared in a similar way:



Although the carbon–lithium bond of an alkyllithium (RLi) has covalent character, it is polarized so as to make the carbon negative: $\overset{\delta-}{R} \leftarrow \overset{\delta+}{Li}$. Alkyllithium reagents react as though they contain alkanide ($R:^-$) ions and, being the conjugate bases of alkanes, alkanide ions are the strongest bases that we shall encounter. Ethyllithium (CH_3CH_2Li), for example, acts as though it contains an ethanide ($CH_3CH_2:^-$) carbanion. It reacts with ethyne in the following way:



Alkyllithiums can be easily prepared by allowing an alkyl bromide to react with lithium metal in an ether solvent (such as diethyl ether).

Practice Problem 3.18

Write equations for the acid–base reaction that would occur when each of the following compounds or solutions are mixed. In each case label the stronger acid and stronger base, and the weaker acid and weaker base, by using the appropriate pK_a values (Table 3.1). (If no appreciable acid–base reaction would occur, you should indicate this.)

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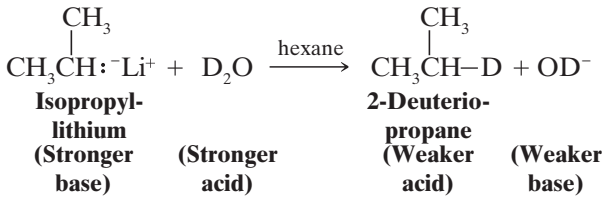
(a) NaH is added to CH_3OH.
(b) $NaNH_2$ is added to CH_3CH_2OH.
(c) Gaseous NH_3 is added to ethyllithium in hexane.
(d) NH_4Cl is added to sodium amide in liquid ammonia.
(e) $(CH_3)_3CONa$ is added to H_2O.
(f) NaOH is added to $(CH_3)_3COH$.

3.15 | ACID–BASE REACTIONS AND THE SYNTHESIS OF DEUTERIUM- AND TRITIUM-LABELED COMPOUNDS

Chemists often use compounds in which deuterium or tritium atoms have replaced one or more hydrogen atoms of the compound as a method of "labeling" or identifying particular hydrogen atoms. Deuterium (^2H) and tritium (^3H) are isotopes of hydrogen with masses of 2 and 3 atomic mass units (amu), respectively.

For most chemical purposes, deuterium and tritium atoms in a molecule behave in much the same way that ordinary hydrogen atoms behave. The extra mass and additional neutrons associated with a deuterium or tritium atom often make its position in a molecule easy to locate by certain spectroscopic methods. Tritium is also radioactive, which makes it very easy to locate. (The extra mass associated with these labeled atoms may also cause compounds containing deuterium or tritium atoms to react more slowly than compounds with ordinary hydrogen atoms. This effect, called an "isotope effect," has been useful in studying the mechanisms of many reactions.)

One way to introduce a deuterium or tritium atom into a specific location in a molecule is through the acid–base reaction that takes place when a very strong base is treated with D_2O or T_2O (water that has deuterium or tritium in place of its hydrogens). For example, treating a solution containing $(CH_3)_2CHLi$ (isopropyllithium) with D_2O results in the formation of propane labeled with deuterium at the central atom:

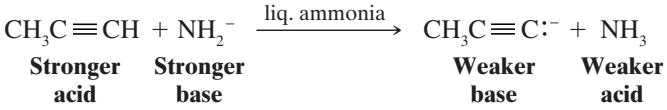


Solved Problem 3.6

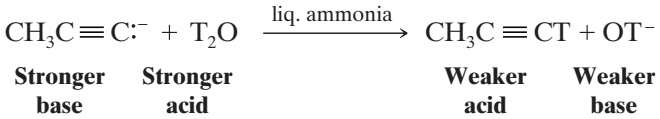
Assuming you have available propyne, a solution of sodium amide in liquid ammonia, and T_2O, show how you would prepare the tritium-labeled compound $CH_3C{\equiv}CT$.

Answer

First add propyne to sodium amide in liquid ammonia. The following acid–base reaction will take place:



Then adding T_2O (a much stronger acid than NH_3) to the solution will produce $CH_3C{\equiv}CT$:



Practice Problem 3.19

Complete the following acid–base reactions:

(a) $HC{\equiv}CH + NaH \xrightarrow{\text{hexane}}$
(b) The solution obtained in **(a)** $+ D_2O \rightarrow$
(c) $CH_3CH_2Li + D_2O \xrightarrow{\text{hexane}}$
(d) $CH_3CH_2OH + NaH \xrightarrow{\text{hexane}}$
(e) The solution obtained in **(d)** $+ T_2O \rightarrow$
(f) $CH_3CH_2CH_2Li + D_2O \xrightarrow{\text{hexane}}$

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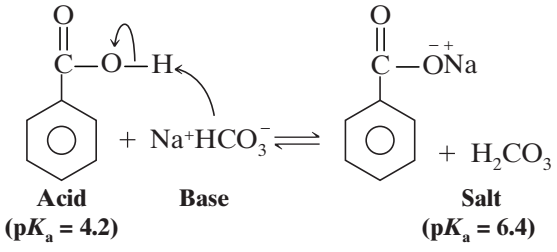
3.16 | REACTIONS OF $NaHCO_3$ AS A BASE

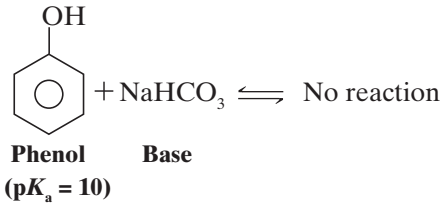
$NaHCO_3$ is used to separate a binary mixture of phenol and benzoic acid. Phenol will not react with $NaHCO_3$ because of the presence of a weakly acidic phenolic hydrogen (O<u>H</u>). Following examples explain this reaction.

1. Benzoic acid reacts with $NaHCO_3$ in the following way:



$$H_2CO_3 \rightleftharpoons H_2O + CO_2$$

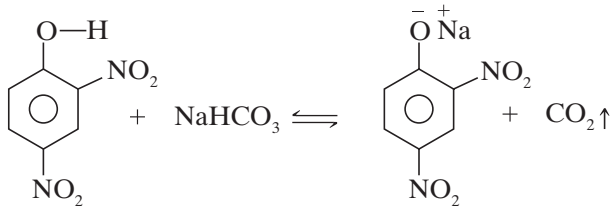
2. Phenol does not react with $NaHCO_3$.



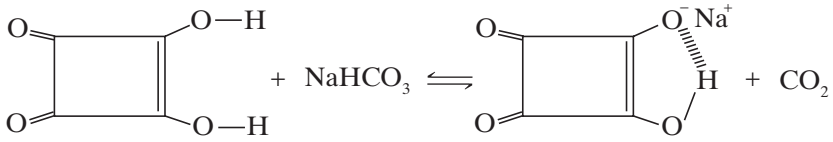
3. $Ph-\overset{O}{\overset{\|}{C}}-O-H + NaH\overset{*}{C}O_3 \rightleftharpoons Ph-\overset{O}{\overset{\|}{C}}-O^-\,Na^+ + \overset{*}{C}O_2$

($\overset{*}{C} = {}^{14}C$)

4. 2,4-Dinitrophenol reacts with $NaHCO_3$ in the following way:



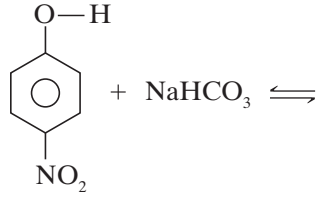
5. Squaric acid reacts with $NaHCO_3$ because both its hydrogens are quite acidic like in a carboxylic acid.



Solved Problem 3.7

Which gas is evolved in the following reactions?

1. $Ph-\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}-O-H + NaHCO_3 \rightleftharpoons$

2. 

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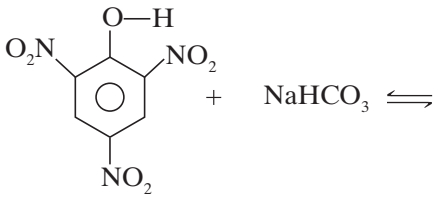
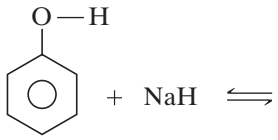
3. 

4. 

Answer

1. CO_2 **2.** CO_2 **3.** CO_2 **4.** H_2

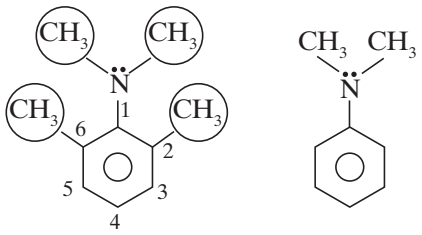
3.17 | STERIC INHIBITION OF RESONANCE (SIR) EFFECT

Restriction in exhibition of resonance due to steric hindrance is known as SIR effect.



(X) (Y)

For instance, the carbon atom of the phenyl ring and nitrogen of amino moiety lie in the same plane. When the substituents are present in 2 and 6 positions, this coplanarity is inhibited and the lone pair of nitrogen is not involved in resonance. Next, consider compounds (P) and (Q)

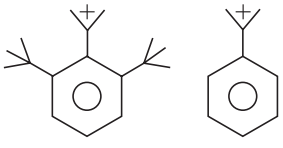


(P) (Q)

In compound (P) due to steric hindrance across nitrogen, bond rotation across C1 and nitrogen will be hindered and the lone pair of electrons on nitrogen is configured perpendicular to ring thereafter, will not be involved in resonance with the phenyl ring. As a result, the compound (P) is more basic than compound (Q), because the lone pair of nitrogen is not involved in resonance in (P).

Solved Problem 3.8

Compare the stabilities in the following pair of carbocations.



(A) (B)

Answer

Carbocation (B) is more stable than (A) because structure of (B) is resonance stabilized. Resonance is not possible in cation (A) because of steric inhibition.

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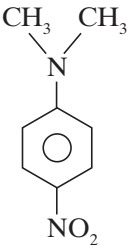
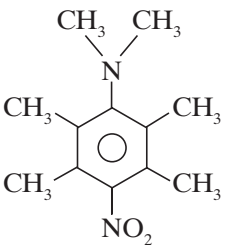
SIR can affect dipole moment of the compounds as shown in the following examples:

1.

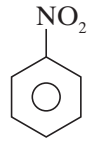


$\mu = 6.87$ D

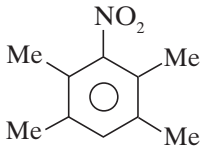


$\mu = 4.11$ D

2.

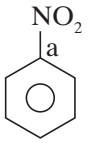


$\mu = 3.95$ D

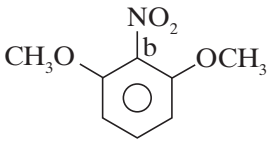


$\mu = 3.39$ D

SIR can also affect bond length. This is shown in the following examples.



(X)



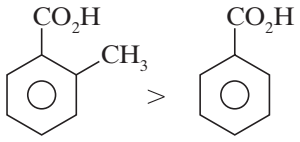
(Y)

Bond lengths of C–N are of the order b > a because of the SIR effect in compound (Y). NO_2 group will not participate in resonance with the phenyl ring in (Y) and, therefore, the bond b retains single bond character. But, NO_2 group is involved in resonance with phenyl ring lending double bond character to bond a. Nitrogen and phenyl ring being coplanar; therefore, resonance will take place.

3.18 | ORTHO AND PARA EFFECTS

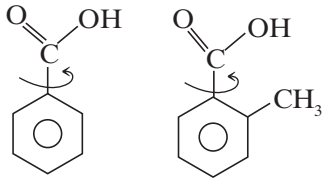
Basic concepts of resonance, steric effect and steric inhibition of resonance have been widely used for interpreting reactivities of crowded conjugated molecules. Ortho and para effects are helpful in inferring the following:

1. Ortho-substituted benzoic acid is stronger than benzoic acid.



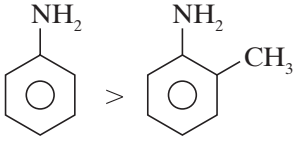
Benzoic acid **o-Toluic acid**

The explanation in case of benzoic acid is given as follows:



Due to steric crowding between carboxylic and the methyl group (+M effect will not operate), the bond rotation across the phenyl ring and carboxylic group is checked, and the two groups are held perpendicular to each other; as such, resonance does not take place between them. The inhibition of +M effect in o-toluic acid, makes it a stronger acid compared to benzoic acid.

2. Ortho-substituted aniline is a weaker base than aniline.



Aniline ***o*-Toluidine**

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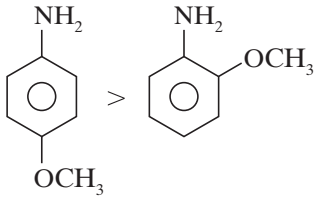
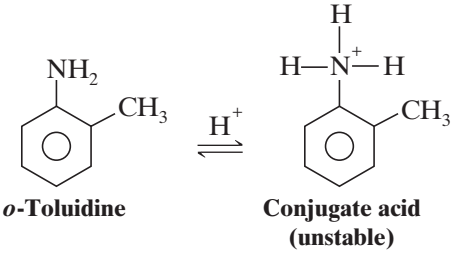
3. Para-substituted aniline is a stronger base than aniline.





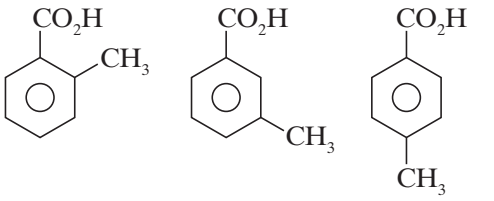
***o*-Toluidine** **Conjugate acid (unstable)**

Increase in the bond angle of H–N–H leads to increase in steric hindrance; therefore, the conjugate acid of the substituted aniline is unstable. This hinders the protonation of amino group. Thus, ortho effect of aniline is also known as steric inhibition of protonation (SIP). However, the ortho effect of aniline will not operate when the *o*–substituent in aniline are –OH and $-OCH_3$.

Solved Problem 3.9

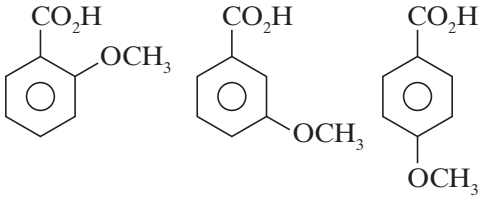
Compare acid strength of the following sets of compounds:

1.



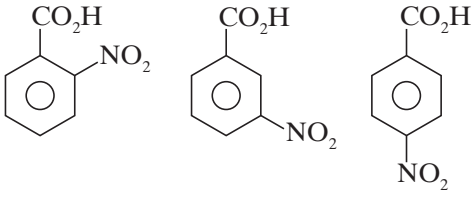
(A) (B) (C)

2.



(A) (B) (C)

3.



(A) (B) (C)

Answer

1. A > B > C

Ortho effect — **+I effect** — **+H effect**

2. A > B > C

Ortho effect — **–I effect of $-OCH_3$** — **+M effect of $-OCH_3$**

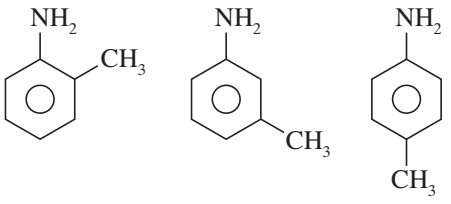
3. A > C > B

Ortho effect — **–M effect of $-NO_2$ (para is more acidic)** — **–I effect**

Solved Problem 3.10

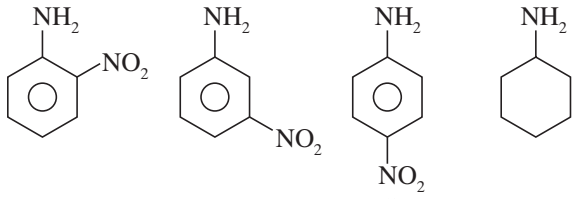
Compare base strength of the following sets of compounds:

1.



(A) (B) (C)

2.



(A) (B) (C) (D)

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Answer

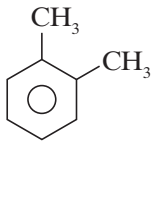
1. C > B > A
(C: +H effect; B: +I effect; A: Ortho effect)

2. D > B > C > A
(D: Lone pair is not involved in resonance; B: –I effect of NO_2; C: –R effect of $–NO_2$; A: Ortho effect)

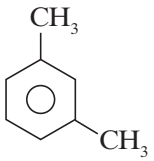
3.18A Structure of Compounds and Acid Strength

Case I

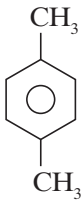
When the phenyl ring has substituent groups showing hyperconjugation (+H) and inductive (+I) effects. Consider, for example the following set of alkyl-substituted benzenes.



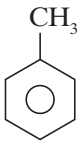
***o*-Xylene**



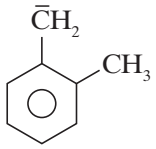
***m*-Xylene**



Toluene

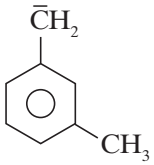


***p*-Xylene**



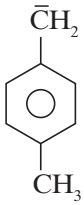
(A)

Resulting carbanion is destabilized by hyperconjugation and +I effects. (+I is maximum in this case)



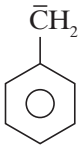
(B)

Resulting carbanion is destabilized by +I effect



(C)

Resulting carbanion is destabilized by hyperconjugation and +I effects. (+I is minimum in this case)



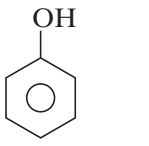
(D)

Resulting carbanion is stabilized carbanion

D > B > C > A
Acid strength

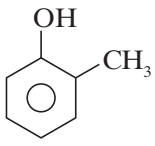
More stable the conjugate base, the more will be the acidic strength. Thus, the acid strength in the above example follows the order:

Another example is the following set of phenols:



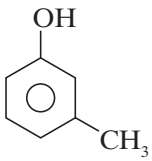
Phenol

(A)



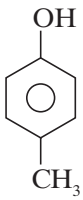
***o*-Cresol**

(B)



***m*-Cresol**

(C)



***p*-Cresol**

(D)

In this case, acidic strength follows the order: A > C > D > B

Case II

When the phenyl ring has substituent groups showing –M and –I effects.

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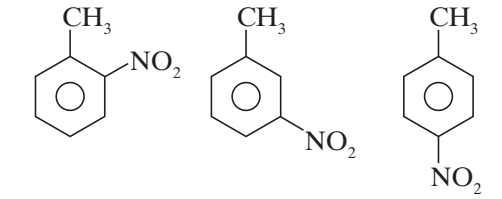
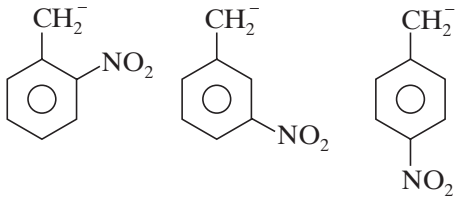
For example, the following set of nitrotoluenes



o-Nitrotoluene **m-Nitrotoluene** **p-Nitrotoluene**



(A) **(B)** **(C)**

Carbanion stabilized by – R of NO_2 – I of NO_2 (– I is maximum)

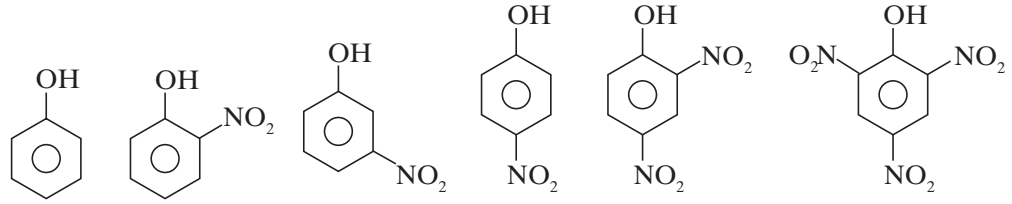
Carbanion stabilized by (– I) effect of NO_2 only

Carbanion stabilized by – R of NO_2 – I of NO_2 (– I is minimum)

Thus, acidic strength follows the order:

$$A > C > B$$

Another example is the following set of nitrophenols



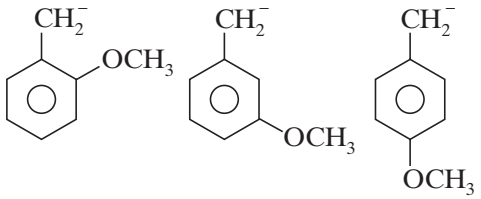
(A) **(B)** **(C)** **(D)** **(E)** **(F)**

Here, the order of acid strength will be: F > E > D > B > C > A

The ortho isomer (B) is less acidic than the para isomer (D) due to intramolecular hydrogen bonding.

Case III

When the phenyl ring has substituent groups showing +R and –I effects. Consider, for example, the following compounds.



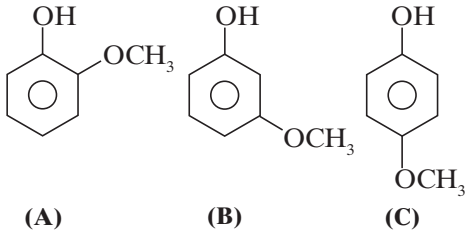
(A) **The anion destabilized by R effect of OCH_3 and stabilized by –I effect of OCH_3 (–I is maximum)**

(B) **The anion stabilized by –I effect of OCH_3**

(C) **The anion destabilized by +R effect of OCH_3 and stabilized by –I effect of OCH_3 (–I effect is minimum)**

Thus, the acidic strength follows the order: B > A > C.

Next, consider the following compounds:



(A) **(B)** **(C)**

Here the acidic strength follows the order: B > A > C

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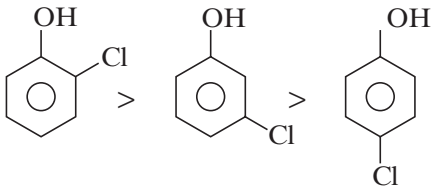
Case IV

When the phenyl ring has a halogen substituent which shows –I effect and this effect is greater than +R effect.



***o*-Chlorophenol** ***m*-Chlorophenol** ***p*-Chlorophenol**

Here, the –I effect is maximum in the *ortho* isomer and minimum in the *para* isomer. Tables 3.3–3.25 explain the inductive effect on the properties of compounds.

Table 3.3 Inductive effect of substituent groups of some substituted acetic acids

Acid	pK_a	I effect of the substituent
$\boxed{H}-CH_2-CO_2H$	4.75	H = reference point
$\boxed{CH_3}-CH_2-CO_2H$	4.90	+I
$\boxed{CH_3-O}-CH_2-CO_2H$	4.30	–I
$\boxed{I}-CH_2-CO_2H$	3.00	–I
$\boxed{Br}-CH_2-CO_2H$	2.90	–I
$\boxed{Cl}-CH_2-CO_2H$	2.80	–I
$\boxed{(CH_3)_3\overset{+}{N}}-CH_2-CO_2H$	1.80	–I

Here, –I effect ∝ Acid strength.

Table 3.4 Position of the substituent and inductive effect

Acid	pK_a	I effect of the substituent
$CH_3-CH_2-\overset{\alpha}{C}H(\boxed{Cl})-CO_2H$	2.84	–I
$CH_3-\overset{\beta}{C}H(\boxed{Cl})-\overset{\alpha}{C}H_2-CO_2H$	4.06	–I
$\overset{\gamma}{C}H_2(\boxed{Cl})-\overset{\beta}{C}H_2-\overset{\alpha}{C}H_2-CO_2H$	4.52	–1

Substituent at the α-position exerts the maximum effect.

Table 3.5 Distance between the groups and the extent of inductive effect

Acid	pK_a	I effect of the substituent
$\boxed{HO_2C}-CO_2H$	1.23	–I
$\boxed{HO_2C}-CH_2-CO_2H$	2.28	–I
$\boxed{HO_2C}-CH_2-CH_2-CO_2H$	4.19	–I

Inductive effect is distance dependent; as distance increases, inductive effect decreases.

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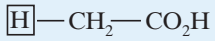
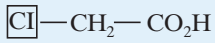
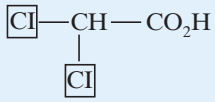
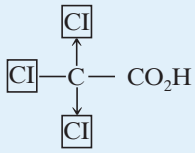
Table 3.6 Additive nature of inductive effect

Acid	pK_a	I effect of the substituent
	4.75	H = reference point
	2.86	One (–I) effect
	1.25	Two (–I) effects
	0.65	Three (–I) effects

Inductive effect is an additive effect.

Table 3.7 Aromatic acids and inductive effect

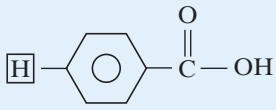
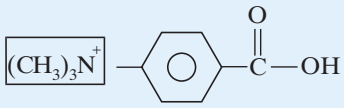
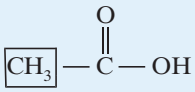
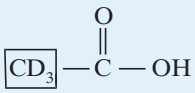
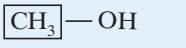
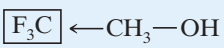
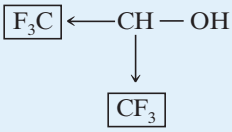
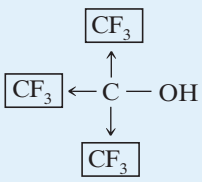
Acid	pK_a	I effect of the substituent
	4.2	H = reference point
	3.9	–I effect

Table 3.8 Isotopic substituents and inductive effect

Acid	pK_a	I effect of the substituent
	4.75	+I
	4.6	+I

+I effect of deuterium is stronger than that of hydrogen. +I ($-CD_3 > -CH_3$).

Table 3.9 Electron withdrawing groups and inductive effect

Acid	pK_a	I effect of the substituent
	15.5	+I
	12.4	–I
	9.3	–I
	5.4	–I

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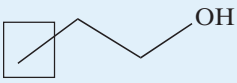
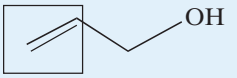
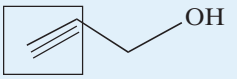
Electron withdrawing groups lower the pK_a of alcohols

Table 3.10 Hybridization state of the carbon atom in the substituent and inductive effect

Acid	pK_a	I effect of the substituent
	16	+I effect
	15.5	–I effect
	13.5	–I effect

More the *s* character of an orbital, the more strongly it holds its electrons. This makes an *sp* hybridized carbon more electron withdrawing, which affects the inductive effect accordingly. This is reflected in the pK_a values of the compounds shown above.

Table 3.11 State of hybridization and base strength

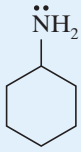
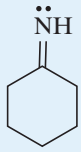
	Base	Base Strength	Comment
(a)		Decreases ↓	Lone pair on sp^3 hybridized atom is more protonating
(b)			

Table 3.12 Carbon chain length and base strength

	Base	Base Strength	Comment
(a)	CH_3-NH_2	Increases ↓	+I effect increases with the length alkyl chain and so does base strength.
(b)	$CH_3-CH_2-CH_2-NH_2$		

Table 3.13 Central atom and base strength

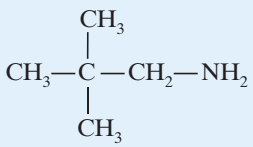
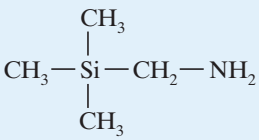
	Base	Base Strength	Comment
(a)		Increases ↓	Here, the central atom silicon being more electropositive than carbon, pushes the electron density more.
(b)			

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Table 3.14 Extent of inductive effect and base strength

	Base	Base Strength	Comment
(a)	$Cl_3C-CH_2-NH_2$	↓ Increases	–I effect ∝ (1/basic strength) –I effect of Cl_3C group in less effective in (b) than in (a)
(b)	$Cl_3C-CH_2-CH_2-NH_2$		

Table 3.15 Inductive effect and base strength

	Base	Base Strength	Comment
(a)	$F_3C-CH_2-NH_2$	↓ Increases	–I effect of $-CF_3 > -CCl_3$
(b)	$Cl_3C-CH_2-NH_2$		

Table 3.16 Delocalization of lone pair and base strength

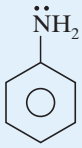
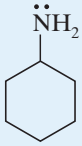
	Base	Base Strength	Comment
(a)	 **Aniline**	↓ Increases	Lone pair of electrons on nitrogen in aniline is delocalized.
(b)	 **Cyclohexylamine**		

Table 3.17 Delocalization of negative charge and base strength

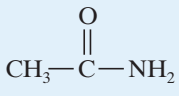
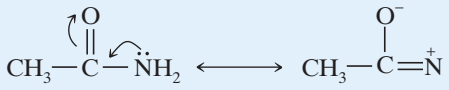
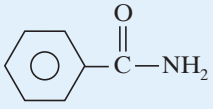
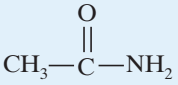
	Base	Base Strength	Comment
(a)	 **Acetamide**	↓ Increases	 **Effective delocalization of negative charge on oxygen.**
(b)	 **Benzamide**		 **– I effect decreases basic strength.**

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Table 3.18 Basic strength of pyridine and pyrrole

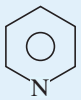
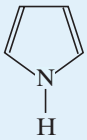
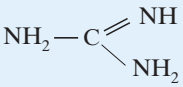
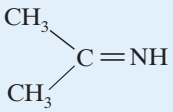
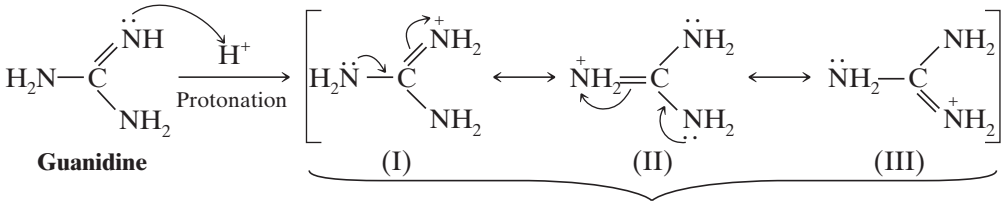
	Base	Base Strength	Comment
(a)	 **Pyridine**	Decreases ↓	Lone pair of nitrogen is delocalized in pyrrole because it is conjugated to the *p* bond. Therefore, it is not available for protonation.
(b)	 **Pyrrole**		

Table 3.19 Basic strength of guanidine and imine

	Base	Base Strength	Comment
(a)	 Guanidine	Decreases ↓	Guanidine is the strongest organic nitrogen base. On protonation, the postive charge can be delocalized over three nitrogen atoms to give a very stable cation.
(b)	 Imine		

Explanation:



All three have equal contribution in resonance hybrid. This makes guanidine the strongest base.

Table 3.20 Amine inversion and base strength

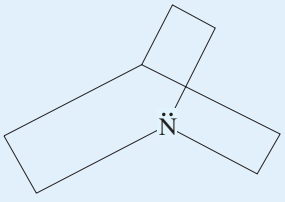
	Base	Base Strength	Comment
(a)	 Quinuclidene	Decreases ↓	Quinuclidene will not undergo amine inversion.
(b)	$Et_3\ddot{N}$ Triethylamine		

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Table 3.21 Bredt's rule and base strength

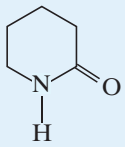
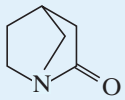
	Base	Base Strength	Comment
(a)		Increases ↓	Lone pair is not delocalized in (b) because it violates Bredt's rule.
(b)			

Table 3.22 Mesomeric effect and base strength

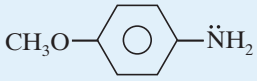
	Base	Base Strength	Comment
(a)		Decreases ↓	+M ∝ basic strength $-M \propto \frac{1}{\text{basic strength}}$
(b)			

Table 3.23 Delocalization of lone pair and base strength

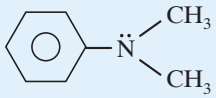
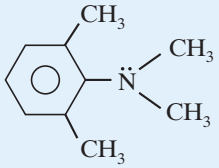
	Base	Base Strength	Comment
(a)		Increases ↓	Lone pair of electrons is not delocalized in (b) due to SIR and so it is more basic.
(b)			

Table 3.24 Ortho effect and base strength

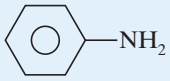
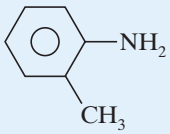
	Base	Base Strength	Comment
(a)		Decreases ↓	Base strength decreases due to ortho effect.
(b)			

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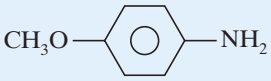
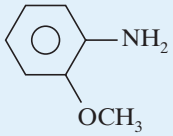
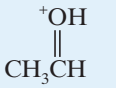
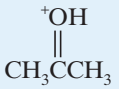
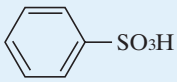
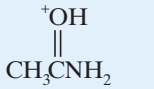
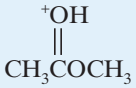
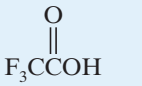
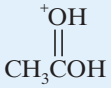
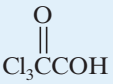
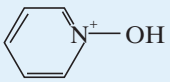
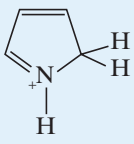
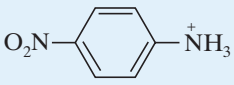
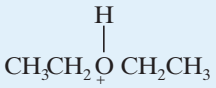
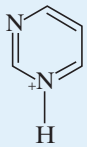
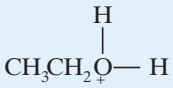
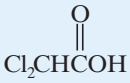
Table 3.25 Para effect and base strength

	Base	Base Strength	Comment
(a)		Decreases	Base strength decreases due to para effect.
(b)			

The pK_a values of the various compounds are given below in Table 3.26.

Table 3.26 The pK_a values of different compounds

Compound	pK_a	Compound	pK_a
HBr	–9	$CH_3C{\equiv}\overset{+}{N}H$	–10.1
	–8	HI	–10
	–7.3	CH_3SO_3H	–1.2
HCl	–7		–0.60
$CH_3\overset{+}{S}H_2$	–6.8		0.0
	–6.5		0.2
	–6.1		0.64
H_2SO_4	–5		0.79
	–3.8		1.0
	–3.6		1.0
	–2.4		1.3

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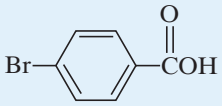
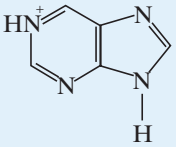
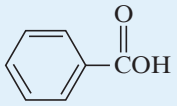
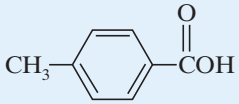
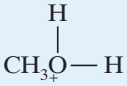
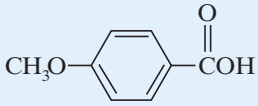
Compound	pK_a	Compound	pK_a
HSO_4^-	2.0		4.0
H_3PO_4	2.1		
	2.5		4.2
			4.3
	–2.5		4.5
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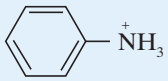
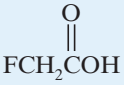
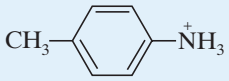
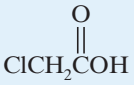
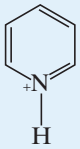
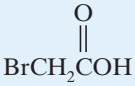
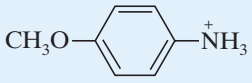
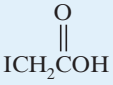
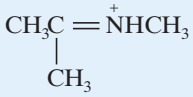
HNO_3	–1.3		4.6
	2.7		5.1
	2.8		5.2
	2.9		5.3
	3.2		5.5
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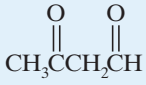
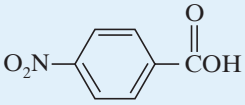
HNO_2	3.4		5.9
	3.4	$HO\overset{+}{N}H_3$	6.0
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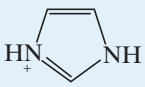
	3.8		6.8
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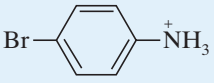
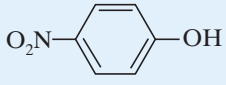
	3.9		7.1
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(*Continued*)

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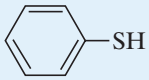
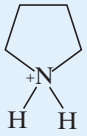
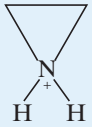
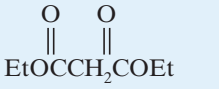
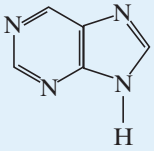
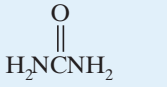
	7.8		11.3
	8.0	HPO_4^{2-}	12.3
		CF_3CH_2OH	12.4
$H_2\overset{+}{N}NH_3$	8.1		13.3
	8.9	$HC{\equiv}CCH_2OH$	13.5
			13.7
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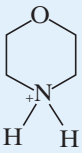
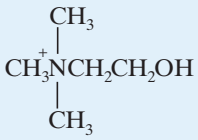
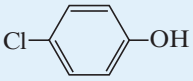
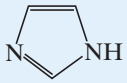
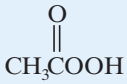
	9.3		13.9
	9.4		14.4
$\overset{+}{N}H_4$	9.4		8.2
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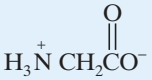	9.8	$(CH_3)_2\overset{+}{N}H_2$	10.7
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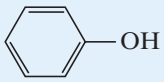
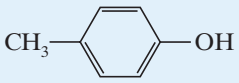
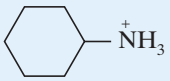
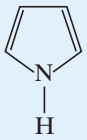
	10.0	$CH_3\overset{+}{N}H_3$	10.7
	10.2		10.7
HCO_3^-	10.2		~17
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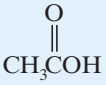
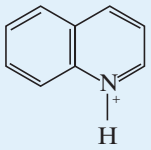
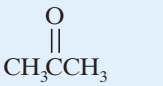
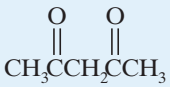
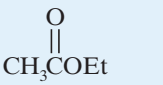
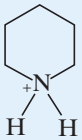
	4.8		17
	4.9	$(CH_3)_3COH$	18
			20
	8.9		24.5
		$HC{\equiv}CH$	25
	11.1	$CH_3C{\equiv}N$	25
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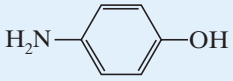
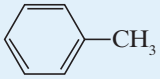
Compound	pK_a	Compound	pK_a
	10.3	CH_3NH_2	40
CH_3CH_2SH	10.5		41
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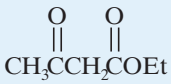	10.7		43
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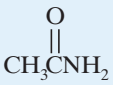
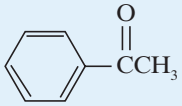
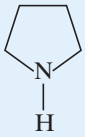
	16	$CH_2{=}CH_2$	44
	16.0		46
		CH_4	50
NH_3	36	CH_3CH_3	50
		CH_3OH	15.5
	36	H_2O	15.7
		CH_3CH_2OH	16.0

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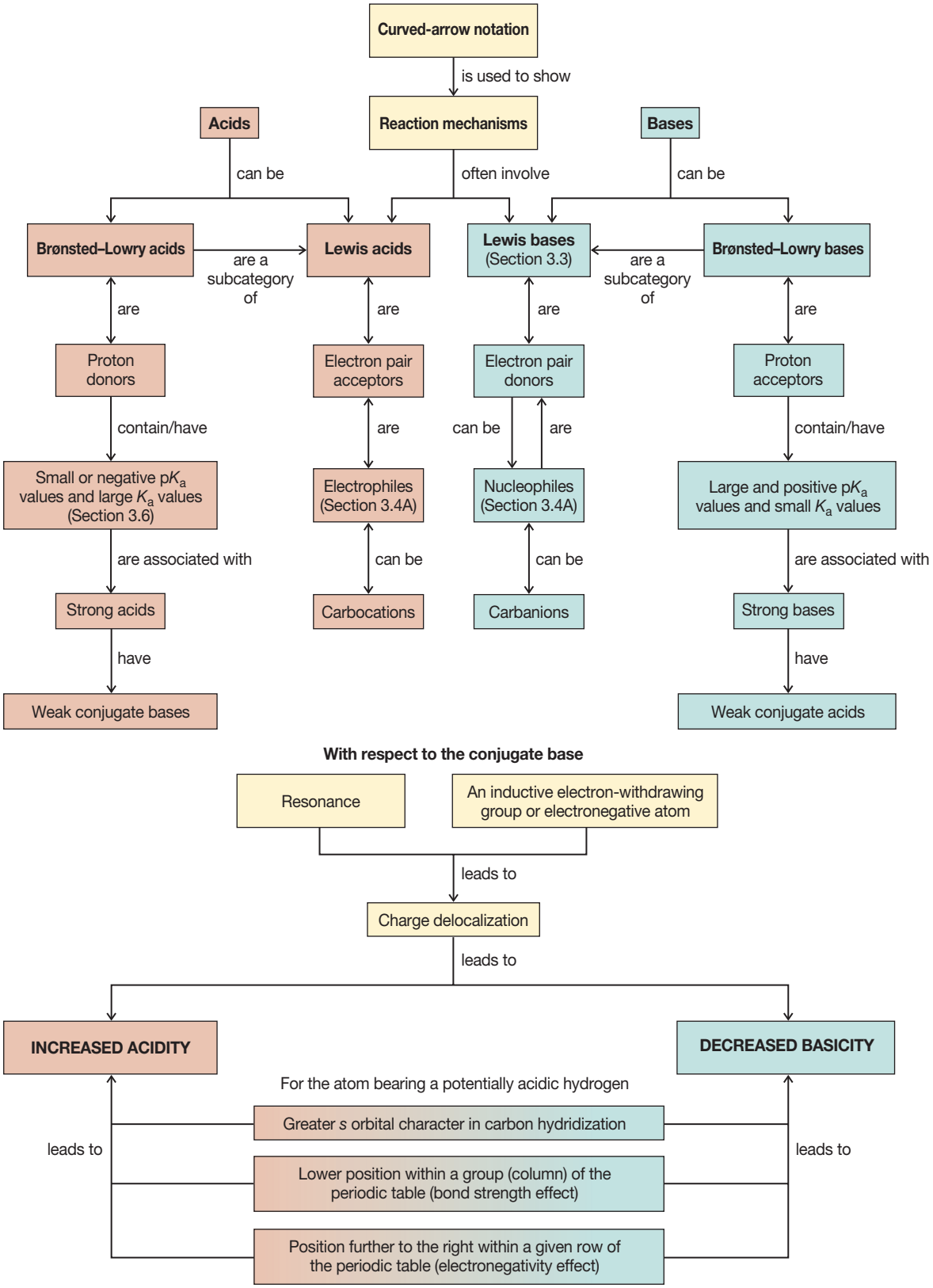
[CONCEPT MAP]



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REVIEW PROBLEMS

Bronsted–Lowry Acids and Bases

3.20 What is the conjugate base of each of the following acids?
(a) NH_3 **(b)** H_2O **(c)** H_2
(d) $HC{\equiv}CH$ **(e)** CH_3OH **(f)** H_3O^+

3.21 List the bases you gave as answers to Problem 3.20 in order of decreasing basicity.

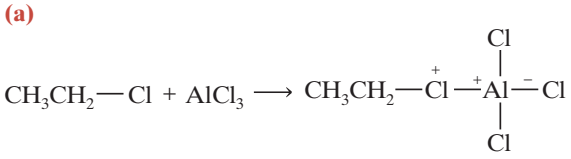
3.22 What is the conjugate acid of each of the following bases?
(a) $\mathbf{HSO_4^-}$ **(c)** CH_3NH_2 **(e)** $CH_3CH_2^-$
(b) H_2O **(d)** NH_2 **(f)** $CH_3CO_2^-$

3.23 List the acids you gave as answers to Problem 3.21 in order of decreasing acidity.

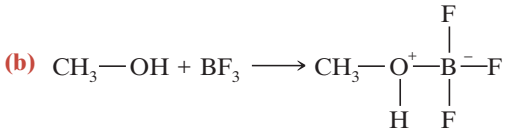
Lewis Acids and Bases

3.24 Designate the Lewis acid and Lewis base in each of the following reactions:

(a)



(b)



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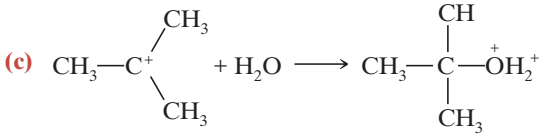


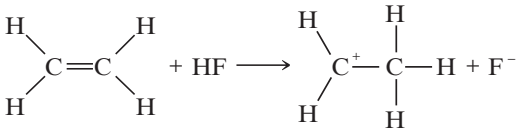
Curved-Arrow Notation

3.25 Rewrite each of the following reactions using curved arrows and show all nonbonding electron pairs:

(a) $CH_3OH + HI \rightarrow CH_3 + \overset{+}{O}H_2 + I^-$

(b) $CH_3NH_2 + HCl \rightarrow CH_3 + \overset{+}{N}H_3 + Cl^-$

(c)



Acid–Base Strength and Equilibria

3.26 When methyl alcohol is treated with NaH, the product is $CH_3O^-Na^+$ (and H_2) and not Na^+–CH_2OH (and H_2).

Explain why this is so.

3.27 What reaction will take place if ethyl alcohol is added to a solution of $HC{\equiv}C{:}^-Na^+$ in liquid ammonia?

3.28 **(a)** The K_a of formic acid (HCO_2H) is 1.77×10^{24}. What is the pK_a?
(b) What is the K_a of an acid whose $pK_a = 13$?

3.29 Acid HA has a $pK_a = 20$; acid HB has a $pK_a = 10$.
(a) Which is the stronger acid?
(b) Will an acid–base reaction with an equilibrium lying to the right take place if Na^+A^- is added to HB? Explain your answer.

3.30 Write an equation, using the curved-arrow notation, for the acid–base reaction that will take place when each of the following are mixed. If no appreciable acid–base reaction takes place, because the equilibrium is unfavorable, you should so indicate.
(a) Aqueous NaOH and $CH_3CH_2CO_2H$
(b) Aqueous NaOH and $C_6H_5SO_3H$
(c) CH_3CH_2ONa in ethyl alcohol and ethyne
(d) CH_3CH_2Li in hexane and ethyne
(e) CH_3CH_2Li in hexane and ethyl alcohol

3.31 Starting with appropriate unlabeled organic compounds, show syntheses of each of the following:
(a) $C_6H_5{-}C{\equiv}C{-}T$
(b) $CH_3{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}O{-}D$
(c) $CH_3CH_2CH_2OD$

3.32 **(a)** Arrange the following compounds in order of decreasing acidity and explain your answer: $CH_3CH_2NH_2$, CH_3CH_2OH, and $CH_3CH_2CH_3$.
(b) Arrange the conjugate bases of the acids given in part
(c) in order of increasing basicity and explain this answer.

3.33 Arrange the following compounds in order of decreasing acidity:
(a) $CH_3CH{=}CH_2$, $CH_3CH_2CH_3$, $CH_3C{\equiv}CH$
(b) $CH_3CH_2CH_2OH$, $CH_3CH_2CO_2H$, $CH_3CHClCO_2H$
(c) CH_3CH_2OH, $CH_3CH_2O{+}H_2{+}$, CH_3OCH_3

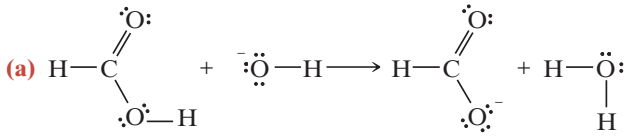
3.34 Arrange the following in order of increasing basicity:
(a) CH_3NH_2, $CH_3NH_3^+$, CH_3NH^-
(b) CH_3O^-, CH_3NH^-, $CH_3CH_2^-$
(c) $CH_3CH{=}CH^-$, $CH_3CH_2CH_2^-$, $CH_3C{\equiv}C^-$

General Problems

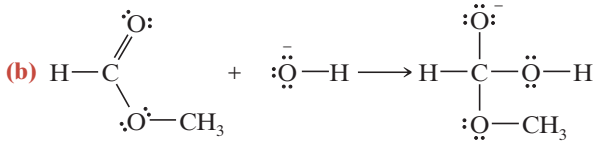
3.35 Whereas H_3PO_4 is a triprotic acid, H_3PO_3 is a diprotic acid. Draw structures for these two acids that account for this difference in behavior.

3.36 Supply the curved arrows necessary for the following reactions:

(a)



(b)



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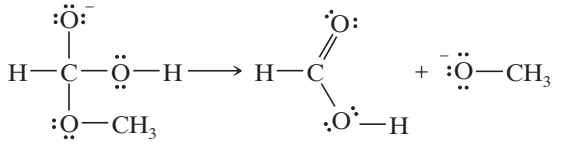
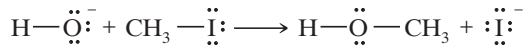
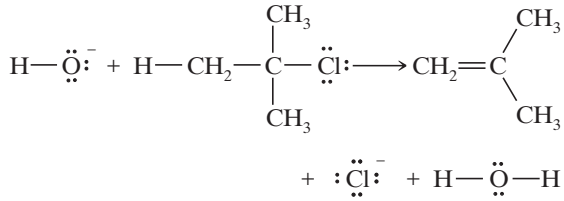
(c)



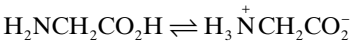
(d)



(e)



3.37 Glycine is an amino acid that can be obtained from most proteins. In solution, glycine exists in equilibrium between the two forms:



(a) Consult Table 3.1 and state which form is favored at equilibrium.

(b) A handbook gives the melting point of glycine as 262°C (with decomposition). Which structure better represents glycine?

3.38 Malonic acid, $HO_2CCH_2CO_2H$, is a diprotic acid. The pK_a for the loss of the first proton is 2.83; the pK_a for the loss of the second proton is 5.69.

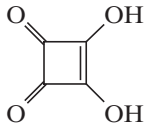
(a) Explain why malonic acid is a stronger acid than acetic acid ($pK_a = 4.75$).

(b) Explain why the anion, $^-O_2CCH_2CO_2H$, is so much less acidic than malonic acid itself.

3.39 The free-energy change, $\Delta G°$, for the ionization of acid HA is 21 kJ mol^{-1}; for acid HB it is 221 kJ mol^{-1}. Which is the stronger acid?

3.40 At 25°C the enthalpy change, $\Delta H°$, for the ionization of trichloroacetic acid is +6.3 kJ mol^{-1} and the entropy change, $\Delta S°$, is +0.0084 kJ mol^{-1} K^{-1}. What is the pK_a of trichloroacetic acid?

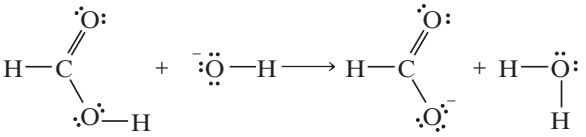
3.41 The compound below has (for obvious reasons) been given the trivial name **squaric acid.** Squaric acid is a diprotic acid, with both protons being more acidic than acetic acid. In the dianion obtained after the loss of both protons, all of the carbon–carbon bonds are the same length as well as all of the carbon–oxygen bonds. Provide a resonance explanation for these observations.



Squaric acid

3.42 $CH_3CH_2SH + CH_3O^- \longrightarrow$ A (contains sulfur) + B

(a)



$C + H_2O \longrightarrow D + E$ (which is inorganic)

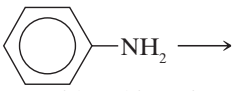
(a) Given the above sequence of reactions, draw structures for A through E.

(b) Rewrite the reaction sequence, showing all nonbonding electron pairs and using curved arrows to show electron pair movements.

3.43 First, complete and balance each of the equations below. Then, choosing among ethanol, hexane, and liquid ammonia, state which (there may be more than one) might be suitable solvents for each of these reactions. Disregard the practical limitations that come from consideration of "like dissolves like" and base your answers only on relative acidities.

(a) $CH_3(CH_2)_8OD + CH_3(CH)_2Li \rightarrow$

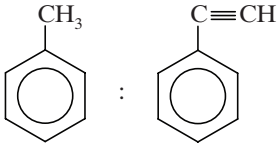
(b) $NaNH_2 + CH_3C \equiv CH \rightarrow$

(c) HCl +  $\longrightarrow$

(The conjugate acid of this amine, aniline, has pK_a 4.6.)

ADDITIONAL OBJECTIVE QUESTIONS

Single Correct Choice Type

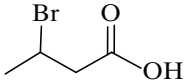
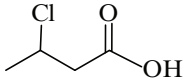


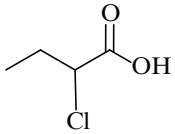
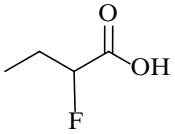
1. **(I)** **(II)**

In compound (I) and (II) inductive effect of phenyl is

(a) +I, +I **(b)** –I, +I **(c)** –I, –I **(d)** +I, –I

2. Rank the following carboxylic acids with respect to strength, listing the strongest one first.

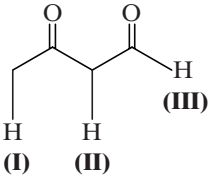
(I)  **(II)** 

(III)  **(IV)** 

(a) I > II > IV > III **(b)** I > II > III > IV

(c) III > IV > I > II **(d)** IV > III > II > I

3. Choose the order that has the indicated hydrogen atoms correctly arranged with respect to increasing acidity.



(a) (I) < (II) < (III) **(b)** (I) < (III) < (II)

(c) (III) < (I) < (II) **(d)** (II) < (III) < (I)

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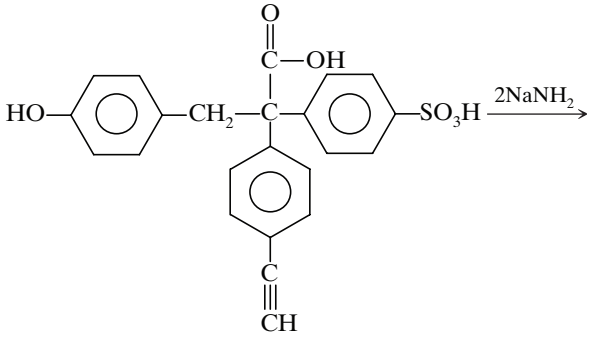
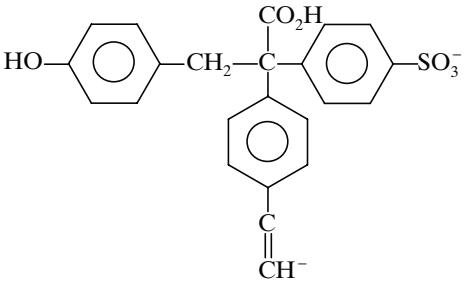
4. Which of the following is the strongest acid?

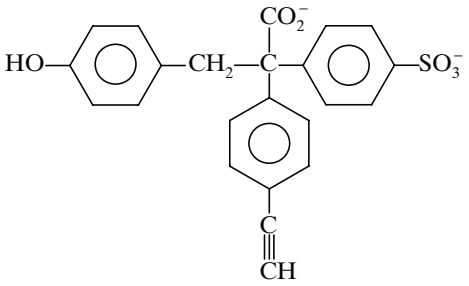
(a) $CH_3CH_2CO_2H$ **(b)** $ClCH_2CH_2CO_2H$

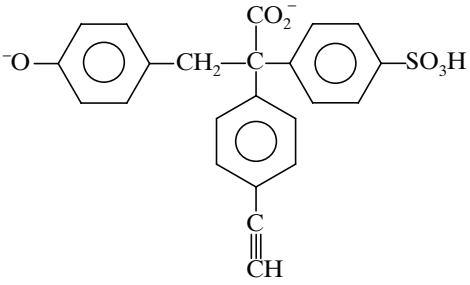
(c) $ClCH_2CO_2H$ **(d)** CH_3CO_2H

5. 

Product of the above reaction is

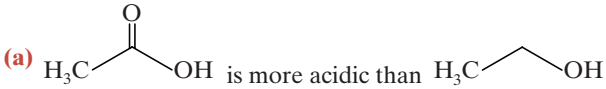
(a) 

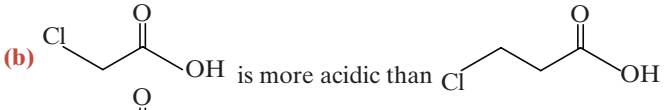
(b) 

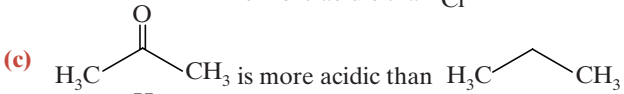
(c) 

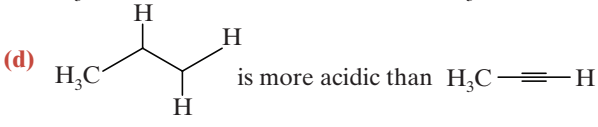
(d) None of these.

6. Shown below are five comparisons of acid strengths. Which one of the comparisons is incorrect?

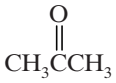
(a) 

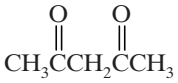
(b) 

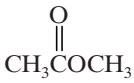
(c) 

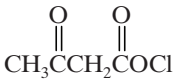
(d) 

7. Which of the following compounds has the largest pK_a?

(a) 

(b) 

(c) 

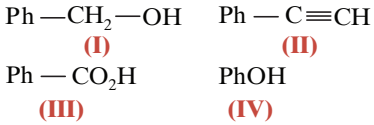
(d) 

8. When benzene sulphonic acid and *p*-nitrophenol are treated with $NaHCO_3$, the gases released, respectively, are

(a) SO_2, NO_2 **(b)** SO_2, NO

(c) SO_2, CO_2 **(d)** CO_2, CO_2

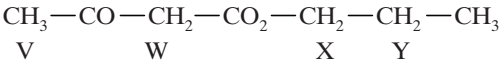
9. Compare acidic-strength of the below compounds



(a) (III) > (IV) > (II) > (I) **(b)** (III) > (II) > (IV) > (I)

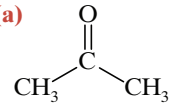
(c) (III) > (IV) > (I) > (II) **(d)** (IV) > (III) > (II) > (I)

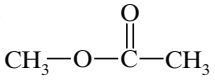
10. What is the most acidic of the hydrogens on propyl acetoacetate?

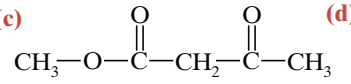


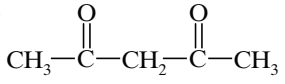
(a) V **(b)** W **(c)** X **(d)** Y

11. Which of the following compounds has the most acidic α-hydrogens?

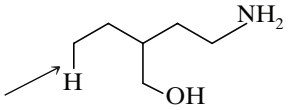
(a) 

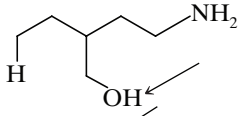
(b) 

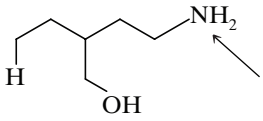
(c) 

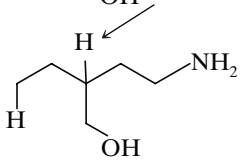
(d) 

12. Which hydrogen in the following molecule would you expect to be the most acidic (i.e., most easily removed as H^+)?

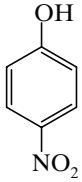
(a) 

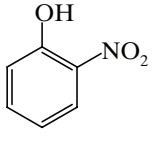
(b) 

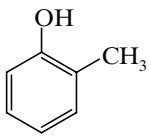
(c) 

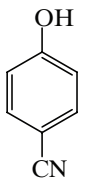
(d) 

13. Most acidic phenol derivative is

(a) 

(b) 

(c) 

(d) 

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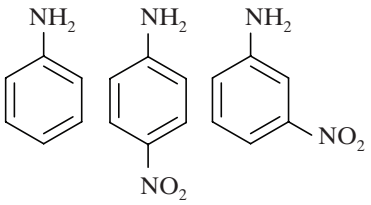
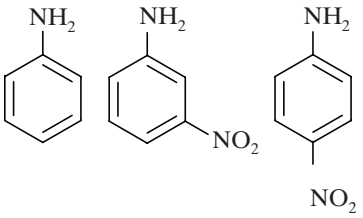
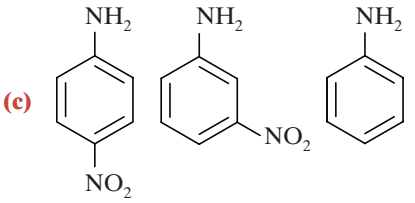
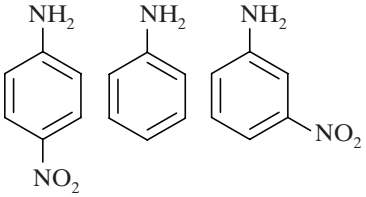
14. Choose the order that has the following compounds correctly arranged with respect to increasing basicity:

(a) 

(b) 

(c) 

(d) 

15. The correct decreasing order of basic strength of the following species is _____. H_2O, NH_3, OH^-, NH_2^-

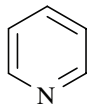
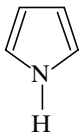
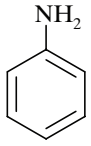
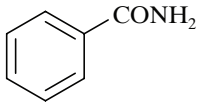
(a) $NH_2^- > OH^- > NH_3 > H_2O$

(b) $OH^- > NH_2^- > H_2O > NH_3$

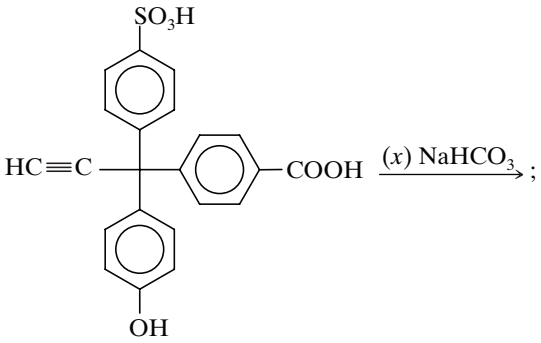
(c) $NH_3 > H_2O > NH_2^- > OH^-$

(d) $H_2O > NH_3 > OH^- > NH_2^-$

16. The compound having most basic nitrogen is

(a)  **(b)**  **(c)**  **(d)** 

Integer Type

1. 

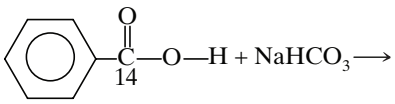
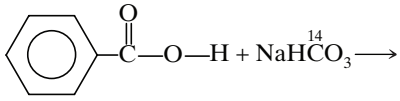
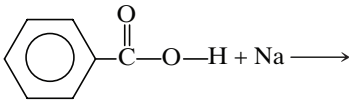
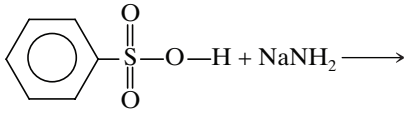
Total number of moles of $NaHCO_3$ consumed during given reaction will be (x). So the value of x will be

Matrix Match Type

1.

Column I (Acid)	Column II (pK_a)
(a) CH_3COOH	**(p)** 5.69
(b) $(CH_3)_3N^+CH_2COOH$	**(q)** 4.27
(c) $(CH_3)_3N^+(CH_2)_4COOH$	**(r)** 1.83
(d) $O_2^-C–CH_2–COOH$	**(s)** 4.80

2.

Column I	Column II
(a) 	**(p)** NH_3
(b) 	**(q)** $^{14}CO_2$
(c) 	**(r)** CO_2
(d) 	**(s)** H_2

ANSWER KEY

Single Correct Choice Type

1. (b)	**2.** (d)	**3.** (c)	**4.** (c)	**5.** (b)
6. (d)	**7.** (c)	**8.** (d)	**9.** (c)	**10.** (b)

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11. (d) **12.** (b) **13.** (a) **14.** (c) **15.** (a)
16. (a)

Integer Type

1. (2)

Matrix Match Type

1. a→(s); b→(r); c→(q); d→(p)
2. a→(r); b→(q); c→(s); d→(p)

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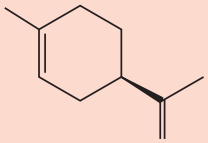
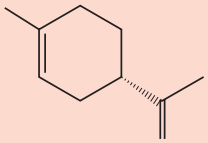
4

Stereochemistry: Chiral Molecules



(+)-Limonene (the enantiomer of limonene found in oranges)



(–)-Limonene (the enantiomer of limonene found in lemons)

We are all aware of the fact that certain everyday objects such as gloves and shoes possess the quality of "handedness." A right-handed glove only fits a right hand; a left-handed shoe only fits a left foot. Objects that can exist in right-handed and left-handed forms are said to be **chiral**. In this chapter we shall find that molecules can also be chiral and can exist in right- and left-handed forms. For example, one chiral form of the molecule shown in the chapter opener image is a painkiller (Darvon), and the other, a cough suppressant (Novrad)! It is easy to see why it is important to understand chirality in molecules.

4.1 | CHIRALITY AND STEREOCHEMISTRY

Chirality is a phenomenon that pervades the universe. How can we know whether a particular object is **chiral** or **achiral** (not chiral)? We can tell if an object has **chirality** by examining the object and its mirror image.

Every object has a mirror image. Many objects are achiral. By this we mean that *the object and its mirror image are identical*, that is, the object and its mirror image are **superposable** one on the other. Superposable means that one can, in one's mind's eye, place one object on the other so that all parts of each coincide. Simple geometrical objects such as a sphere or a cube are achiral. So is an object like a water glass. To be superposable is different than to be *super*imposable. Any two objects can be superimposed simply by putting one object on top of the other, whether or not the objects are the same. To *superpose* two objects (as in the property of superposition) means, on the other hand, that **all parts of each object must coincide**. The condition of superposability must be met for two things to be **identical**.

Helpful Hint: A chiral object is one that cannot be superposed on its mirror image.

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4.1 | Chirality and Stereochemistry
4.2 | Isomerism: Constitutional Isomers and Stereoisomers
4.3 | Enantiomers and Chiral Molecules
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4.5 | More about the Biological Importance of Chirality
4.6 | HOW TO Test for Chirality: Planes of Symmetry
4.7 | Naming Enantiomers: The R,S-System
4.8 | Properties of Enantiomers: Optical Activity
4.9 | The Origin of Optical Activity
4.10 | The Synthesis of Chiral Molecules
4.11 | Chiral Drugs
4.12 | Molecules with more than One Chirality Center
4.13 | Fischer Projection Formulas
4.14 | Stereoisomerism of Cyclic Compounds
4.15 | Relating Configurations through Reactions in Which No Bonds to the Chirality Center are Broken
4.16 | Separation of Enantiomers: Resolution
4.17 | Compounds with Chirality Centers Other than Carbon
4.18 | Chiral Molecules that do not Possess a Chirality Center
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4.21 | Tautomerism
4.22 | Gero Entropy

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Each of our hands is chiral. When you view your right hand in a mirror, the image that you see in the mirror *is a left hand* (Fig. 4.1). However, as we see in Fig. 4.2, your left hand and your right hand are not identical because *they are not superposable*. Your hands are chiral. In fact, the word chiral comes from the Greek word *cheir* meaning hand. An object such as a mug may or may not be chiral. If it has no markings on it, it is achiral. If the mug has a logo or image on one side, it is chiral.

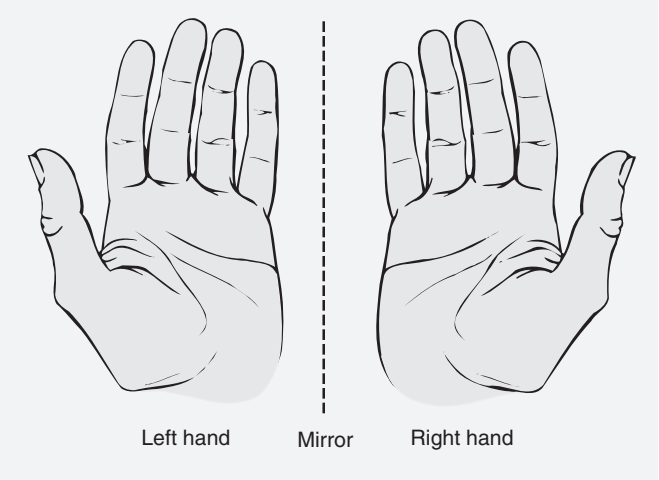

Figure 4.1 The mirror image a left hand is a right hand.

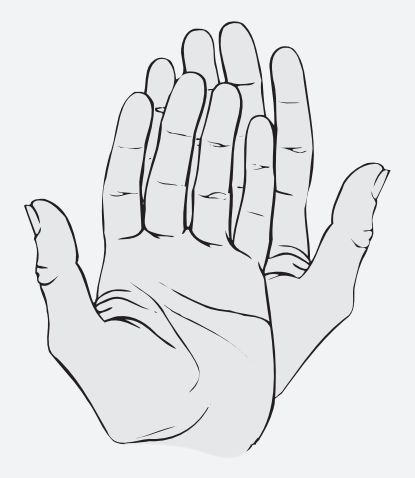

Figure 4.2 Left and rights hands are not superposable.

4.1A The Biological Significance of Chirality

The human body is structurally chiral, with the heart lying to the left of center and the liver to the right. Helical seashells are chiral and most are spiral, such as a right-handed screw. Many plants show chirality in the way they wind around supporting structures. Honeysuckle winds as a left-handed helix; bindweed winds in a right-handed way. DNA is a chiral molecule. The double helical form of DNA turns in a right-handed way.

Chirality in molecules, however, involves more than the fact that some molecules adopt left-or right-handed conformations. As we shall see in this chapter, it is the nature of groups bonded at specific atoms that can bestow chirality on a molecule. Indeed, all but one of the 20 amino acids that make up naturally occurring proteins are chiral, and all of these are classified as being left-handed. The molecules of natural sugars are almost all classified as being right-handed. In fact, most of the molecules of life are chiral, and most are found in only one mirror image form.

Chirality has tremendous importance in our daily lives. Most pharmaceuticals are chiral. Usually only one mirror-image form of a drug provides the desired effect. The other mirror-image form is often inactive or, at best, less active.

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In some cases the other mirror-image form of a drug actually has severe side effects or toxicity (see Section 4.5 regarding thalidomide). Our senses of taste and smell also depend on chirality. As we shall see, one mirror-image form of a chiral molecule may have a certain odor or taste while its mirror image smells and tastes completely different. The food we eat is largely made of molecules of one mirror-image form. If we were to eat food that was somehow made of molecules with the unnatural mirror-image form, we would likely starve because the enzymes in our bodies are chiral and preferentially react with the natural mirror-image form of their substrates.

Let us now consider what causes some molecules to be chiral. To begin, we will return to aspects of isomerism.

4.2 | ISOMERISM: CONSTITUTIONAL ISOMERS AND STEREOISOMERS

4.2A Constitutional Isomers

Isomers are different compounds that have the same molecular formula. In our study thus far, much of our attention has been directed toward isomers we have called constitutional isomers.

- **Constitutional isomers** have the same molecular formula but different connectivity, meaning that their atoms are connected in a different order. Examples of constitutional isomers are the following:

Molecular formula	Constitutional isomers		
C_4H_{10}	$CH_3CH_2CH_2CH_3$ Butane	and	$CH_3CH(CH_3)CH_3$ Isobutane
C_3H_7Cl	$CH_3CH_2CH_2Cl$ 1-Chloropropane	and	$CH_3CH(Cl)CH_3$ 2-Chloropropane
C_2H_6O	CH_3CH_2OH Ethanol	and	CH_3OCH_3 Dimethyl ether

4.2B Stereoisomers

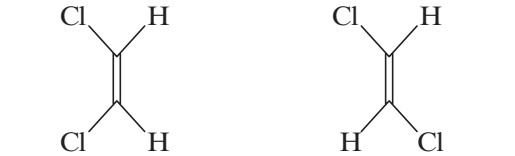
Stereoisomers are not constitutional isomers. **Stereoisomers** have their atoms connected in the same sequence (the same constitution), but they differ in the arrangement of their atoms in space. The consideration of such spatial aspects of molecular structure is called **stereochemistry**. We have already seen examples of some types of stereoisomers. The *cis* and *trans* forms of alkenes are stereoisomers, as are the *cis* and *trans* forms of substituted cyclic molecules.

4.2C Enantiomers and Diastereomers

Stereoisomers can be subdivided into two general categories: those that are **enantiomers** of each other, and those that are **diasteromers** of each other.

1. **Enantiomers are stereoisomers whose molecules are nonsuperposable mirror images of each other**.
2. **Diastereomers are stereoisomers whose molecules are not mirror images of each other**. All other stereoisomers are diastereomers.

   The alkene isomers *cis*- and *trans*-1, 2-dichloroethene shown here are stereoisomers that are **diastereomers**.



cis-1,2-Dichloroethene ($C_2H_2Cl_2$) *trans*-1,2-Dichloroethene ($C_2H_2Cl_2$)

By examining the structural formulas for *cis*- and *trans*-1, 2-dichloroethene, we see that they have the same molecular formula ($C_2H_2Cl_2$) and the same connectivity (both compounds have two central carbon atoms joined by a double

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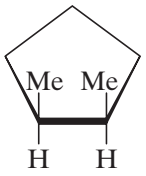
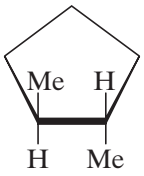
bond, and both compounds have one chlorine and one hydrogen atom attached to each carbon atom). But, their atoms have a different arrangement in space that is not interconvertible from one to another (due to the large barrier to rotation of the carbon–carbon double bond), making them stereoisomers. Furthermore, they are stereoisomers that are not mirror images of each other; therefore they are diastereomers and not enantiomers.

Cis and *trans* isomers of cycloalkanes furnish us with another example of stereoisomers that are diastereomers. Consider the following two compounds:



cis-1,2-Dimethylcyclopentane
(C_7H_{14})

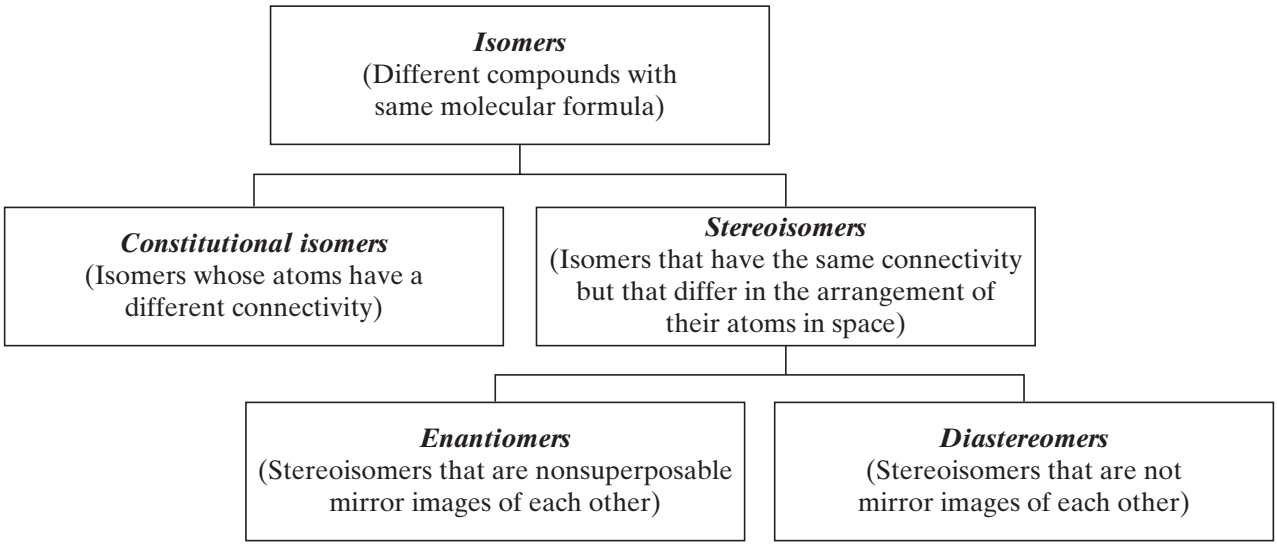


trans-1,2-Dimethylcyclopentane
(C_7H_{14})

These two compounds have the same molecular formula (C_7H_{14}), the same sequence of connections for their atoms, but different arrangements of their atoms in space. In one compound both methyl groups are bonded to the same face of the ring, while in the other compound the two methyl groups are bonded to opposite faces of the ring. Furthermore, the positions of the methyl groups cannot be interconverted by conformational changes. Therefore, these compounds are stereoisomers, and because they are stereoisomers that are not mirror images of each other, they can be further classified as diastereomers.

In Section 4.12 we shall study other molecules that can exist as diastereomers but are not *cis* and *trans* isomers of each other. First, however, we need to consider enantiomers further.

Subdivision of isomers



4.3 | ENANTIOMERS AND CHIRAL MOLECULES

Enantiomers always have the possibility of existing in pairs. We may not always find that nature (or a reaction) has produced a pair of enantiomers, however. In fact, in nature we often find only one enantiomer of the two that are possible. We shall find out later why this is often the case. Typically, when we carry out a chemical reaction, we find that the reaction produces a pair of enantiomers. Again, we will explain later why this occurs.

1. What structural feature must be present for two molecules to exist as enantiomers? Enantiomers occur only with compounds whose molecules are chiral.
2. How do we recognize a chiral molecule? A **chiral molecule** is one that is not superposable on its mirror image.
3. What is the relationship between a chiral molecule and its mirror image? The relationship is one that is enantiomeric. A chiral molecule and its mirror image are said to be enantiomers of each other.

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Practice Problem 4.1

Classify each of the following objects as to whether it is chiral or achiral:

(a) A screwdriver **(b)** A baseball bat **(c)** A golf club **(d)** A tennis shoe
(e) An ear **(f)** A woodscrew **(g)** A car **(h)** A hammer

The chirality of molecules can be demonstrated with relatively simple compounds. Consider, for example, 2-butanol:

$CH_3CHCH_2CH_3$ (OH) — 2-Butanol

Until now, we have presented the formula for 2-butanol as though it represented only one compound and we have not mentioned that molecules of 2-butanol are chiral. Because they are, there are actually two different 2-butanols and these two 2-butanols are enantiomers. We can understand this if we examine the drawings and models in Fig. 4.3.

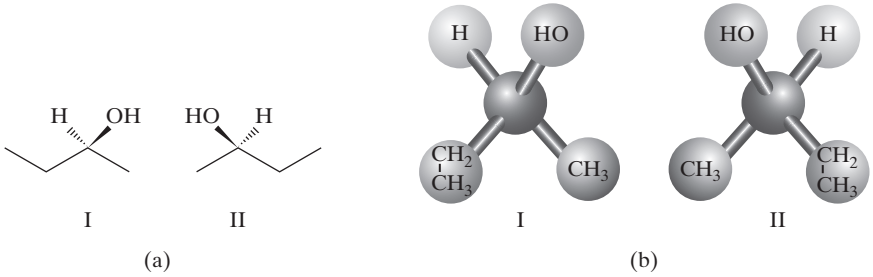

Figure 4.3 (a) Three-dimensional drawings of the 2-butanol enantiomers I and II. (b) Models of the 2-butanol enantiomers. (c) An unsuccessful attempt to superpose models of I and II.

If model I is held before a mirror, model II is seen in the mirror and vice versa. Models I and II are not superposable on each other; therefore, they represent different, but isomeric, molecules. ***Because models I and II are nonsuperposable mirror images of each other, the molecules that they represent are enantiomers.***

Practice Problem 4.2

Construct handheld models of the 2-butanols represented in Fig. 4.3 and demonstrate for yourself that they are not mutually superposable.

(a) Make similar models of 2-bromo-propane. Are they superposable?
(b) Is a molecule of 2-bromopropane chiral?
(c) Would you expect to find enantiomeric forms of 2-bromopropane?

4.4 | A SINGLE CHIRALITY CENTER CAUSES A MOLECULE TO BE CHIRAL

What structural feature can we use to know when to expect the possible existence of a pair of enantiomers?

One way (but not the only way) is to recognize that *a pair of enantiomers is always possible for molecules that contain* **a single tetrahedral atom with four different groups attached to it**.

Traditionally such atoms have been called *asymmetric atoms*, or *stereogenic atoms*, or *stereocenters*. In 1996, however, the IUPAC recommended that such atoms be called **chirality centers**, and this is the usage that we shall follow in this text. It is also important to state that chirality is a property of the molecule as a whole, and that a chirality center is a structural feature that can cause a molecule to be chiral.

Chirality centers are often designated with an asterisk (*). In 2-butanol the chirality center is C2 (Fig. 4.4). The four different groups that are attached to C2 are a hydroxyl group, a hydrogen atom, a methyl group, and an ethyl group.

(hydrogen) H
(methyl) $^{1}CH_3-\overset{2}{\underset{|}{C^*}}(OH)-{}^{3}CH_2{}^{4}CH_3$ (ethyl)
(hydroxyl)

Figure 4.4 The tetrahedral carbon atom of 2-butanol that bears four different groups. [By convention, chirality centers are often designated with an asterisk (*).]

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An ability to find chirality centers in structural formulas will help us in recognizing molecules that are chiral, and that can exist as enantiomers. **The presence of a single chirality center in a molecule guarantees that the molecule is chiral and that enantiomeric forms are possible**. *However, as we shall see in Section* 4.12*, there are molecules with more than one chirality center that are not chiral, and there are molecules that do not contain a chirality center that are chiral.*

Figure 4.5 demonstrates that enantiomeric compounds can exist whenever a molecule contains a single chirality center.

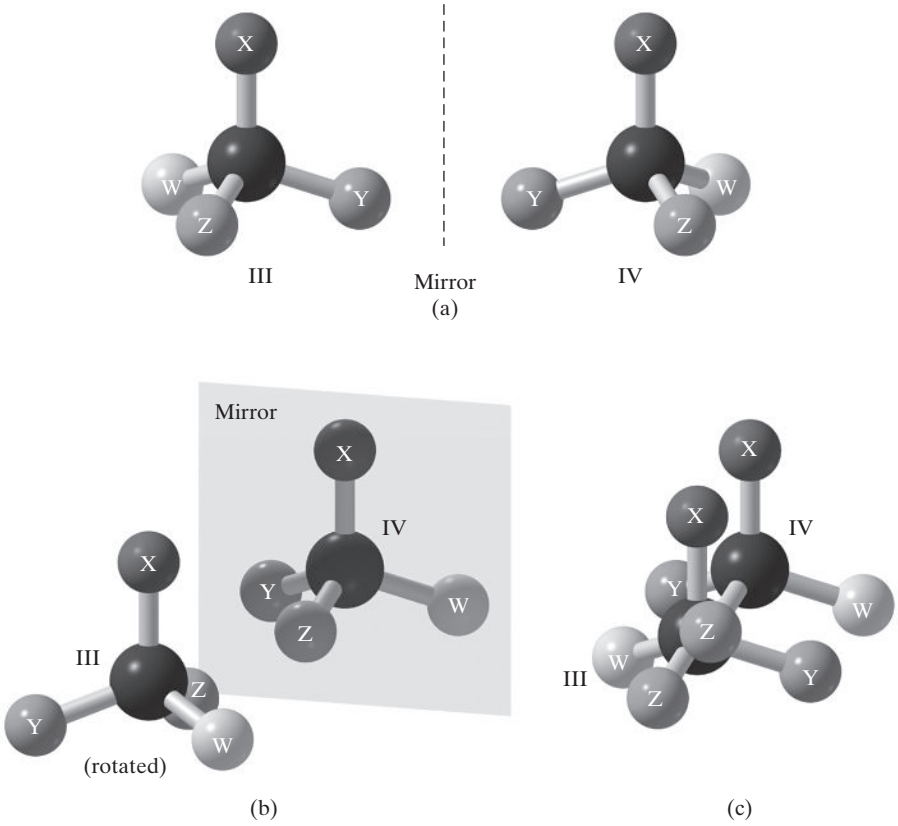

Figure 4.5 A demonstration of chirality of a generalized molecule containing one chirality center. (a) The four different groups around the carbon atom in III and IV are arbitrary. (b) III is rotated and placed in front of a mirror. III and IV are found to be related as an object and its mirror image. (c) III and IV are not superposable; therefore, the molecules that they represent are chiral and are enantiomers.

An important property of enantiomers with a single chirality center, such as 2-butanol, is that *interchanging any two groups at the chirality center converts one enantiomer into the other*. In Fig. 4.3 it is easy to see that interchanging the methyl and ethyl groups converts one enantiomer into the other. You should now convince yourself that interchanging any other two groups has the same result.

Helpful Hint: Interchanging two groups of a model or three-dimensional formula is a useful test for determining whether structures of two chiral molecules are the same or different.

Any atom at which an interchange of groups produces a stereoisomer is called a **stereogenic center**. (If the atom is a carbon atom it is usually called a **stereogenic carbon**.) When we discuss interchanging groups like this, we must take care to notice that what we are describing is *something we do to a molecular model* or *something we do on paper*. An interchange of groups in a real molecule, if it can be done, requires breaking covalent bonds, and this is something that requires a large input of energy. This means that enantiomers such as the 2-butanol enantiomers ***do not interconvert*** spontaneously.

The *chirality center* of 2-butanol is one example of a *stereogenic center*, but there are stereogenic centers that are *not* chirality centers. The carbon atoms of *cis*-1,2-dichloroethene and of *trans*-1,2-dichloroethene (Section 4.2C) are stereogenic centers because an interchange of groups at either carbon atom produces the other stereoisomer.

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The carbon atoms of *cis*-1,2-dichloroethene and *trans*-1,2-dichloroethene are not chirality centers, however, because they do not have four different groups attached to them.

Practice Problem 4.3

Demonstrate the validity of what we have represented in Fig. 4.5 by constructing models. Demonstrate for yourself that III and IV are related as an object and its mirror image *and that they are not superposable* (i.e., that III and IV are chiral molecules and are enantiomers). **(a)** Take IV and exchange the positions of any two groups. What is the new relationship between the molecules? **(b)** Now take either model and exchange the positions of any two groups. What is the relationship between the molecules now?

If all of the tetrahedral atoms in a molecule have two or more groups attached that *are the same*, the molecule does not have a chirality center. The molecule is superposable on its mirror image and is **achiral**. An example of a molecule of this type is 2-propanol; carbon atoms 1 and 3 bear three identical hydrogen atoms and the central atom bears two identical methyl groups. If we write three-dimensional formulas for 2-propanol, we find (Fig. 4.6) that one structure can be superposed on its mirror image.

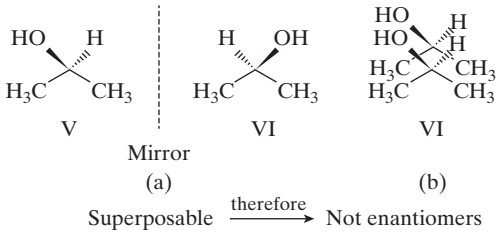

Figure 4.6 (a) 2-Propanol (V) and its mirror image (VI). (b) When either one is rotated, the two structures are superposable and so do not represent enantiomers. They represent two molecules of the same compound. 2-Propanol does not have a chirality center.

Thus, we would not predict the existence of enantiomeric forms of 2-propanol, and experimentally only one form of 2-propanol has ever been found.

Practice Problem 4.4

Some of the molecules listed here have a chirality center; some do not. Write three-dimensional formulas for both enantiomers of those molecules that do have a chirality center.

(a) 2-Fluoropropane
(b) 2-Methylbutane
(c) 2-Chlorobutane
(d) 2-Methyl-1-butanol
(e) *trans*-2-Butene
(f) 2-Bromopentane
(g) 3-Methylpentane
(h) 3-Methylhexane
(i) 2-Methyl-2-pentene
(j) 1-Chloro-2-methylbutane

It is important to clarify the difference between stereogenic centers, in general, and a chirality center, which is one type of stereogenic center. The chirality center in 2-butanol is a tetrahedral stereogenic center. The carbon atoms of *cis*- and *trans*-1,2-dichloroethene are also stereogenic centers, but they are trigonal stereogenic centers. They are *not* chirality centers. An interchange of groups at the alkene carbons of either 1,2-dichloroethene isomer produces a stereoisomer (a molecule with the same connectivity but a different arrangement of atoms in space), but it does not produce a nonsuperposable mirror image. A chirality center, on the other hand, is one that must have the possibility of nonsuperposable mirror images.

1. Chirality centers are tetrahedral stereogenic centers.
2. *Cis* and *trans* alkene isomers contain trigonal stereogenic centers.

4.5 | MORE ABOUT THE BIOLOGICAL IMPORTANCE OF CHIRALITY

The origin of biological properties relating to chirality is often likened to the specificity of our hands for their respective gloves; the binding specificity for a chiral molecule (like a hand) at a chiral receptor site (a glove) is only favorable in

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one way. If either the molecule or the biological receptor site had the wrong handedness, the natural physiological response (e.g., neural impulse, reaction catalysis) would not occur. A diagram showing how only one amino acid in a pair of enantiomers can interact in an optimal way with a hypothetical binding site (e.g., in an enzyme) is shown in Fig. 4.7. Because of the chirality center of the amino acid, three-point binding can occur with proper alignment for only one of the two enantiomers.

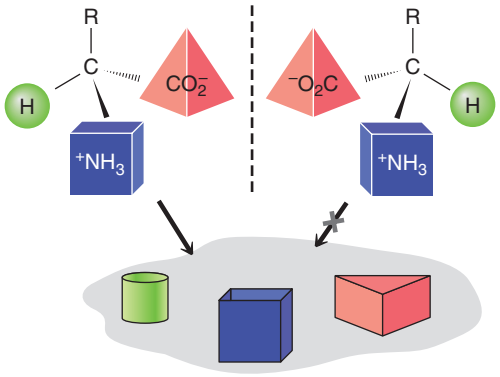
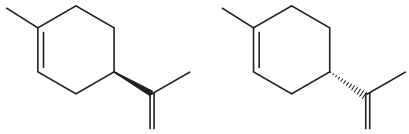


Figure 4.7 Only one of the two amino acid enantiomers shown (the left-hand one) can achieve three-point binding with the hypothetical binding site (e.g., in an enzyme).

Chiral molecules can show their handedness in many ways, including the way they affect human beings. One enantiomeric form of a compound called limonene is primarily responsible for the odor of oranges and the other enantiomer for the odor of lemons.

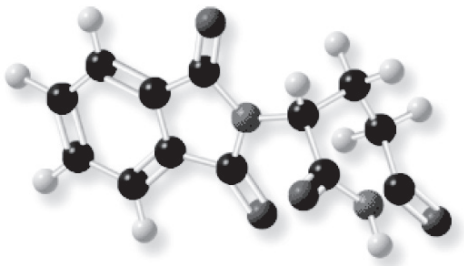


(+)-Limonene (the enantiomer of limonene found in oranges)

(–)-Limonene (the enantiomer of limonene found in lemons)

One enantiomer of a compound called carvone is the essence of caraway, and the other is the essence of spearmint.

The activity of drugs containing chirality centers can similarly vary between enantiomers, sometimes with serious or even tragic consequences. For several years before 1963 the drug thalidomide was used to alleviate the symptoms of morning sickness in pregnant women. In 1963 it was discovered that thalidomide was the cause of horrible birth defects in many children born subsequent to the use of the drug.



Thalidomide (Thalomid®)

Even later, evidence began to appear indicating that whereas one of the thalidomide enantiomers (the right-handed molecule) has the intended effect of curing morning sickness, the other enantiomer, which was also present in the drug (in an equal amount), may be the cause of the birth defects. The evidence regarding the effects of the two enantiomers is complicated by the fact that, under physiological conditions, the two enantiomers are interconverted. Now, however, thalidomide is approved under highly strict regulations for treatment of some forms of cancer and a serious complication associated with leprosy. Its potential for use against other conditions including AIDS and rheumatoid arthritis is also under investigation. We shall consider other aspects of chiral drugs in Section 4.11.

Practice Problem 4.5

Which atom is the chirality center of **(a)** limonene; **(b)** of thalidomide; **(c)** lactic acid; **(d)** glyceraldehyde; **(e)** ascorbic acid; **(f)** estradiol?

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4.6 | HOW TO TEST FOR CHIRALITY: PLANES OF SYMMETRY

The ultimate way to test for molecular chirality is to construct models of the molecule and its mirror image and then determine whether they are superposable. If the two models are superposable, the molecule that they represent is achiral. If the models are not superposable, then the molecules that they represent are chiral. We can apply this test with actual models, as we have just described, or we can apply it by drawing three-dimensional structures and attempting to superpose them in our minds.

There are other aids, however, that will assist us in recognizing chiral molecules. We have mentioned one already: **the presence of a *single* chirality center**. Other aids are based on the absence of certain symmetry elements in the molecule.

4.6A Plane of Symmetry

A **plane of symmetry** (also called a mirror plane) is defined as an imaginary plane that bisects a molecule in such a way that the two halves of the molecule are mirror images of each other. A molecule will not be chiral if it possesses a plane of symmetry.

The plane may pass through atoms, between atoms, or both. For example, 2-chloropropane has a plane of symmetry (Fig. 4.8), whereas 2-chlorobutane does not (Fig. 4.8). For this operation, consider the original shape of this molecule and apply the tool to its Fischer projection formula of compounds.

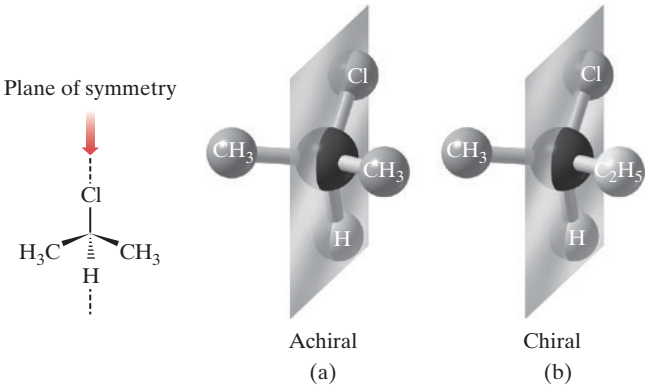
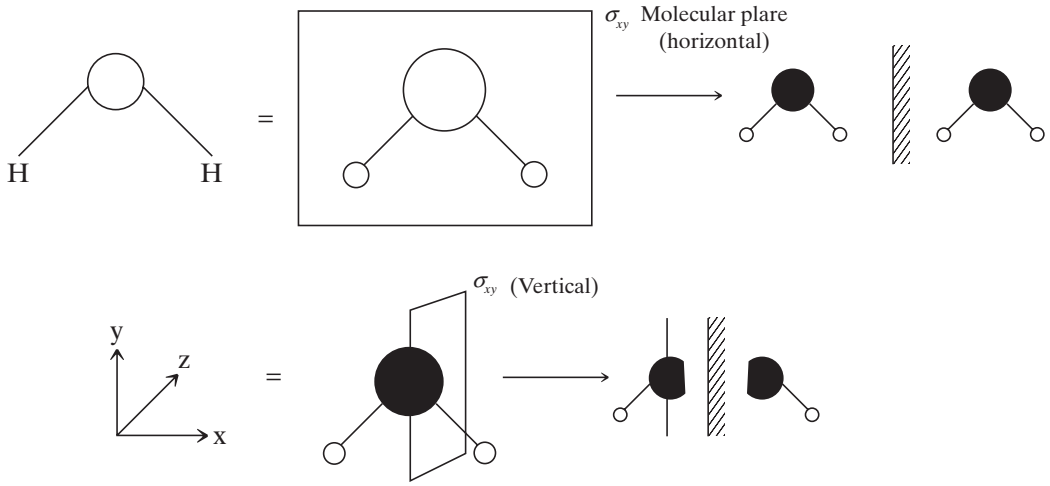


Figure 4.8 (a) 2-Chloropropane has a plane of symmetry and is achiral. (b) 2-Chlorobutane does not possess a plane of symmetry and is chiral.

All molecules with a plane of symmetry in their most symmetric conformation are achiral. Other examples include

1. Water molecule



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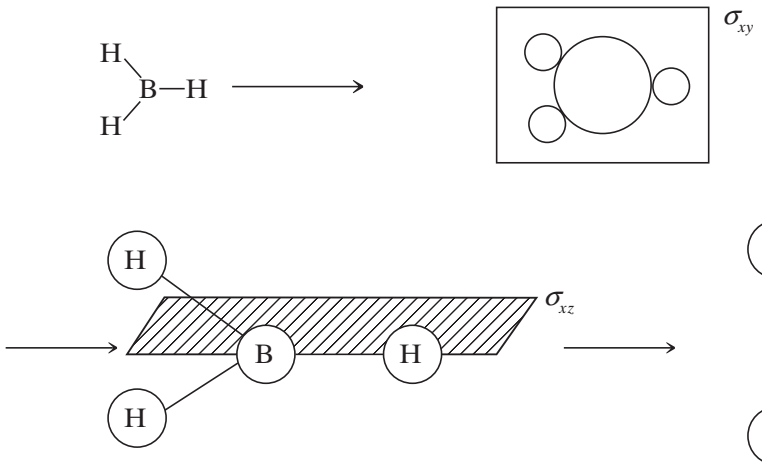
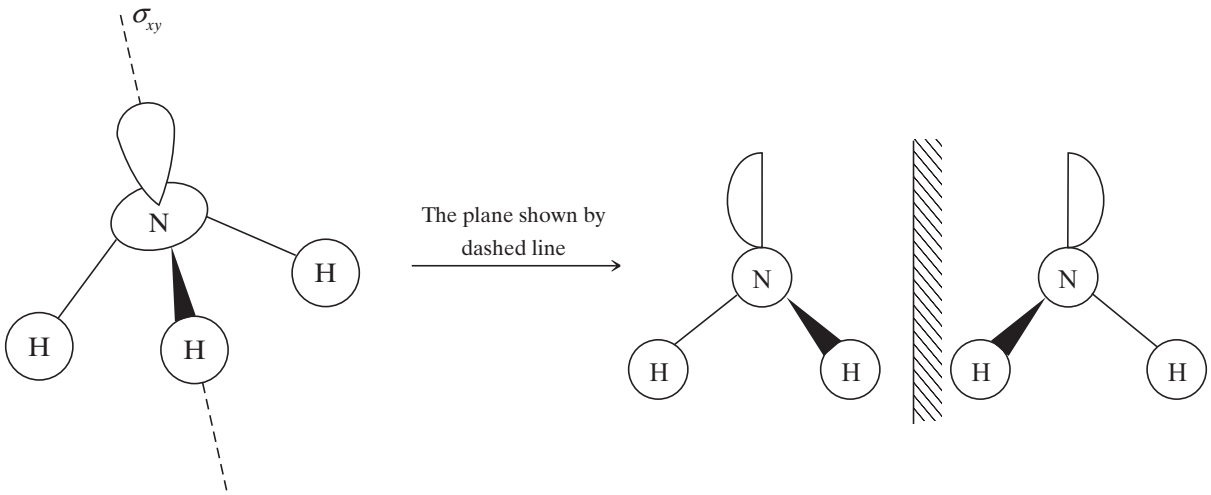
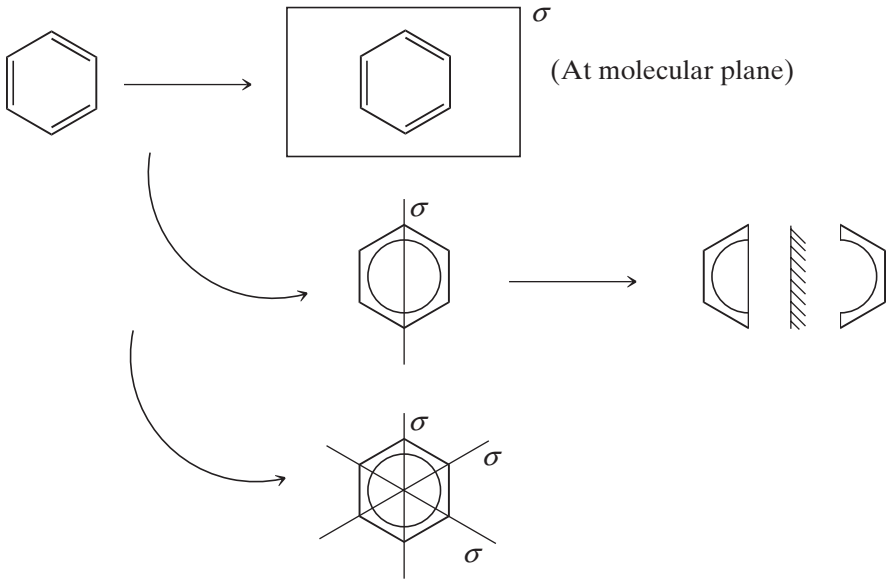
2. Borance molecule



3. Ammonia molecule



4. Benzene molecule has total 7 planes of symmetry



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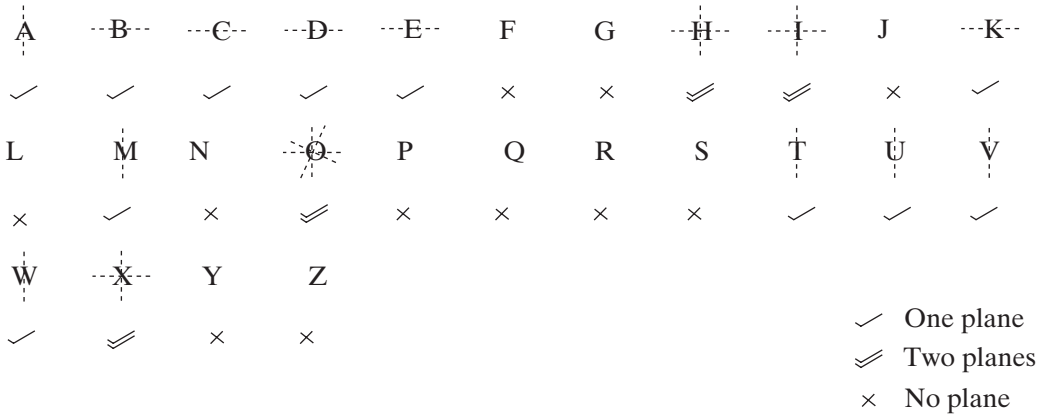
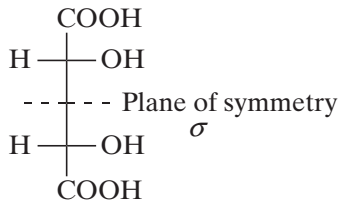
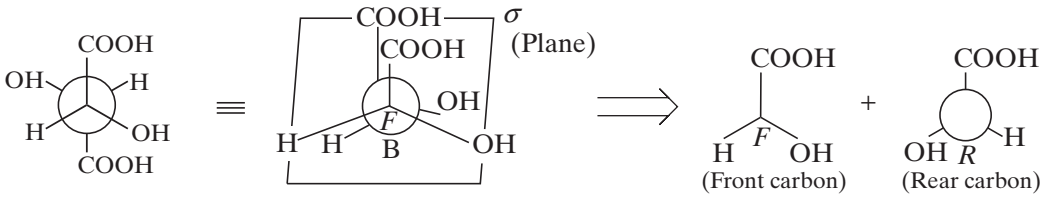
5. Most of the alphabets from A to Z have a molecular plane(horizontal) and a vertical plane. The vertical plane is shown as follow:



6. Mesotartaric acid

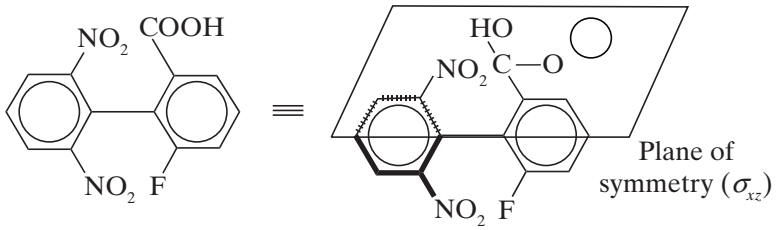


(Fischer Projection Formula)

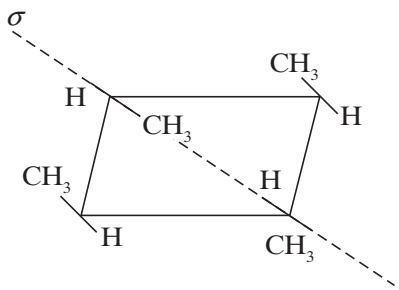


(Newman Formula)

7. A tetrasubstituted biphenyl



8. 1,2,3,4-Tetramethyl cyclobutance



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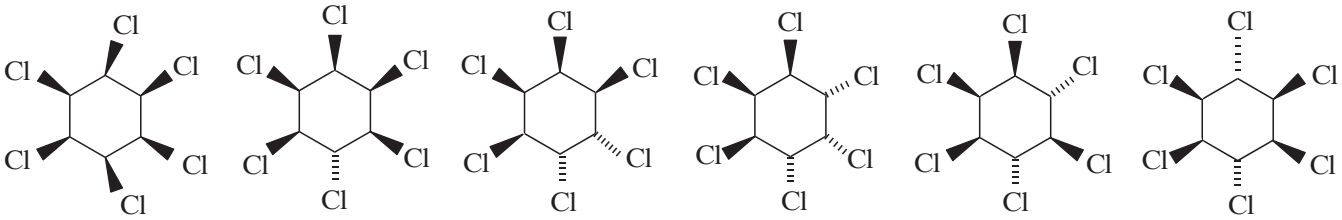
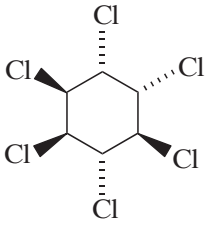
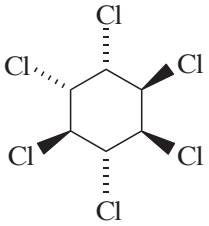
9. 1,2,3,4,5,6-Hexachlorocyclohexane



Each of the above structures possess plane of symmetry and therefore are optically inactive

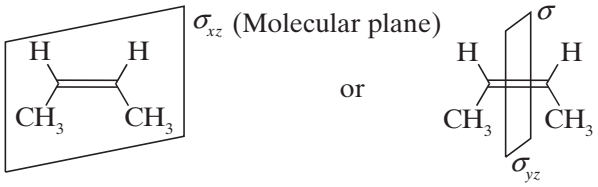


No plane of symmetry

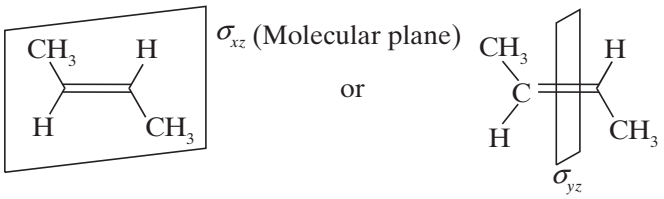


So this structure is optically active

10. *Cis* 2-butene

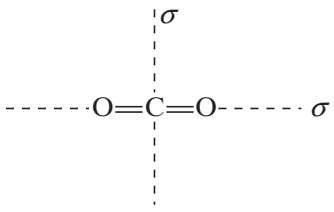


11. *Trans* 2-butene

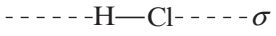


(Not possible)

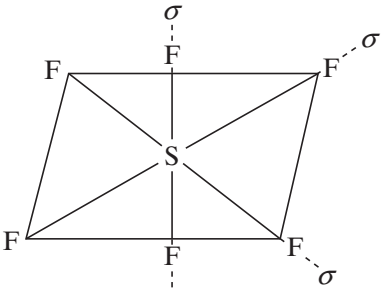
12. Carbon dioxide



13. Hydrogen chloride



14. Sulphur hexafluoride



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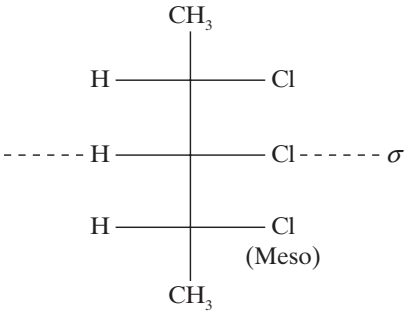
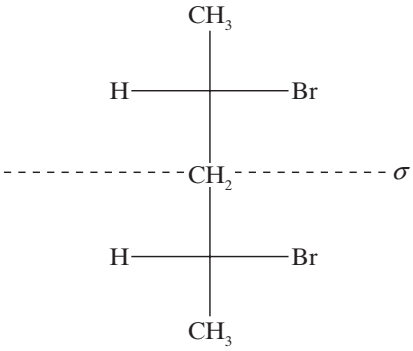
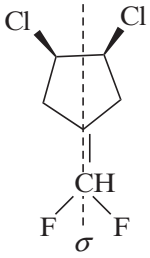
15. 2,3,4-Trichloropentane



16. 2,4-Dibromopentane



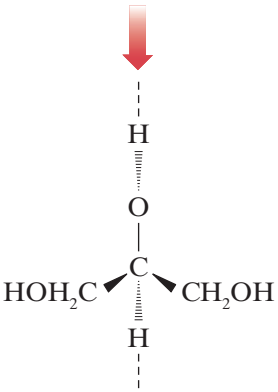
17. A trisubstituted cyclopentane



Solved Problem 4.1

Glycerol, $CH_2OHCHOHCH_2OH$, is an important constituent in the biological synthesis of fats. **(a)** Does glycerol have a plane of symmetry? If so, write a three-dimensional structure for glycerol and indicate where it is. **(b)** Is glycerol chiral?

Plane of symmetry



Answer

(a) Yes, glycerol has a plane symmetry. Notice we have to choose the proper conformation and orientation of the molecule to see the plane of symmetry. **(b)** No, it is achiral because it has a conformation containing a plane of symmetry.

Practice Problem 4.6

Which of the objects listed in Practice Problem 4.1 possess a plane of symmetry and are, therefore, achiral?

Practice Problem 4.7

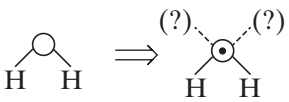
Write three-dimensional formulas and designate a plane of symmetry for all of the achiral molecules in Practice Problem 4.4. (In order to be able to designate a plane of symmetry you may need to write the molecule in an appropriate conformation.

4.6B Center of Symmetry (COS)

An imaginary point through which a line is drawn in a direction from an atom or group to the same atom or group placed at the same distance just opposite to the imaginary center. This rule is applicable for each atom of the molecule.

This operation is only applicable for three-dimensional formula and not for Fisher projection formula.

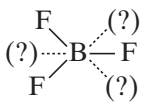
1. Water molecule



Centre of Symmetry

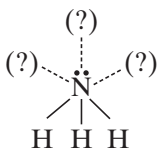
(COS) absent

2. Boron trifluoride



COS absent

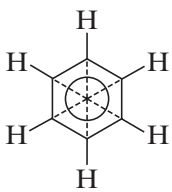
3. Ammonia molecule



COS absent

(c)

4. Benzene molecule



COS present

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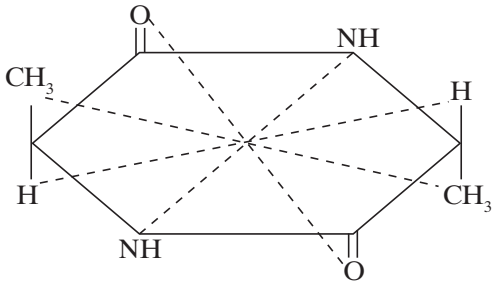
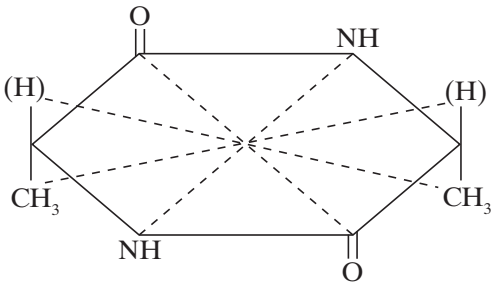
5.



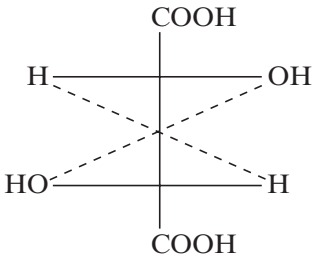
(*Trans*)
COS present

6.



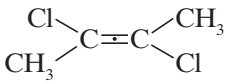
(*Cis*)
COS absent

7.



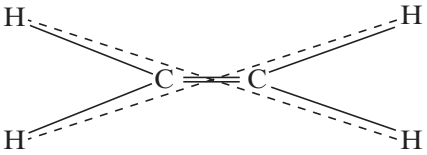
COS is not visible

8.



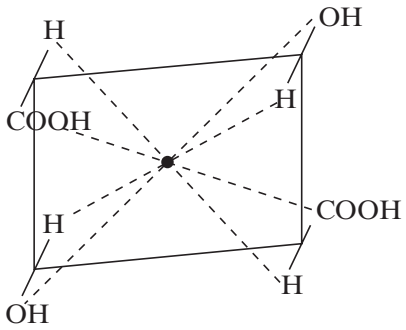
COS present

9.



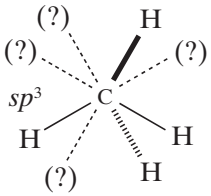
COS present

10.



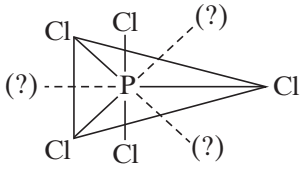
COS present

11.



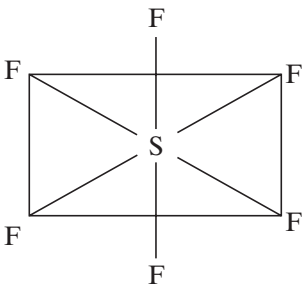
COS absent in
sp^3 atom

12.



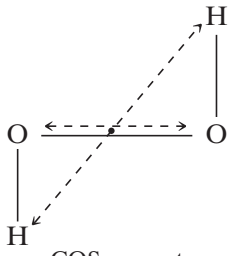
COS absent

13.



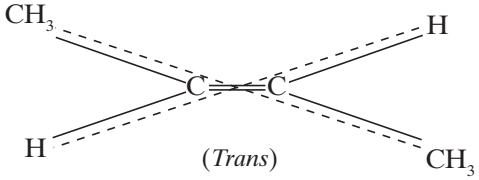
COS present

14.



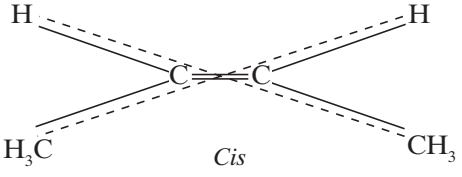
COS present

15.



(*Trans*)
COS present

16.



Cis
COS absent

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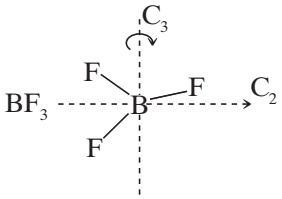
4.6C Axis of Symmetry

An imaginary axis around which by rotating through a minimum angle of rotation ($360°/\theta$), the same compound is obtained is known as axis of symmetry (AOS). For example

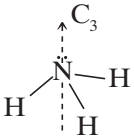
1.



$n = 360/120 = 3$

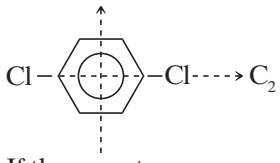
Therefore, $C_n = C_3$ axis.

2.



If there are two or more types of C_n axes, then the axis with higher value of n is the passes through more number of atoms

3.



If there are two or more possible AOS with the same value of n, then preference is given to the axis that passes through more number of atoms.

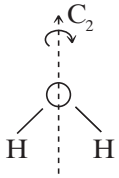
4.



5.



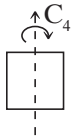
6.



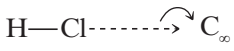
7.



8.



9.



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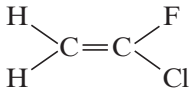
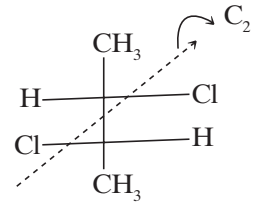


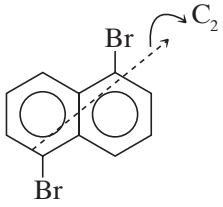
(AOS absent)

11.



(In Fisher projection formula, AOS is visible.)

12.



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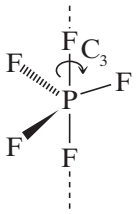

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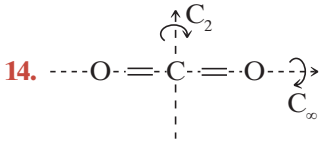

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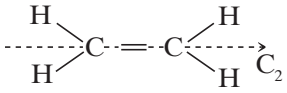

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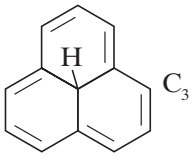

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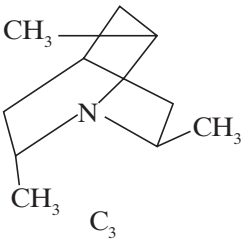

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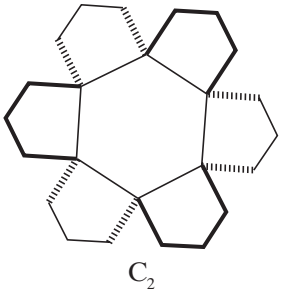

4.6D Alternating Axis of Symmetry (S_n or σ) or Improper Axis or Rotational Reflection Axis of Symmetry

Some compounds which do not have σ or i inspite of being optically active. Therefore, a new symmetry element – alternating axis of symmetry (S_n) is introduced. This operation involves rotation followed by reflection, that is, rotation by an angle of $360°/n$ about the axis and followed by reflection in a plane perpendicular to the axis of rotation. The resultant molecule is identical to the original molecule. The following expressions are true for S_n symmetry:

$S_1 = \sigma$; $S_2 = i$; S_4 = For cyclobutane and spiro N–C compounds

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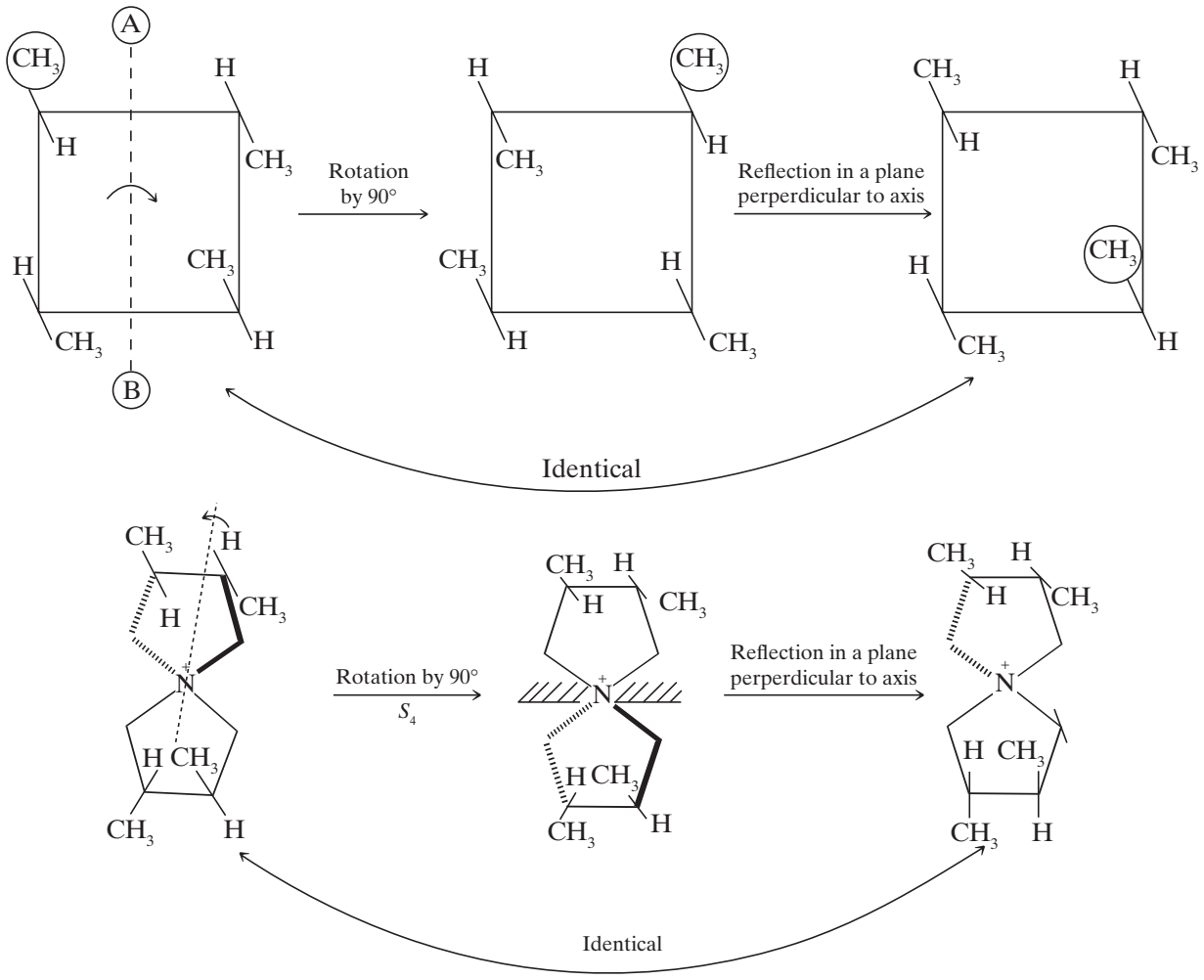
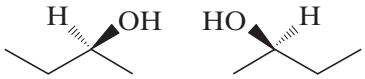


4.7 | NAMING ENANTIOMERS: THE *R,S*-SYSTEM

The two enantiomers of 2-butanol are the following:



I II

If we name these two enantiomers using only the IUPAC system of nomenclature that we have learned so far, both enantiomers will have the same name: 2-butanol (or *sec*-butyl alcohol) (Section 4.3F). This is undesirable because *each compound must have its own distinct name*. Moreover, the name that is given a compound should allow a chemist who is familiar with the rules of nomenclature to write the structure of the compound from its name alone. Given the name 2-butanol, a chemist could write either structure I or structure II.

Three chemists, R. S. Cahn (England), C. K. Ingold (England), and V. Prelog (Switzerland), devised a system of nomenclature that, when added to the IUPAC system, solves both of these problems. This system, called the ***R*, *S*-system** or the Cahn–Ingold–Prelog system, is part of the IUPAC rules.

According to this system, one enantiomer of 2-butanol should be designated (*R*)-2-butanol and the other enantiomer should be designated (*S*)-2-butanol. [(*R*) and (*S*) are from the Latin words *rectus* and *sinister*, meaning right and left, respectively.] These molecules are said to have opposite **configurations** at C2.

4.7A HOW TO Assign (*R*) and (*S*) Configurations

We assign (*R*) and (*S*) configurations on the basis of the following procedure.

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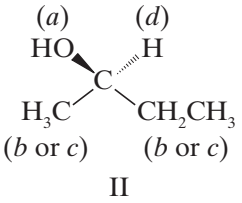
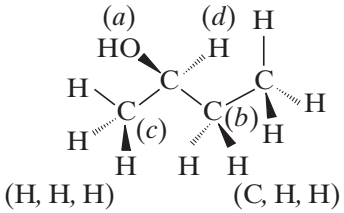
1. Each of the four groups attached to the chirality center is assigned a **priority** or **preference** *a*, *b*, *c*, or *d*. Priority is first assigned on the basis of the **atomic number** of the atom that is directly attached to the chirality center. The group with the lowest atomic number is given the lowest priority, *d*; the group with next higher atomic number is given the next higher priority, *c*; and so on. (In the case of isotopes, the isotope of greatest atomic mass has highest priority.)



II

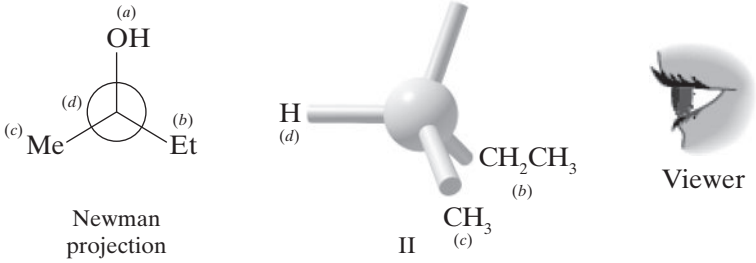
We can illustrate the application of the rule with the 2-butanol enantiomer, II: Oxygen has the highest atomic number of the four atoms attached to the chirality center and is assigned the highest priority, *a*. Hydrogen has the lowest atomic number and is assigned the lowest priority, *d*. A priority cannot be assigned for the methyl group and the ethyl group by this approach because the atom that is directly attached to the chirality center is a carbon atom in both groups.

2. When a priority cannot be assigned on the basis of the atomic number of the atoms that are directly attached to the chirality center, then the next set of atoms in the unassigned groups is examined. This process is continued until a decision can be made. *We assign a priority at the first point of difference.*

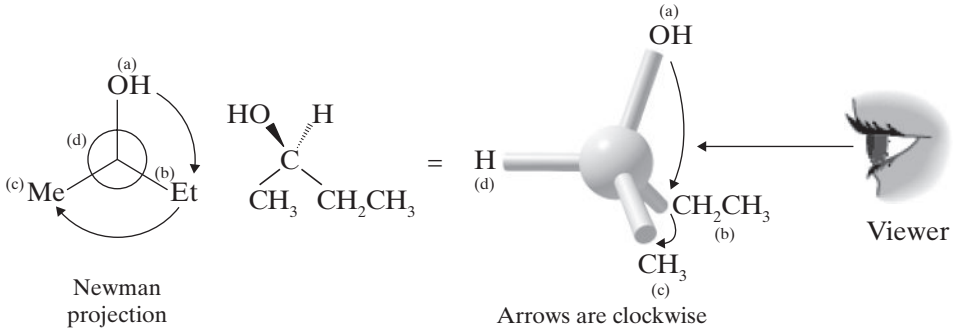


When we examine the methyl group of enantiomer II, we find that the next set of atoms consists of three hydrogen atoms (H, H, H). In the ethyl group of II the next set of atoms consists of one carbon atom and two hydrogen atoms (C, H, H). Carbon has a higher atomic number than hydrogen, so we assign the ethyl group the higher priority, *b*, and the methyl group the lower priority, *c*, since (C, H, H) > (H, H, H):

3. We now rotate the formula (or model) so that the group with lowest priority (*d*) is directed away from us:



Then we trace a path from *a* to *b* to *c*. If, as we do this, the direction of our finger (or pencil) is *clockwise*, the enantiomer is designated (*R*). If the direction is *counterclockwise*, the enantiomer is designated (*S*).
On this basis the 2-butanol enantiomer II is (*R*)-2-butanol:



(*R*)-2-butanol

Practice Problem 4.8

Write the enantiomeric forms of bromochlorofluoromethane and assign each enantiomer its correct (*R*) or (*S*) designation.

Practice Problem 4.9

Give (*R*) and (*S*) designations for each pair of enantiomers given as answers to Practice Problem 4.4.

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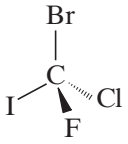
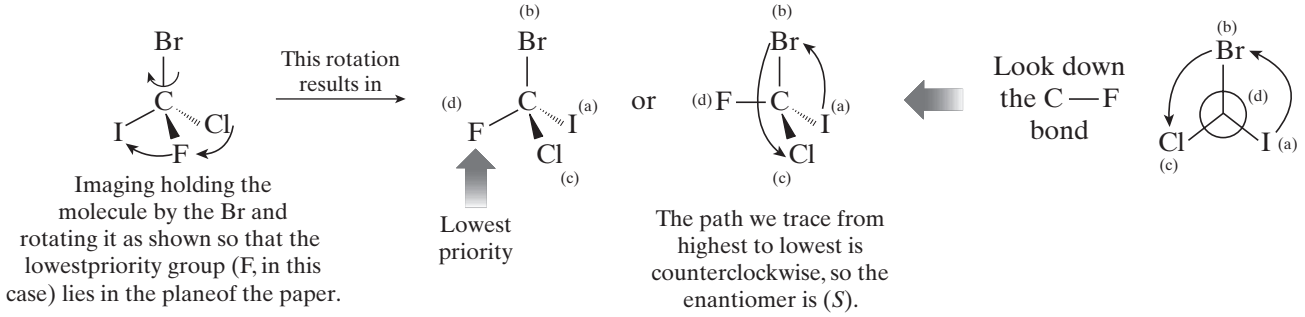
Solved Problem 4.2

Shown here is an enantiomer of bromochlorofluoroiodomethane. Is it (*R*) or (*S*)?

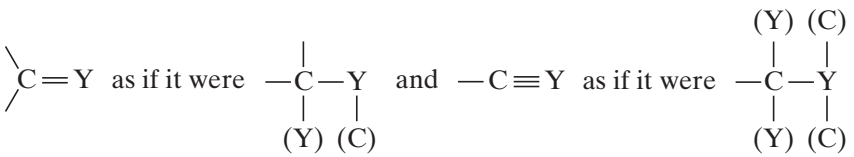


Answer



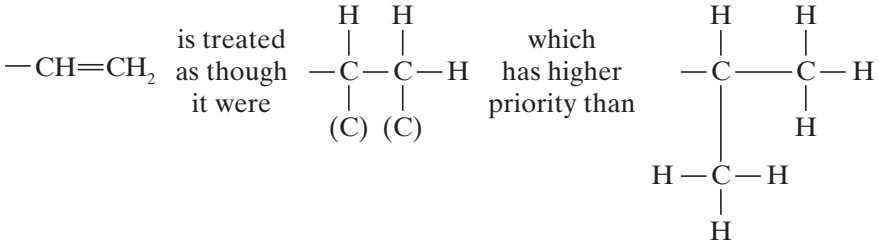
The first three rules of the Cahn–Ingold–Prelog system allow us to make an (*R*) or (*S*) designation for most compounds containing single bonds. For compounds containing multiple bonds one other rule is necessary:

4. Groups containing double or triple bonds are assigned priorities as if both atoms were duplicated or triplicated, that is,

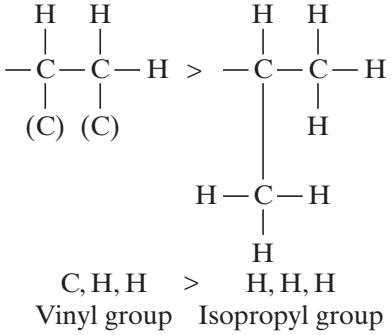


where the symbols in parentheses are duplicate or triplicate representations of the atoms at the other end of the multiple bond.

Thus, the vinyl group, —CH═CH_2, is of higher priority than the isopropyl group, —$CH(CH_3)_2$. That is,



because at the second set of atoms out, the vinyl group (see the following structure) is C, H, H, whereas the isopropyl group along either branch is H, H, H. (At the first set of atoms both groups are the same: C, C, H.)



Other rules exist for more complicated structures, but we shall not study them here.

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Practice Problem 4.10

List the substituents in each of the following sets in order of priority, from highest to lowest:

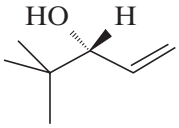
(a) —Cl, —OH, —SH, —H
(b) —CH_3, —CH_2Br, —CH_2Cl, —CH_2OH
(c) —H, —OH, —CHO, —CH_3
(d) —$CH(CH_3)_2$, —$C(CH_3)_3$, —H, —$CH=CH_2$
(e) —H, —$N(CH_3)_2$, —OCH_3, —CH_3
(f) —OH, —OPO_3H_2, —H, —CHO

Practice Problem 4.11

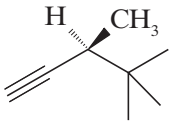
Assign (*R*) or (*S*) designations to each of the following compounds:



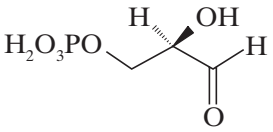
(a)



(b)



(c)

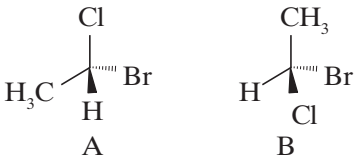


D-Glyceraldehyde-3-phosphate
(a glycolysis intermediate)

(d)

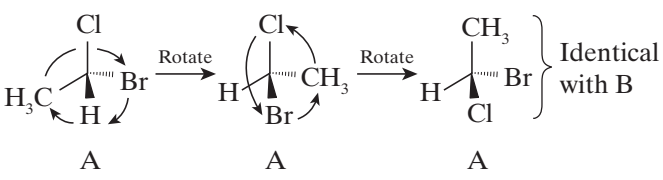
Solved Problem 4.3

Consider the following pair of structures and tell whether they represent enantiomers or two molecules of the same compound in different orientations:

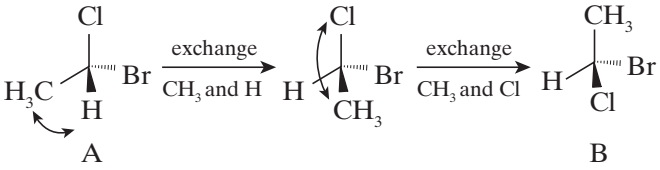


Answer

One way to approach this kind of problem is to take one structure and, in your mind, hold it by one group. Then rotate the other groups until at least one group is in the same place as it is in the other structure. (Until you can do this easily in your mind, practice with models.) By a series of rotations like this you will be able to convert the structure you are manipulating into one that is either identical with or the mirror image of the other. For example, take A, hold it by the Cl atom and then rotate the other groups about the C*—Cl bond until the hydrogen occupies the same position as in B. Then hold it by the H and rotate the other groups about the C*—H bond. This will make B identical with A:



Another approach is to recognize that exchanging two groups at the chirality center *inverts the configuration of* that carbon atom and converts a structure *with only one chirality center* into its enantiomer; a second exchange recreates the original molecule. So we proceed this way, keeping track of how many exchanges are required to convert A into B. In this instance we find that two exchanges are required, and, again, we conclude that A and B are the same:



A useful check is to name each compound including its (*R*, *S*) designation. If the names are the same, then the structures are the same. In this instance both structures are (*R*)-1-bromo-1-chloroethane.

Another method for assigning (*R*) and (*S*) configurations using one's hands as chiral templates has been described (Huheey, J. E. *J. Chem. Educ.* 1986, 63, 598–600). Groups at a chirality center are correlated from lowest to highest priority with one's wrist, thumb, index finger, and second finger, respectively. With the ring and little finger closed against the palm and viewing one's hand with the wrist away, if the correlation between the chirality center is with the left hand, the configuration is (*S*), and if with the right hand, (*R*).

A and B are two molecules of the same compound oriented differently.

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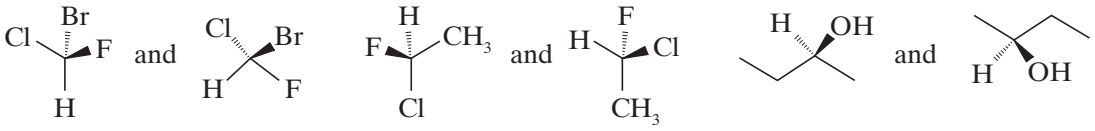
Practice Problem 4.12

Tell whether the two structures in each pair represent enantiomers or two molecules of the same compound in different orientations.



(a) (b) (c)

4.8 | PROPERTIES OF ENANTIOMERS: OPTICAL ACTIVITY

The molecules of enantiomers are not superposable and, on this basis alone, we have concluded that enantiomers are different compounds. How are they different? Do enantiomers resemble constitutional isomers and diastereomers in having different melting and boiling points? The answer is *no*. Pure enantiomers have *identical* melting and boiling points. Do pure enantiomers have different indexes of refraction, different solubilities in common solvents, different infrared spectra, and different rates of reaction with achiral reagents? The answer to each of these questions is also *no*.

Many of these properties (e.g., boiling points, melting points, and solubilities) are dependent on the magnitude of the intermolecular forces operating between the molecules (Section 2.13), and for molecules that are mirror images of each other these forces will be identical. We can see an example of this if we examine Table 4.1, where boiling points of the 2-butanol enantiomers are listed.

Table 4.1 Physical Properties of 2-Butanol and Tartaric Acid Enantiomers

Compound	Boiling point (bp) or Melting point (mp)
(*R*)-2-Butanol	99.5°C (bp)
(*S*)-2-Butanol	99.5°C (bp)
(+)-(*R*, *R*)-Tartaric acid	168–170°C (mp)
(−)-(*S*, *S*)-Tartaric acid	168–170°C (mp)
(+/−)-Tartaric acid	210–212°C (mp)

Mixtures of the enantiomers of a compound have different properties than pure samples of each, however. The data in Table 4.1 illustrate this for tartaric acid. The natural isomer, (+)-tartaric acid, has a melting point of 168–170°C, as does its unnatural enantiomer, (−)-tartaric acid. An equal mixture tartaric acid enantiomers, (+/−)-tartaric acid, has a melting point of 210–212°C, however.

Enantiomers show different behavior only when they interact with other chiral substances, including their own enantiomer, as shown by the melting point data above. Enantiomers show different rates of reaction toward other chiral molecules, that is, toward reagents that consist of a single enantiomer or an excess of a single enantiomer. Enantiomers also show different solubilities in solvents that consist of a single enantiomer or an excess of a single enantiomer.

One easily observable way in which enantiomers differ is in *their behavior toward plane-polarized light*. When a beam of plane-polarized light passes through an enantiomer, the plane of polarization **rotates**. Moreover, separate enantiomers rotate the plane of plane-polarized light equal amounts *but in opposite directions*. Because of their effect on plane-polarized light, separate enantiomers are said to be **optically active compounds**.

In order to understand this behavior of enantiomers, we need to understand the nature of plane-polarized light. We also need to understand how an instrument called a polarimeter operates.

4.8A Plane-Polarized Light

Light is an electromagnetic phenomenon. A beam of light consists of two mutually perpendicular oscillating fields: an oscillating electric field and an oscillating magnetic field (Fig. 4.9).

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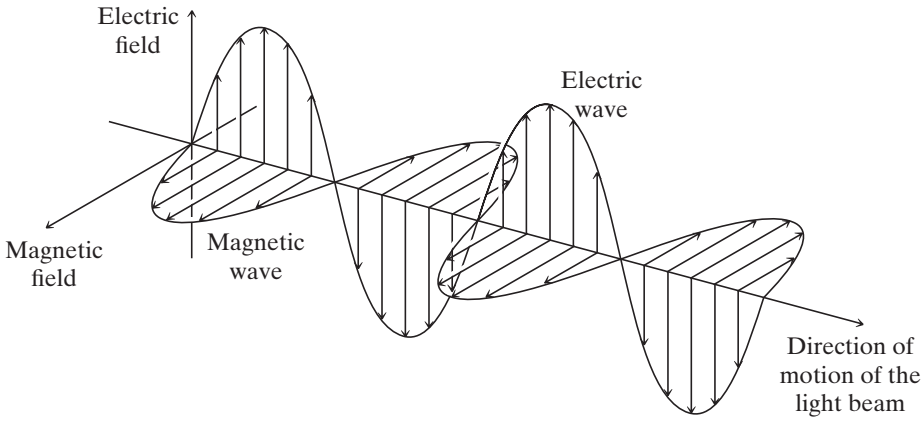

Figure 4.9 The oscillating electric and magnetic fields of a beam of ordinary light in one plane. The waves depicted here occur in all possible planes in ordinary light.

If we were to view a beam of ordinary light from one end, and if we could actually see the planes in which the electrical oscillations were occurring, we would find that oscillations of the electric field were occurring in all possible planes perpendicular to the direction of propagation (Fig. 4.10). (The same would be true of the magnetic field.)

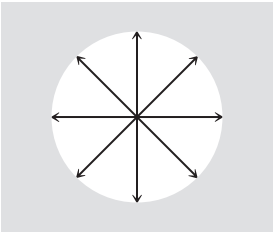

Figure 4.10 Oscillation of the electric field of ordinary light occurs in all possible planes perpendicular to the direction of propagation.

Figure 4.11 The plane of oscillation of the electric field of plane-polarized light. In this example the plane of polarization is vertical.

When ordinary light is passed through a polarizer, the polarizer interacts with the electric field so that the electric field of the light that emerges from the polarizer (and the magnetic field perpendicular to it) is oscillating only in one plane. Such light is called **plane-polarized light** (Fig. 4.11). If the plane-polarized beam encounters a filter with perpendicular polarization, the light is blocked (Fig. 4.11). This phenomenon can readily be demonstrated with lenses from a pair of polarizing sunglasses or a sheet of polarizing film (Fig. 4.11).

4.8B The Polarimeter

The device that is used for measuring the effect of optically active compounds on plane-polarized light is a **polarimeter**. A sketch of a polarimeter is shown in Fig. 4.12. The principal working parts of a polarimeter are (1) a light source (usually a sodium lamp), (2) a polarizer, (3) a cell for holding the optically active substance (or solution) in the light beam, (4) an analyzer, and (5) a scale for measuring the angle (in degrees) that the plane of polarized light has been rotated.

The analyzer of a polarimeter (Fig. 4.12) is nothing more than another polarizer. If the cell of the polarimeter is empty or if an optically *inactive* substance is present, the axes of the plane-polarized light and the analyzer will be exactly parallel when the instrument reads 0°, and the observer will detect the maximum amount of light passing through. If, by contrast, the cell contains an optically active substance, a solution of one enantiomer, for example, the plane of polarization of the light will be rotated as it passes through the cell. In order to detect the maximum brightness of light, the observer will have to rotate the axis of the analyzer in either a clockwise or counterclockwise direction. If the analyzer is rotated in a clockwise direction, the rotation, a (measured in degrees), is said to be positive (+). If the rotation is counterclockwise, the rotation is said to be negative (−). A substance that rotates plane-polarized light in the clockwise direction is also said to be **dextrorotatory**, and one that rotates plane-polarized light in a counterclockwise direction is said to be **levorotatory** (Latin: *dexter*, right, and *laevus*, left).

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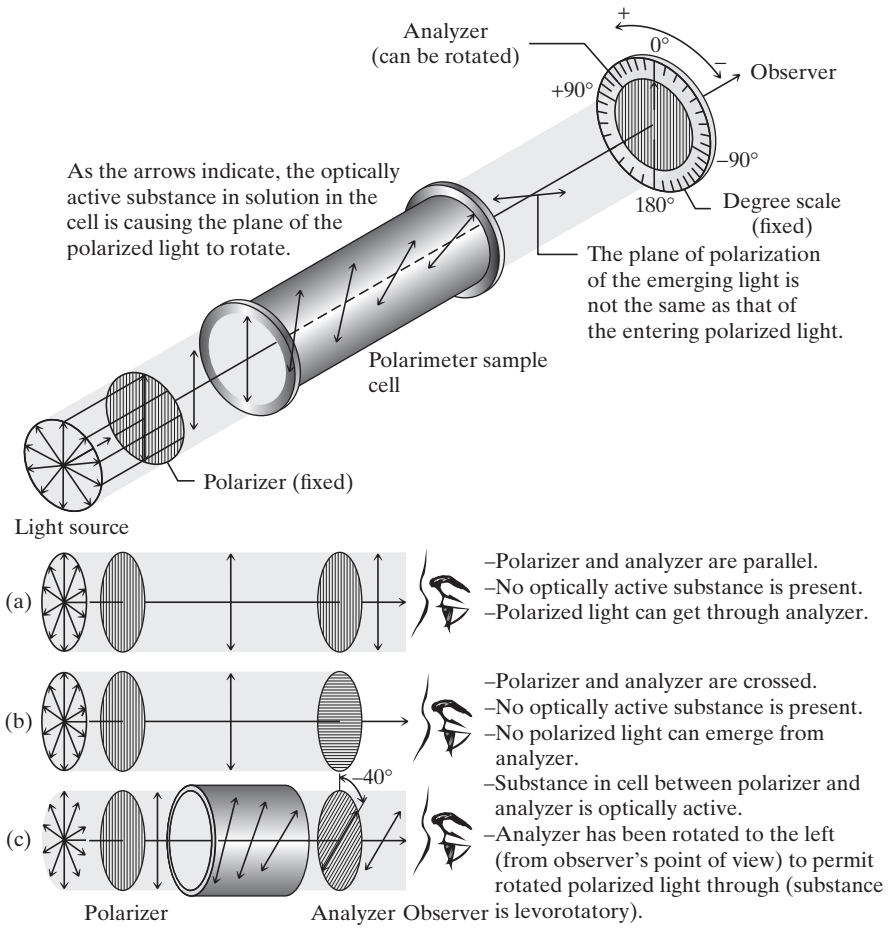

Figure 4.12 The principal working parts of a polarimeter and the measurement of optical rotation. (Reprinted with permission of John Wiley & Sons, Inc. from Holum, J. R., Organic Chemistry: A Brief Course, p. 316. Copyright 1975.)

4.8C Specific Rotation

The number of degrees that the plane of polarization is rotated as the light passes through a solution of an enantiomer depends on the number of chiral molecules that it encounters. This, of course, depends on the length of the tube and the concentration of the enantiomer. In order to place measured rotations on a standard basis, chemists calculate a quantity called the **specific rotation**, $[\alpha]$, by the following equation:

$$[\alpha] = \frac{\alpha}{c \cdot l}$$

where

$[\alpha]$ = the specific rotation

α = the observed rotation

c = the concentration of the solution in grams per milliliter of solution(or density in g mL^{-1} for neat liquids)

l = the length of the cell in decimeters (1 dm = 10 cm)

The specific rotation also depends on the temperature and the wavelength of light that is employed. Specific rotations are reported so as to incorporate these quantities as well. A specific rotation might be given as follows:

$$[\alpha]_D^{25} = +3.12$$

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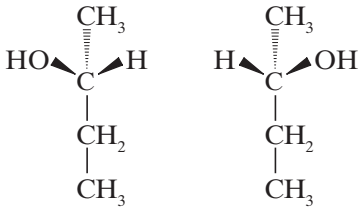
This means that the D line of a sodium lamp ($\propto$ = 589.6 nm) was used for the light, that a temperature of 25°C was maintained, and that a sample containing 1.00 g mL^{-1} of the optically active substance, in a 1-dm tube, produced a rotation of 3.12° in a clockwise direction.

The specific rotations of (*R*)-2-butanol and (*S*)-2-butanol are given here:



(*R*)-2-Butanol
$[\alpha]_D^{25} = -13.52$

(*S*)-2-Butanol
$[\alpha]_D^{25} = +13.52$

The direction of rotation of plane-polarized light is often incorporated into the names of optically active compounds. The following two sets of enantiomers show how this is done:



(*R*)-(+)-2-Methyl-1-butanol
$[\alpha]_D^{25} = +5.756$

(*S*)-(−)-2-Methyl-1-butanol
$[\alpha]_D^{25} = -5.756$

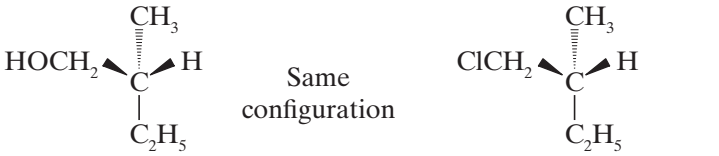


(*R*)-(−)-1-Chloro-2-methylbutane
$[\alpha]_D^{25} = -1.64$

(*S*)-(+)-1-Chloro-2-methylbutane
$[\alpha]_D^{25} = +1.64$

The previous compounds also illustrate an important principle: *No obvious correlation exists between the (R) and (S) configurations of enantiomers and the direction* [(+) *or* (−)] *in which they rotate plane-polarized light.*

(*R*)-(+)-2-Methyl-1-butanol and (*R*)-(−)-1-chloro-2-methylbutane have the same *configuration*; that is, they have the same general arrangement of their atoms in space. They have, however, an opposite effect on the direction of rotation of the plane of plane-polarized light:



(*R*)-(+)-2-Methyl-1-butanol

(*R*)-(−)-1-Chloro-2-methyl butane

These same compounds also illustrate a second important principle: *No necessary correlation exists between the (R) and (S) designation and the direction of rotation of plane-polarized light.* (*R*)-2-Methyl-1-butanol is dextrorotatory (+), and (*R*)-1-chloro-2-methylbutane is levorotatory (−).

A method based on the measurement of optical rotation at many different wavelengths, called optical rotatory dispersion, has been used to correlate configurations of chiral molecules. A discussion of the technique of optical rotatory dispersion, however, is beyond the scope of this text.

Practice Problem 4.13

Shown below is the configuration of (1)-carvone. (1)-Carvone is the principal component of caraway seed oil and is responsible for its characteristic odor. (2)-Carvone, its enantiomer, is the main component of spearmint oil and gives it

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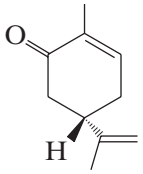
its characteristic odor. The fact that the carvone enantiomers do not smell the same suggests that the receptor sites in the nose for these compounds are chiral, and only the correct enantiomer will fit its particular site (just as a hand requires a glove of the correct chirality for a proper fit). Give the correct (*R*) and (*S*) designations for (1)- and (2)-carvone.



(1)-Carvone

4.9 | THE ORIGIN OF OPTICAL ACTIVITY

Optical activity is measured by the degree of rotation of plane-polarized light passing through a chiral medium. The theoretical explanation for the origin of optical activity requires consideration of *circularly*-polarized light, however, and its interaction with chiral molecules. While it is not possible to provide a full theoretical explanation for the origin of optical activity here, the following explanation will suffice. A beam of plane-polarized light (Fig. 4.13*a*)

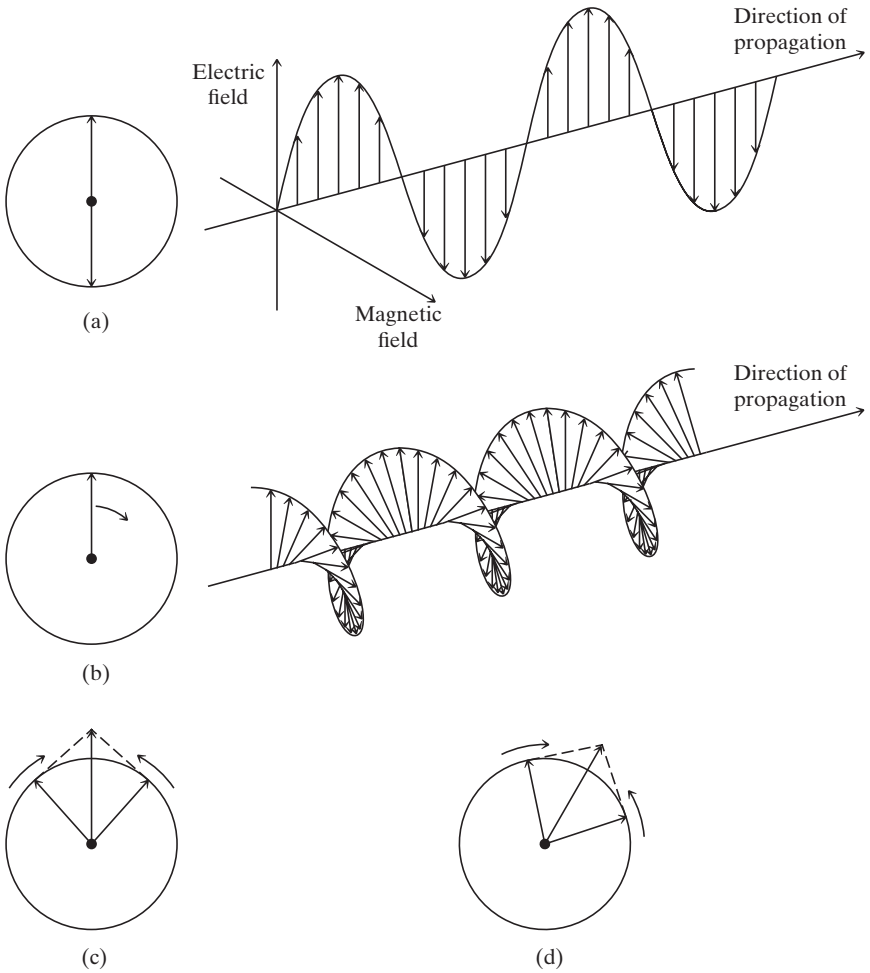


Figure 4.13 (a) Plane-polarized light. (b) Circularly-polarized light. (c, next page) Two circularly-polarized beams counterrotating at the same velocity (in phase) and their vector sum. The net result is like (a). (d, next page) Two circularly-polarized beams counterrotating at different velocities, such as after interaction with a chiral molecule, and their vector sum. The net result is like (b). Parts c and d: From ADAMSON. A TEXTBOOK OF PHYSICAL CHEMISTRY, 3E. © 1986 Brooks/Cole, a part of Cengage Learning, Inc. Reproduced by permission. www.cengage.com/permissions

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can be described in terms of circularly-polarized light. A beam of circularly-polarized light rotating in one direction is shown in Fig. 4.13*b*. The vector sum of *two* counter-rotating in-phase circularly-polarized beams is a beam of plane-polarized light (Fig. 4.13*c*). The optical activity of chiral molecules results from the fact that the two *counter-rotating circularly-polarized beams travel with different velocities through the chiral medium*. As the difference between the two circularly-polarized beams propagates through the sample, their vector sum describes a plane that is progressively rotated (Fig. 4.13*d*). What we measure when light emerges from the sample is the net rotation of the plane-polarized light caused by differences in velocity of the circularly-polarized beam components. The origin of the differing velocities has ultimately to do with interactions between electrons in the chiral molecule and light.

Molecules that are not chiral cause no difference in velocity of the two circularly-polarized beams; hence there is no rotation of the plane of polarized light described by their vector sum. Achiral molecules, therefore, are not optically active.

4.9A Racemic Forms

A sample that consists exclusively or predominantly of one enantiomer causes a net rotation of plane-polarized light. Figure 4.14*a* depicts a plane of polarized light as it encounters a molecule of (*R*)-2-butanol, causing the plane of polarization to rotate slightly in one direction. (For the remaining purposes of our discussion we shall limit our description of polarized light to the resultant plane, neglecting consideration of the circularly-polarized components from which plane-polarized light arises.) Each additional molecule of (*R*)-2-butanol that the beam encounters would cause further rotation in the same direction. If, on the other hand, the mixture contained molecules of (*S*)-2-butanol, each molecule of that enantiomer would cause the plane of polarization to rotate in the opposite direction (Fig. 4.14). If the (*R*) and (*S*) enantiomers were present in equal amounts, there would be no net rotation of the plane of polarized light.

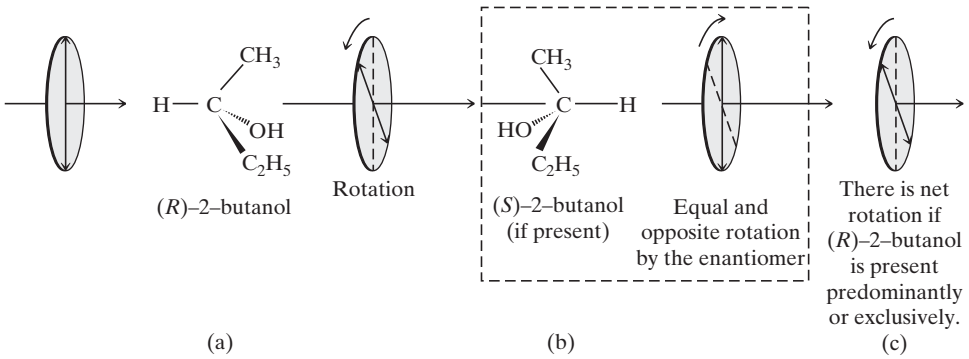

Figure 4.14 (a) A beam of plane-polarized light encounters a molecule of (*R*)-2-butanol, a chiral molecule. This encounter produces a slight rotation of the plane of polarization. (b) Exact cancellation of this rotation occurs if a molecule of (*S*)-2-butanol is encountered. (c) Net rotation of the plane of polarization occurs if (*R*)-2-butanol is present predominantly or exclusively.

An equimolar mixture of two enantiomers is called a **racemic mixture (or racemate or racemic form)**. **A racemic mixture causes no net rotation of plane-polarized light**.

In a racemic mixture the effect of each molecule of one enantiomer on the circularly-polarized beam cancels the effect of molecules of the other enantiomer, resulting in no net optical activity.

The racemic form of a sample is often designated as being (±). A racemic mixture of (*R*)-(-)-2-butanol and (*S*)-(+)-2-butanol might be indicated as

$$(\pm)\text{-2-butanol} \quad \text{or} \quad (\pm)-\mathrm{CH_3CH_2CHOHCH_3}$$

4.9B Racemic Forms and Enantiomeric Excess

A sample of an optically active substance that consists of a single enantiomer is said to be **enantiomerically pure** or to have an **enantiomeric excess** of 100%. An enantiomerically pure sample of (*S*)-(+)-2-butanol shows a specific rotation

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of +13.52 $\left([\alpha]_D^{25} = +13.52\right)$. On the other hand, a sample of (*S*)-(+)-2-butanol that contains less than an equimolar amount of (*R*)-(−)-2-butanol will show a specific rotation that is less than +13.52 but greater than zero. Such a sample is said to have an *enantiomeric excess* less than 100%. The **enantiomeric excess (ee)**, also known as the **optical purity**, is defined as follows:

$$\%\ \text{Enantiomeric excess} = \frac{\text{moles of one enantiomer} - \text{moles of other enantiomer}}{\text{total moles of both enantiomers}} \times 100$$

The enantiomeric excess can be calculated from optical rotations:

$$\%\ \text{Enantiomeric excess*} = \frac{\text{observed specific rotation}}{\text{Specific rotation of the pure enantiomer}} \times 100$$

Let us suppose, for example, that a mixture of the 2-butanol enantiomers showed a specific rotation of +6.76. We would then say that the enantiomeric excess of the (*S*)-(+)-2-butanol is 50%:

$$\text{Enantiomeric excess} = \frac{+6.76}{+13.52} \times 100 = 50\%$$

When we say that the enantiomeric excess of this mixture is 50%, we mean that 50% of the mixture consists of the (+) enantiomer (the excess) and the other 50% consists of the racemic form. Since for the 50% that is racemic the optical rotations cancel one another out, only the 50% of the mixture that consists of the (+) enantiomer contributes to the observed optical rotation. The observed rotation is, therefore, 50% (or one-half) of what it would have been if the mixture had consisted only of the (+) enantiomer.

Solved Problem 4.4

What is the actual stereoisomeric composition of the mixture referred to above?

Answer

Of the total mixture, 50% consists of the racemic form, which contains equal numbers of the two enantiomers. Therefore, half of this 50%, or 25%, is the (−) enantiomer and 25% is the (+) enantiomer. The other 50% of the mixture (the excess) is also the (+) enantiomer. Consequently, the mixture is 75% (+) enantiomer and 25% (−) enantiomer.

Practice Problem 4.14

A sample of 2-methyl-1-butanol has a specific rotation, $[\alpha]_D^{25}$, equal to +1.151. **(a)** What is the percent enantiomeric excess of the sample? **(b)** Which enantiomer is in excess, the (*R*) or the (*S*)?

4.10 | THE SYNTHESIS OF CHIRAL MOLECULES

4.10A Racemic Forms

Reactions carried out with achiral reactants can often lead to *chiral* products. In the absence of any chiral influence from a catalyst, reagent, or solvent, the outcome of such a reaction is a racemic mixture. In other words, the chiral product is obtained as a 50:50 mixture of enantiomers.

An example is the synthesis of 2-butanol by the nickel-catalyzed hydrogenation of butanone. In this reaction the hydrogen molecule adds across the carbon–oxygen double bond in much the same way that it adds to a carbon–carbon double bond.

*This calculation should be applied to a single enantiomer or to to mixture of enantiomers only. It should no applied to mixtures in which some other compound is present.

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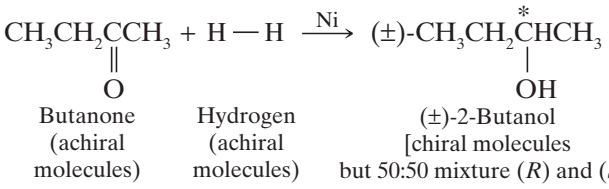

Figure 4.15 illustrates the stereochemical aspects of this reaction. Because butanone is achiral, there is no difference in presentation of either face of the molecule to the surface of the metal catalyst. The two faces of the trigonal planar carbonyl group interact with the metal surface with equal probability. *Trans*fer of the hydrogen atoms from the metal to the carbonyl group produces a chirality center at carbon 2. Since there has been no chiral influence in the reaction pathway, the product is obtained as a racemic mixture of the two enantiomers, (*R*)-(−)-2-butanol and (*S*)-(+)-2-butanol.

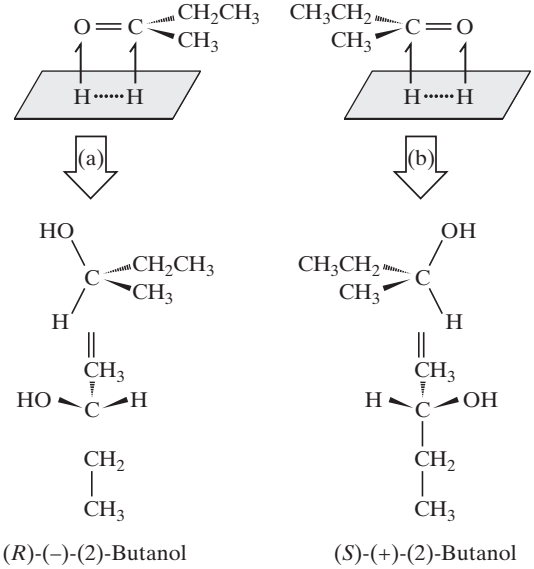

Figure 4.15 The reaction of butanone with hydrogen in the presence of a nickel catalyst. The reaction rate by path (a) is equal to that by path (b) (–)-2-Butanol and (*S*)-(+)-2-butanol are produced in equal amounts, as a racemate.

We shall see that when reactions like this are carried out in the presence of a chiral influence, such as an enzyme or chiral catalyst, the result is usually not a racemic mixture.

4.10B Stereoselective Syntheses

Stereoselective reactions are reactions that lead to a preferential formation of one stereoisomer over other stereoisomers that could possibly be formed.

1. If a reaction produces preferentially one enantiomer over its mirror image, the reaction is said to be **enantioselective**.
2. If a reaction leads preferentially to one diastereomer over others that are possible, the reaction is said to be **diastereoselective**.

For a reaction to be either enantioselective or diastereoselective, a chiral reagent, catalyst, or solvent must assert an influence on the course of the reaction.

In nature, where most reactions are stereoselective, the chiral influences come from protein molecules called **enzymes**. Enzymes are biological catalysts of extraordinary efficiency. Not only do they have the ability to cause reactions to take place much more rapidly than they would otherwise, they also have the ability to assert a *dramatic chiral influence* on a reaction. Enzymes do this because they, too, are chiral, and they possess an active site where the reactant molecules are momentarily bound while the reaction takes place. The active site is chiral (See Fig. 4.7), and only one enantiomer of a chiral reactant fits it properly and is able to undergo the reaction.

Many enzymes have found use in the organic chemistry laboratory, where organic chemists take advantage of their properties to bring about stereoselective reactions. One of these is an enzyme called **lipase**. Lipase catalyzes a reaction called **hydrolysis**, whereby an ester reacts with a molecule of water to produce a carboxylic acid and an alcohol.

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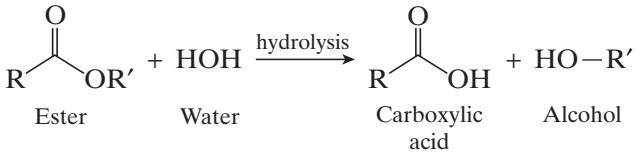
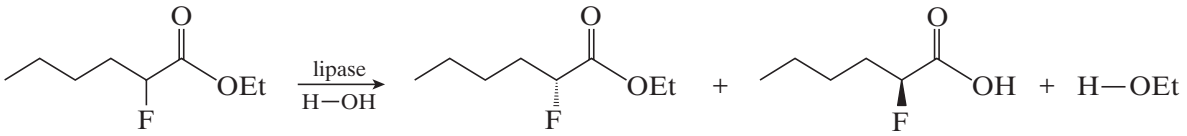


If the starting ester is chiral and present as a mixture of its enantiomers, the lipase enzyme reacts selectively with one enantiomer to release the corresponding chiral carboxylic acid and an alcohol, while the other ester enantiomer remains unchanged or reacts much more slowly. The result is a mixture that consists predominantly of one stereoisomer of the reactant and one stereoisomer of the product, which can usually be separated easily on the basis of their different physical properties. Such a process is called a **kinetic resolution**, where the rate of a reaction with one enantiomer is different than with the other, leading to a preponderance of one product stereoisomer. We shall say more about the resolution of enantiomers in Section 4.16. The following hydrolysis is an example of a kinetic resolution using lipase:



Ethyl (±)-2-fluorohexanoate [an ester that is a racemate of (*R*) and (*S*) forms]

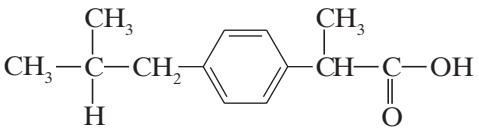
Ethyl (*R*)-(+)-2-fluorohexanoate (>99% enatiomeric excess)

(*S*)-(−)-2-Fluorohexanoic acid (>69% enatiomeric excess)

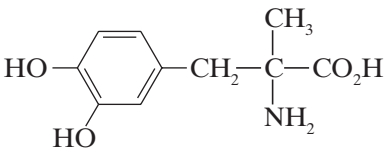
Other enzymes called hydrogenases have been used to effect enantioselective versions of carbonyl reductions. We shall have more to say about the stereo-selectivity of enzymes in Chapter 11 (Alcohols from Carbonyl Compounds).

4.11 | CHIRAL DRUGS

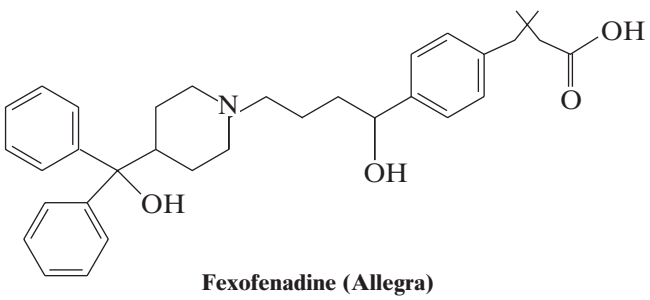
Chiral drugs are those drugs that contain a single enantiomer rather than a racemate. The antihypertensive drug **methyldopa** (Aldomet), for example, owes its effect exclusively to the (*S*) isomer. In the case of **penicillamine**, the (*S*) isomer is a highly potent therapeutic agent for primary chronic arthritis, while the (*R*) isomer has no therapeutic action and is highly toxic. The anti-inflammatory agent **ibuprofen** (Advil, Motrin, Nuprin) is marketed as a racemate even though only the (*S*) enantiomer is the active agent. The (*R*) isomer of ibuprofen has no anti-inflammatory action and is slowly converted to the (*S*) isomer in the body. A formulation of ibuprofen based on solely the (*S*) isomer, however, would be more effective than the racemate. Allegra (fexofenadine) is another chiral drug used as antihistamine.



Ibuprofen



Methyldopa



Fexofenadine (Allegra)

Practice Problem 4.15

Write three-dimensional formulas for the (*S*) isomers of **(a)** methyldopa, **(b)** fexofenadine, and **(c)** ibuprofen.

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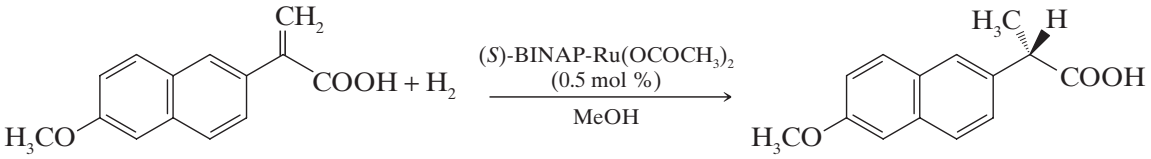
There are many other examples of drugs like these, including drugs where the enantiomers have distinctly different effects. The preparation of enantiomerically pure drugs, therefore, is one factor that makes stereoselective synthesis and the resolution of racemic drugs (separation into pure enantiomers) major areas of research today.

Underscoring the importance of stereoselective synthesis is the fact that the 2001 Nobel Prize in Chemistry was given to researchers who developed reaction catalysts that are now widely used in industry and academia. William Knowles (Monsanto Company, retired) and Ryoji Noyori (Nagoya University) were awarded half of the prize for their development of reagents used for catalytic stereoselective hydrogenation reactions. The other half of the prize was awarded to Barry Sharpless (Scripps Research Institute) for development of catalytic stereoselective oxidation reactions. An important example resulting from the work of Noyori and based on earlier work by Knowles is a synthesis of the anti-inflammatory agent **naproxen**, involving a stereoselective catalytic hydrogenation reaction:

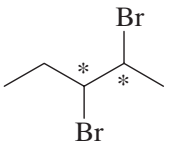


(*S*)-Naproxen
(an anti-in ammatory agent)
(92% yield, 97% ee)

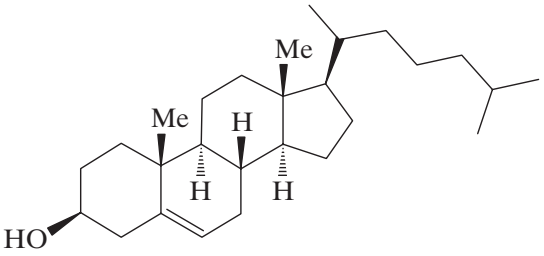
The hydrogenation catalyst in this reaction is an organometallic complex formed from ruthenium and a chiral organic ligand called (*S*)-BINAP. The reaction itself is truly remarkable because it proceeds with excellent enantiomeric excess (97%) and in very high yield (92%).

4.12 | MOLECULES WITH MORE THAN ONE CHIRALITY CENTER

So far we have mainly considered chiral molecules that contain only one chirality center. Many organic molecules, especially those important in biology, contain more than one chirality center. Cholesterol, for example, contains eight chirality centers. (Can you locate them?) We can begin, however, with simpler molecules. Let us consider 2, 3-dibromopentane, shown here in a two-dimensional bond-line formula. 2,3-Dibromopentane has two chirality centers:



2,3-Dibromopentane



Cholesterol

A useful rule gives the maximum number of stereoisomers: In compounds whose stereoisomerism is due to chirality centers, ***the total number of stereoisomers will not exceed 2^n, where n is equal to the number of chirality centers***.

Helpful Hint: Cholesterol, having eight chirality centers, hypothetically could exist in 2^8 (256) stereoisomeric forms, yet biosynthesis via enzymes produces only *one* stereoisomer.

For 2,3-dibromopentane we should not expect more than four stereoisomers ($2^2 = 4$).

Our next task is to write three-dimensional bond-line formulas for the possible stereoisomers. When doing so it is helpful to follow certain conventions. First, it is generally best to write as many carbon atoms in the plane of the paper as possible. Second, when needing to compare the stereochemistry at adjacent carbon atoms, we usually draw the molecule in a fashion that shows eclipsing interactions, even though this would not be the most stable conformation of the molecule. We do so because, as we shall see later, eclipsed conformations make it easy for us to recognize planes of symmetry when they are present. (We do not mean to imply, however, that eclipsed conformations are the most stable ones—they most certainly are not. It is important to remember that free rotation is possible about single

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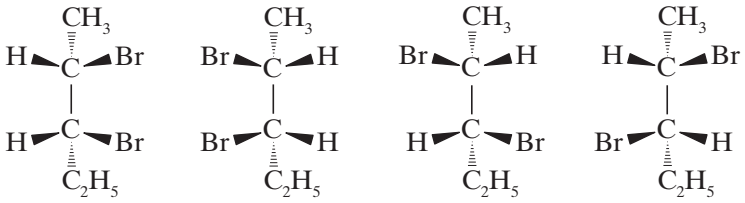
bonds, and that molecules are constantly changing conformations.) Third, if we need to draw the enantiomer of the first stereoisomer, we can easily do so by drawing a mirror image of the first formula, using as our guide an imaginary mirror perpendicular to the page and *between* the molecules.

The structures 1 and 2 are two three-dimensional bond-line formulas for 2,3-dibromopentane. Notice that in drawing these formulas we have followed the conventions above.



1 2 3 4

Since structures 1 and 2 are not superposable, they represent different compounds. Since structures 1 and 2 differ only in the arrangement of their atoms in space, they represent stereoisomers. Structures 1 and 2 are also mirror images of each other; thus 1 and 2 represent a pair of enantiomers.

If we interchange the bromine and hydrogen at C2 (invert the configuration), we find that we have 3, which has a different structural formula than either 1 or 2. Furthermore, we can write a formula for a structure (4) that is a nonsuperposable mirror image of 3, and which is also different from 1 and 2.

Structures 3 and 4 correspond to another pair of enantiomers. Structures 1–4 are all different, so there are, in total, four stereoisomers of 2,3-dibromopentane. Essentially what we have done above is to write all the possible structures that result by successively interchanging two groups at all chirality centers. At this point you should convince yourself that there are no other stereoisomers by writing other structural formulas. You will find that rotation about the single bonds (or of the entire structure) of any other arrangement of the atoms will cause the structure to become superposable with one of the structures that we have written here. Better yet, using different colored balls, make molecular models as you work this out.

The compounds represented by structures 1–4 are all optically active compounds. Any one of them, if placed separately in a polarimeter, would show optical activity. The compounds represented by structures 1 and 2 are enantiomers. The compounds represented by structures 3 and 4 are also enantiomers. But what is the isomeric relation between the compounds represented by 1 and 3?

We can answer this question by observing that 1 and 3 *are stereoisomers* and that they *are not mirror images of each other*. They are, therefore, *diastereomers*. Diastereomers have different physical properties—different melting points and boiling points, different solubilities, and so forth.

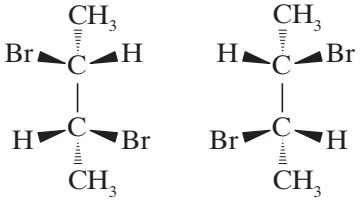
Practice Problem 4.16

(a) If 3 and 4 are enantiomers, what are 1 and 4? **(b)** What are 2 and 3, and 2 and 4? **(c)** Would you expect 1 and 3 to have the same melting point? **(d)** The same boiling point? **(e)** The same vapor pressure?

4.12A Meso Compounds

A structure with two chirality centers does not always have four possible stereoisomers. Sometimes there are only *three*. As we shall see, *some molecules are achiral even though they contain chirality centers*.

To understand this, let us write stereochemical formulas for 2,3-dibromobutane. We begin in the same way as we did before. We write formulas for one stereoisomer and for its mirror image:



A B

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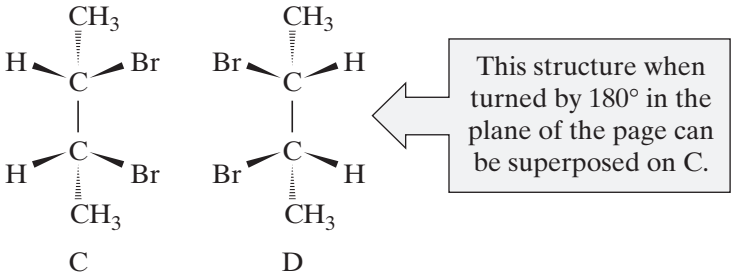
Structures A and B are nonsuperposable and represent a pair of enantiomers.

When we write the new structure C (see below) and its mirror image D, however, the situation is different. *The two structures are superposable*. This means that C and D do not represent a pair of enantiomers. Formulas C and D represent identical orientations of the same compound:



Helpful Hint: If a molecule has an internal plane of symmetry it is achiral

The molecule represented by structure C (or D) is not chiral even though it contains two chirality centers. A **meso compound** is an achiral molecule that contains chirality centers. Meso compounds are not optically active.

The ultimate test for molecular chirality is to construct a model (or write the structure) of the molecule and then test whether or not the model (or structure) is superposable on its mirror image. If it is, the molecule is achiral: If it *is not*, the molecule is chiral.

We have already carried out this test with structure C and found that it is achiral. We can also demonstrate that C is achiral in another way. Figure 4.16 shows that structure C *has an internal plane of symmetry*.

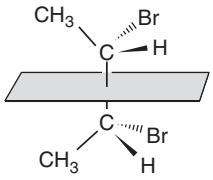


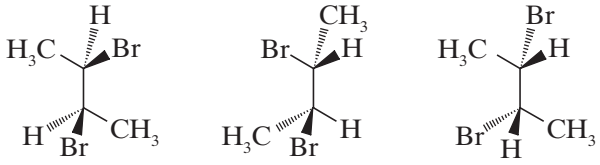
Figure 4.16 The plane of symmetry of meso-2,3-dibromobutane. This plane divides the molecule into halves that are mirror images of each other.

Practice Problem 4.17

Which of the following would be optically active: **(a)** A pure sample of A; **(b)** A pure sample of B; **(c)** A pure sample of C; **(d)** An equimolar mixture of A and B?

Practice Problem 4.18

The following are formulas for three compounds, written in noneclipsed conformations. In each instance tell which compound (A, B, or C above) each formula represents.



Practice Problem 4.19

Write three-dimensional formulas for all of the stereoisomers of each of the following compounds. Label pairs of enantiomers and label meso compounds.

(a) $CH_3CHClCHClCH_3$

(b) $CH_3CHOHCH_2CHOHCH_3$

(c) $CH_2ClCHFCHFCH_2Cl$

(d) $CH_3CHOHCH_2CHClCH_3$

(e) $CH_3CHBrCHFCH_3$

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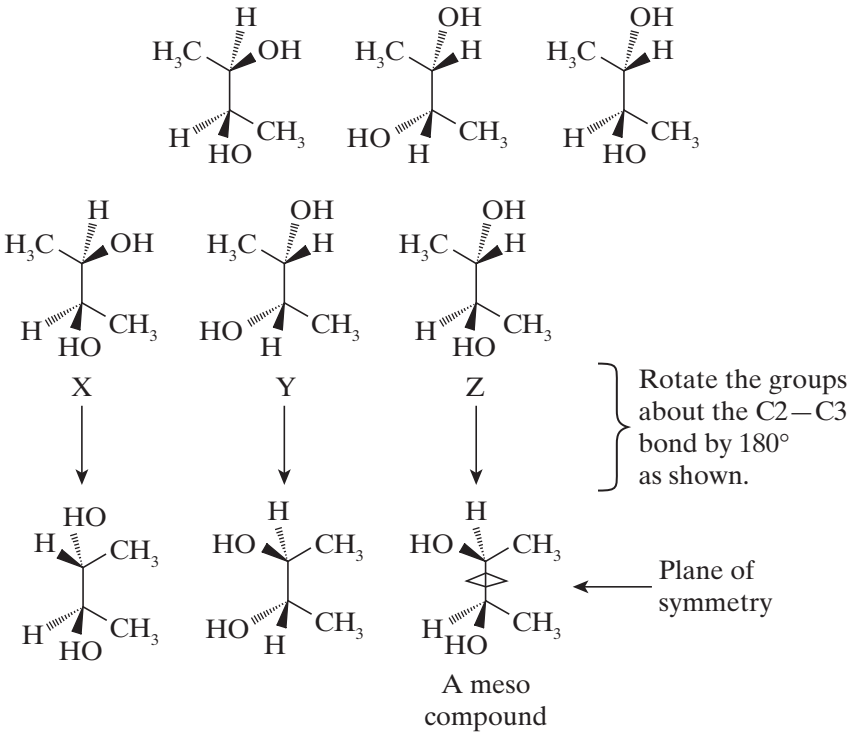
Solved Problem 4.5

Which of the following is a meso compound?



Answer

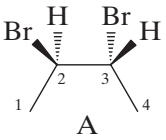
In each molecule, rotating the groups joined by the C2—C3 bond by 180° brings the two methyl groups into comparable position. In the case of compound Z, a plane of symmetry results, and therefore, Z is a meso compound. No plane of symmetry is possible in X and Y.

The following two problems relate to compounds A–D in the preceding paragraphs.

4.12B HOW TO Name Compounds with More than One Chirality Center

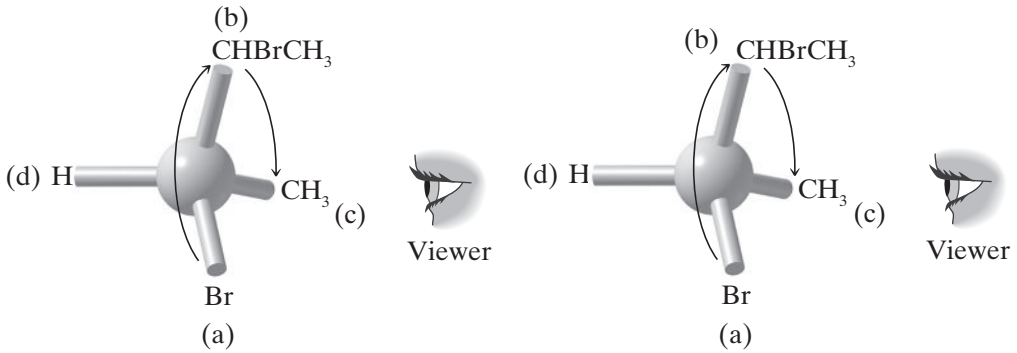
If a compound has more than one chirality center, we analyze each center separately and decide whether it is (*R*) or (*S*). Then, using numbers, we tell which designation refers to which carbon atom.

Consider stereoisomer A of 2,3-dibromobutane:



2, 3-Dibromobutane

When this formula is rotated so that the group of lowest priority attached to C2 is directed away from the viewer, it resembles the following:



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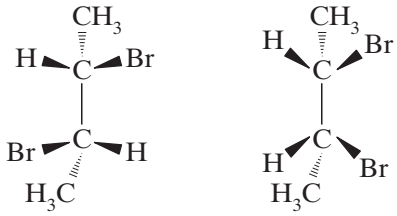
The order of progression from the group of highest priority to that of next highest priority (from —Br, to —$CHBrCH_3$, to —CH_3) is clockwise. So C2 has the (*R*) configuration. When we repeat this procedure with C3, we find that C3 also has the (*R*) configuration. Compound A, therefore, is (2*R*, 3*R*)-2,3-dibromobutane.

Practice Problem 4.20

Give names that include (*R*) and (*S*) designations for compounds B and C:

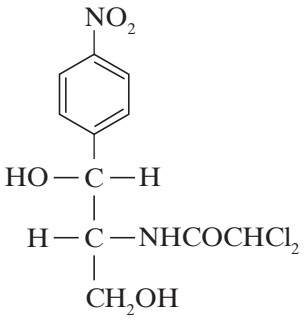


Practice Problem 4.21

Give names that include (*R*) and (*S*) designations for your answers to Practice Problem 4.19.

Practice Problem 4.22

Chloramphenicol (at right) is a potent antibiotic, isolated from *Streptomyces venezuelae*, that is particularly effective against typhoid fever. It was the first naturally occurring substance shown to contain a nitro (—NO_2) group attached to an aromatic ring. Both chirality centers in chloramphenicol are known to have the (*R*) configuration. Identify the two chirality centers and write a three-dimensional formula for chloramphenicol.



Chloramphenicol

4.13 | FISCHER PROJECTION FORMULAS

So far in writing structures for chiral molecules we have only used formulas that show three dimensions with solid and dashed wedges, and we shall largely continue to do so until we study carbohydrates in Chapter 20. The reason is that formulas with solid and dashed wedges unambiguously show three dimensions, and they can be manipulated on paper in any way that we wish so long as we do not break bonds. Their use, moreover, teaches us to see molecules (in our mind's eye) in three dimensions, and this ability will serve us well.

Chemists, however, sometimes use formulas called **Fischer projections** to show three dimensions in chiral molecules such as acyclic carbohydrates. Fischer projection formulas are useful in cases where there are chirality centers at several adjacent carbon atoms, as is often the case in carbohydrates. Use of Fischer projection formulas requires rigid adherence to certain conventions, however. **Used carelessly, these projection formulas can easily lead to incorrect conclusions**.

4.13A HOW TO Draw and Use Fischer Projections

Let us consider how we would relate a three-dimensional formula for 2,3-dibromobutane using solid and dashed wedges to the corresponding Fischer projection formula. First, it is necessary to note that in Fischer projections the carbon chain

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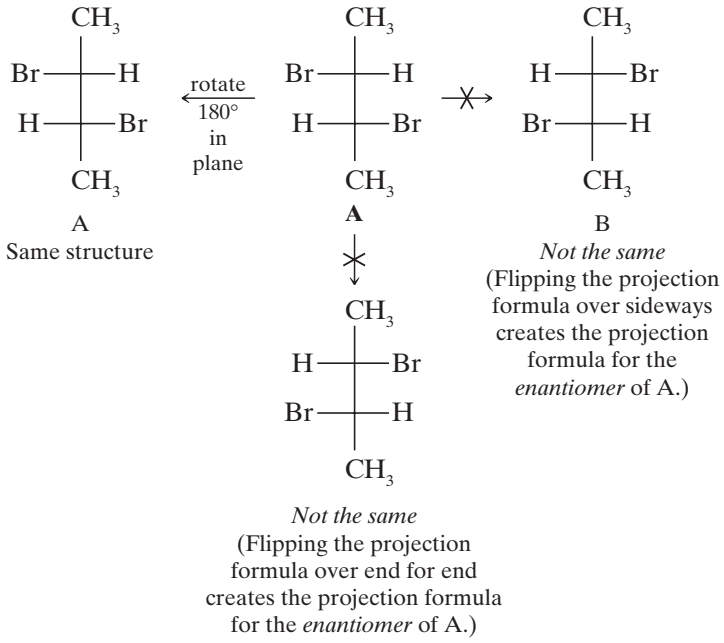
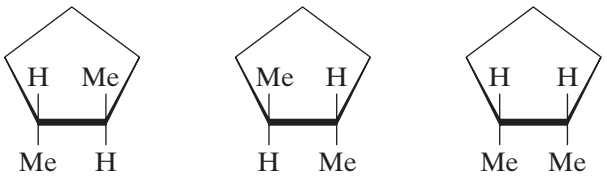
is always drawn from top to bottom, rather than side to side as is often the case with bond-line formulas. We consider the molecule in a conformation that has eclipsing interactions between the groups at each carbon. For 2,3-dibromobutane we turn the bond-line formula so that the carbon chain runs up and down and we orient it so that groups attached to the main carbon chain project out of the plane like a bow tie. The carbon–carbon bonds of the chain, therefore, lie either in the plane of the paper or project behind it. Then to draw the Fischer projection we simply "project" all of the bonds onto the paper, replacing all solid and dashed wedges with ordinary lines. Having done this, the vertical line of the formula now represents the carbon chain, each point of intersection between the vertical line and a horizontal line represents a carbon atom in the chain, and we understand the horizontal lines to be bonds that project out toward us.

To test the superposability of two structures represented by Fischer projections we are allowed to rotate them in the plane of the paper by 180°, *but by no other angle*. We must always keep the Fischer projection formulas in the plane of the paper, and **we are not allowed to flip them over**. If we flip a Fischer projection over, the horizontal bonds project behind the plane instead of in front, and every configuration would be *misrepresented* as the opposite of what was intended.



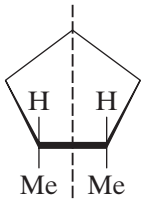
4.14 | STEREOISOMERISM OF CYCLIC COMPOUNDS

Cyclopentane derivatives offer a convenient starting point for a discussion of the stereoisomerism of cyclic compounds. For example, 1,2-dimethylcyclopentane has two chirality centers and exists in three stereoisomeric forms 5, 6, and 7:



Enantiomers
5 6

Meso compound
7



Plane of symmetry
7

The *trans* compound exists as a pair of enantiomers 5 and 6. *cis*-1,2-Dimethylcyclopentane (7) is a meso compound. It has a plane of symmetry that is perpendicular to the plane of the ring:

Practice Problem 4.23

(a) Is *trans*-1,2-dimethylcyclopentane (5) superposable on its mirror image (i.e., on compound 6)? **(b)** Is *cis*-1,2-dimethylcyclopentane (7) superposable on its mirror image? **(c)** Is *cis*-1,2-dimethylcyclopentane a chiral

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molecule? **(d)** Would *cis*-1,2-dimethylcyclopentane show optical activity? **(e)** What is the stereoisomeric relationship between 5 and 7? **(f)** Between 6 and 7?

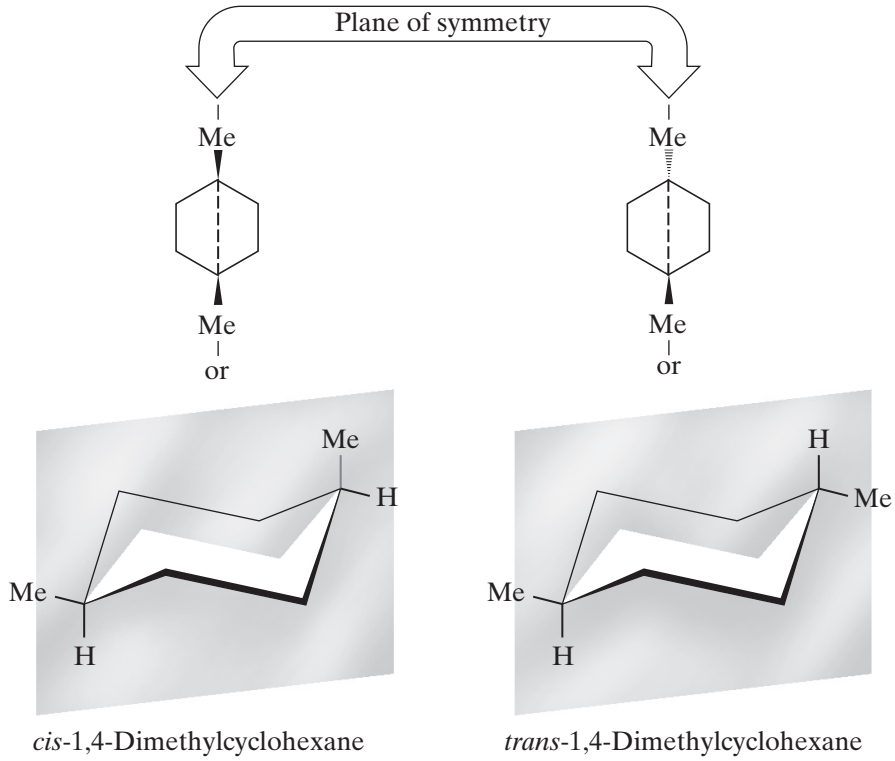
Practice Problem 4.24

Write structural formulas for all of the stereoisomers of 1,3-dimethylcyclopentane. Label pairs of enantiomers and meso compounds if they exist.

4.14A Cyclohexane Derivatives

1,4-Dimethylcyclohexanes

If we examine a formula of 1,4-dimethylcyclohexane, we find that it does not contain any chirality centers. However, it does have two stereogenic centers. As we learned in Section 4.13, 1,4-dimethylcyclohexane can exist as *cis–trans* isomers. The *cis* and *trans* forms (Fig. 4.17) are *diastereomers*. Neither compound is chiral and, therefore, neither is optically active. Notice that both the *cis* and *trans* forms of 1,4-dimethylcyclohexane have a plane of symmetry.



cis-1,4-Dimethylcyclohexane *trans*-1,4-Dimethylcyclohexane

Figure 4.17 The *cis* and *trans* forms of 1,4-dimethylcyclohexane are diastereomers of each other. Both compounds are achiral, as the internal plane of symmetry (blue) shows for each.

Helpful Hint: Build handheld molecular models of the 1,4-, 1,3-, and 1,2-dimethylcyclohexane isomers discussed here and examine their stereochemical properties. Experiment with flipping the chairs and also switching between *cis* and *trans* isomers.

1,3-Dimethylcyclohexanes

1,3-Dimethylcyclohexane has two chirality centers; we can, therefore, expect as many as four stereoisomers ($2^2 = 4$). In reality there are only three. *cis*-1,3-Dimethylcyclohexane has a plane of symmetry (Fig. 4.18) and is achiral.

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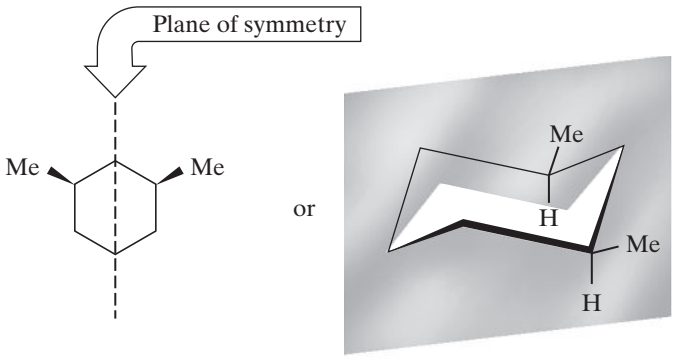

Figure 4.18 *cis*-1,3-Dimethylcyclohexane has a plane of symmetry, shown in blue, and is therefore achiral.

trans-1,3-Dimethylcyclohexane does not have a plane of symmetry and exists as a pair of enantiomers (Fig. 4.19). You may want to make models of the *trans*-1,3-dimethylcyclohexane enantiomers. Having done so, convince yourself that they cannot be superposed as they stand and that they cannot be superposed after one enantiomer has undergone a ring flip.

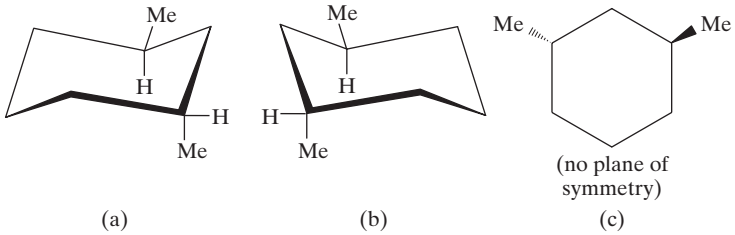

Figure 4.19 *trans*-1,3-Dimethylcyclohexane does not have a plane of symmetry and exists as a pair of enantiomers. The two structures (a and b) shown here are not superposable as they stand, and flipping the ring of either structure does not make it superposable on the other. (c) A simplified representation of (b).

1,2-Dimethylcyclohexanes

1,2-Dimethylcyclohexane also has two chirality centers, and again we might expect as many as four stereoisomers. Indeed there are four, but we find that we can *isolate* only *three* stereoisomers. *trans*-1,2-Dimethylcyclohexane (Fig. 4.20) exists as a pair of enantiomers. Its molecules do not have a plane of symmetry.

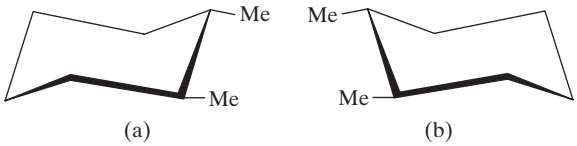

Figure 4.20 *trans*-1,2-Dimethylcyclohexane has no plane of symmetry and exists as a pair of enantiomers (a and b). [Notice that we have written the most stable conformations for (a) and (b). A ring flip of either (a) or (b) would cause both methyl groups to become axial.]

cis-1,2-Dimethylcyclohexane, shown in Fig. 4.21, presents a somewhat more complex situation. If we consider the two conformational structures (*c*) and (*d*), we find that these two mirror-image structures are not identical. Neither has a plane of symmetry and each is a chiral molecule, *but they are interconvertible by a ring flip*. Therefore, although the two structures represent enantiomers, *they cannot be separated* because they rapidly interconvert even at low temperature. They simply represent *different conformations of the same compound*. Therefore, structures (*c*) and (*d*) are not configurational stereoisomers; they are **conformational stereoisomers** (see Section 4.9A). This means that at normal temperatures there are only three *isolable stereoisomers* of 1,2-dimethylcyclohexane.

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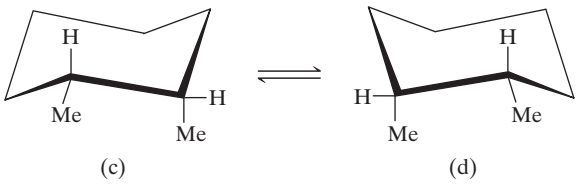


Figure 4.21 *cis*-1,2-Dimethylcyclohexane exists as two rapidly interconverting chair conformations (c) and (d).

As we shall see later, there are some compounds whose conformational stereoisomers *can* be isolated in enantiomeric forms. Isomers of this type are called atropisomers (Section 4.16).

Practice Problem 4.25

Write formulas for all of the isomers of each of the following. Designate pairs of enantiomers and achiral compounds where they exist.

(a) 1-Bromo-2-chlorocyclohexane

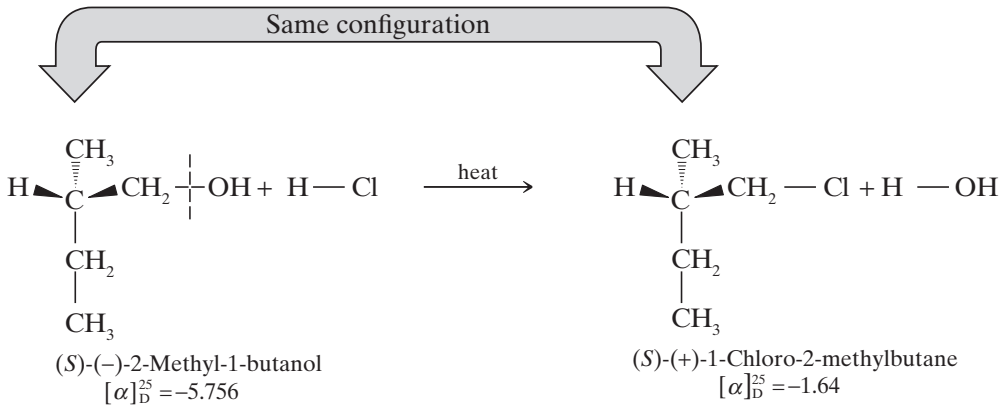
(b) 1-Bromo-3-chlorocyclohexane

(c) 1-Bromo-4-chlorocyclohexane

4.15 | RELATING CONFIGURATIONS THROUGH REACTIONS IN WHICH NO BONDS TO THE CHIRALITY CENTER ARE BROKEN

If a reaction takes place in a way so that no bonds to the chirality center are broken, the product will of necessity have the same general configuration of groups around the chirality center as the reactant.

Such a reaction is said **to proceed with retention of configuration**. Consider as an example the reaction that takes place when (*S*)-(−)-2-methyl-1-butanol is heated with concentrated hydrochloric acid:



We do not need to know now exactly how this reaction takes place to see that the reaction must involve breaking the CH_2—OH bond of the alcohol because the —OH group is replaced by a —Cl. There is no reason to assume that any other bonds are broken. (We shall study how this reaction takes place in Section 10.8A.) Since no bonds to the chirality center are broken, the reaction must take place with retention of configuration, and the product of the reaction *must have the same configuration of groups around the chirality center that the reactant had*. By saying that the two compounds have the same configuration, we simply mean that comparable or identical groups in the two compounds occupy the same relative positions in space around the chirality center. (In this instance the $—CH_2OH$ group and the $—CH_2Cl$ are comparable, and they occupy the same relative position in both compounds; all the other groups are identical and they occupy the same positions.)

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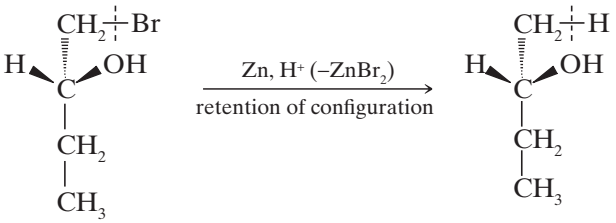
Notice that in this example while the (*R*, *S*) designation *does not change* [both reactant and product are (*S*)], the direction of optical rotation *does change* [the reactant is (–) and the product is (+)]. Neither occurrence is a necessity when a reaction proceeds with retention of configuration. In the next section we shall see examples of reactions in which configurations are retained and where the direction of optical rotation does not change. The following reaction is one that proceeds with retention of configuration but involves a change in the (*R*, *S*) designation:

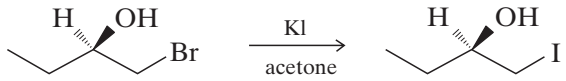


(*R*)-1-Bromo-2-butanol (*S*)-2-Butanol

In this example the (*R*, *S*) designation changes because the $-CH_2Br$ group of the reactant changes to a $-CH_3$ group in the product ($-CH_2Br$ has a higher priority than $-CH_2CH_3$, and $-CH_3$ has a lower priority than $-CH_2CH_3$).

Solved Problem 4.6

When (*R*)-1-bromo-2-butanol reacts with KI in acetone the product is 1-iodo-2-butanol. Would the product be (*R*) or (*S*)?



(*R*)-1-Bromo-2-butanol (*R*)-1-Iodo-2-butanol

Answer

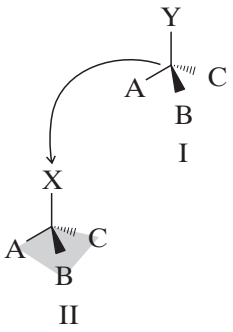
No bonds to the chirality center would be broken, so we can reason that the product would be the following.

The configuration of the product would still be (*R*) because replacing the bromine at C1 with an iodine atom does not change the relative priority of C1.

4.15A Relative and Absolute Configurations

Reactions in which no bonds to the chirality center are broken are useful in relating configurations of chiral molecules. That is, they allow us to demonstrate that certain compounds have the same relative configuration. In each of the examples that we have just cited, the products of the reactions have the same *relative configurations* as the reactants.

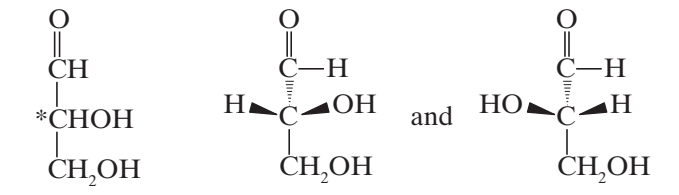
Chirality centers in different molecules have the same **relative configuration** if they share three groups in common and if these groups **with** the central carbon can be superposed in a pyramidal arrangement



The chirality centers in I and II have the same relative configuration. Their common groups and central carbon can be superposed.

Before 1951 only relative configurations of chiral molecules were known. No one prior to that time had been able to demonstrate with certainty what the actual spatial arrangement of groups was in any chiral molecule. To say this another way, no one had been able to determine the absolute configuration of an optically active compound. The **absolute configuration** of a chirality center is its (*R*) or (*S*) designation, which can only be specified by knowledge of the actual arrangement of groups in space at the chirality center.

Prior to any known absolute configurations, the configurations of chiral molecules were related to each other *through reactions of known stereochemistry*. Attempts were also made to relate all configurations to a single compound that had been chosen arbitrarily to be the standard. This standard compound was glyceraldehyde. Glyceraldehyde has one chirality center; therefore, glyceraldehyde exists as a pair of enantiomers:



Glyceraldehyde (*R*)-Glyceraldehyde (*S*)-Glyceraldehyde

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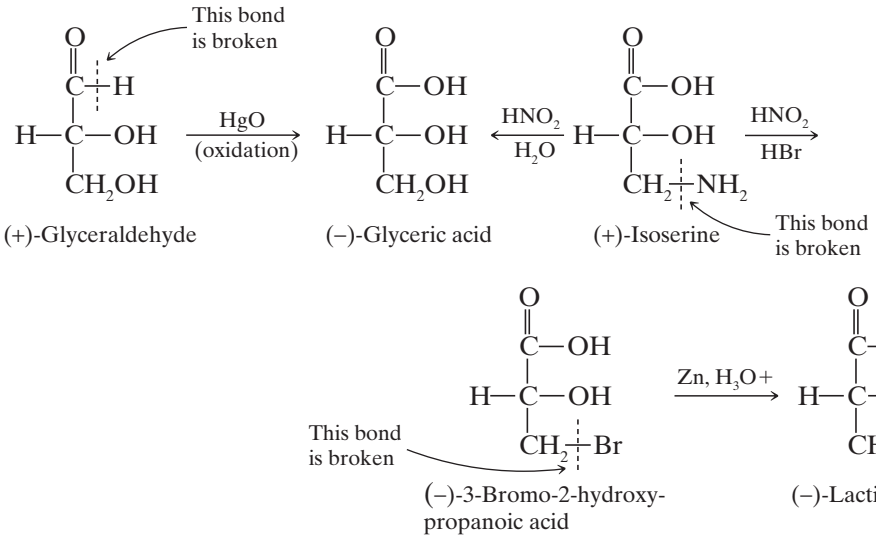
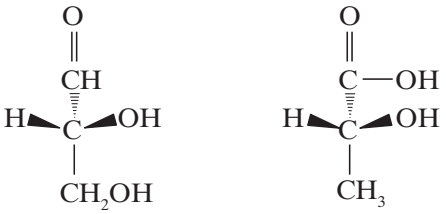
In one system for designating configurations, (*R*)-glyceraldehyde is called D-glyceraldehyde and (*S*)-glyceraldehyde is called L-glyceraldehyde. This system of nomenclature is used with a specialized meaning in the nomenclature of carbohydrates.

One glyceraldehyde enantiomer is dextrorotatory (+) and the other, of course, is levorotatory (–). Before 1951 no one was sure, however, which configuration belonged to which enantiomer. Chemists decided arbitrarily to assign the (*R*) configuration to the (+)-enantiomer. Then, configurations of other molecules were related to one glyceraldehyde enantiomer or the other through reactions of known stereochemistry.

For example, the configuration of (–)-lactic acid can be related to (+)-glyceraldehyde through the following sequence of reactions in which no bond to the chirality center is broken:



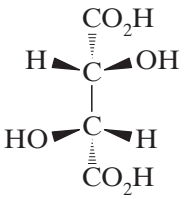
The stereochemistry of all of these reactions is known. Because none of the bonds to the chirality center (shown in red) has been broken during the sequence, its original configuration is retained. If the assumption is made that (+)-glyceraldehyde is the (*R*) stereoisomer, and therefore has the following configuration, then (–)-lactic acid is also an (*R*) stereoisomer and its configuration is



Practice Problem 4.26

Write bond-line three-dimensional formulas for the starting compound, the product, and all of the intermediates in a synthesis similar to the one just given that relates the configuration of (–)-glyceraldehyde with (+)-lactic acid. Label each compound with its proper (*R*) or (*S*) and (+) or (–) designation.

The configuration of (–)-glyceraldehyde was also related through reactions of known stereochemistry to (+)-tartaric acid:



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In 1951 J. M. Bijvoet, the director of the van't Hoff Laboratory of the University of Utrecht in the Netherlands, using a special technique of X-ray diffraction, was able to show conclusively that (+)-tartaric acid had the absolute configuration shown above. This meant that the original arbitrary assignment of the configurations of (+)- and (−)-glyceraldehyde was also correct. It also meant that the configurations of all of the compounds that had been related to one glyceraldehyde enantiomer or the other were now known with certainty and were now **absolute configurations**.

4.16 | SEPARATION OF ENANTIOMERS: RESOLUTION

So far we have left unanswered an important question about optically active compounds and racemic forms: How are enantiomers separated? Enantiomers have identical solubilities in ordinary solvents, and they have identical boiling points. Consequently, the conventional methods for separating organic compounds, such as crystallization and distillation, fail when applied to a racemic form.

4.16A Pasteur's Method for Separating Enantiomers

It was, in fact, Louis Pasteur's separation of a racemic form of a salt of tartaric acid in 1848 that led to the discovery of the phenomenon called enantiomerism. Pasteur, consequently, is often considered to be the founder of the field of stereochemistry.

(+)-Tartaric acid is one of the by-products of wine making (nature usually only synthesizes one enantiomer of a chiral molecule). Pasteur had obtained a sample of racemic tartaric acid from the owner of a chemical plant. In the course of his investigation Pasteur began examining the crystal structure of the sodium ammonium salt of racemic tartaric acid. He noticed that two types of crystals were present. One was identical with crystals of the sodium ammonium salt of (+)-tartaric acid that had been discovered earlier and had been shown to be dextrorotatory. Crystals of the other type were *non* superposable mirror images of the first kind. The two types of crystals were actually chiral. Using tweezers and a magnifying glass, Pasteur separated the two kinds of crystals, dissolved them in water, and placed the solutions in a polarimeter. The solution of crystals of the first type was dextrorotatory, and the crystals themselves proved to be identical with the sodium ammonium salt of (+)-tartaric acid that was already known. The solution of crystals of the second type was levorotatory; it rotated plane-polarized light in the opposite direction and by an equal amount. The crystals of the second type were of the sodium ammonium salt of (−)-tartaric acid. The chirality of the crystals themselves disappeared, of course, as the crystals dissolved into their solutions, *but the optical activity* remained. Pasteur reasoned, therefore, that the molecules themselves must be chiral.

Pasteur's discovery of enantiomerism and his demonstration that the optical activity of the two forms of tartaric acid was a property of the molecules themselves led, in 1874, to the proposal of the tetrahedral structure of carbon by van't Hoff and Le Bel.

Unfortunately, few organic compounds give chiral crystals as do the (+)- and (−)-tartaric acid salts. Few organic compounds crystallize into separate crystals (containing separate enantiomers) that are visibly chiral like the crystals of the sodium ammonium salt of tartaric acid. Pasteur's method, therefore, is not generally applicable to the separation of enantiomers.

4.16B Current Methods for Resolution of Enantiomers

One of the most useful procedures for separating enantiomers is based on the following:

When a racemic mixture reacts with a single enantiomer of another compound, a mixture of diastereomers results, and diastereomers, because they have different melting points, boiling points, and solubilities, can be separated by conventional means.

Diastereomeric recrystallization is one such process. Another method is **resolution** by enzymes, whereby an enzyme selectively converts one enantiomer in a racemic mixture to another compound, after which the unreacted enantiomer and the new compound are separated. The reaction by lipase in Section 4.10B is an example of this type of resolution. Chromatography using chiral media is also widely used to resolve enantiomers. This approach is applied in high-performance liquid chromatography (HPLC) as well as in other forms of chromatography. Diastereomeric interactions between molecules of the racemic mixture and the chiral chromatography medium cause enantiomers of the racemate to move through the chromatography apparatus at different rates. The enantiomers are then collected separately as they elute from the chromatography device.

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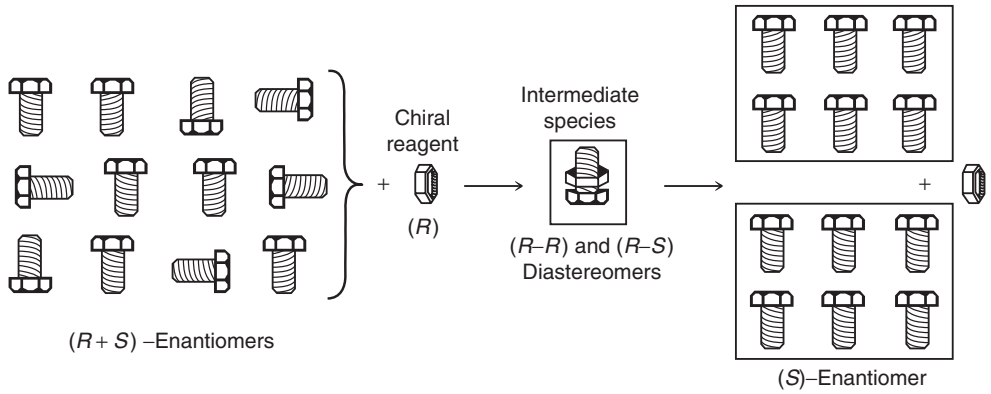
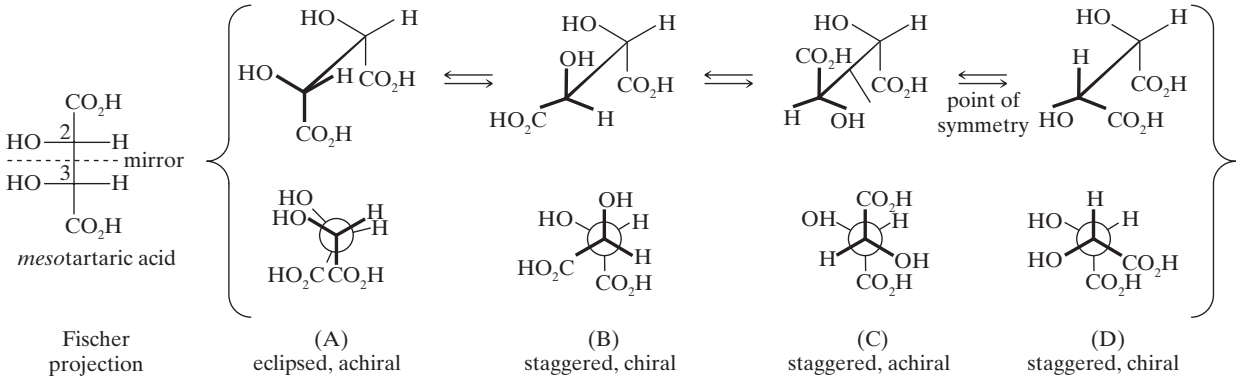
4.16C Resolution of Racemates

As has been noted earlier, chiral compounds synthesized from achiral starting materials and reagents are generally racemic (i.e., a 50:50 mixture of enantiomers). The process of separation of racemates into their component enantiomers is called **resolution**. Since enantiomers have identical physical properties, such as solubility and melting point, resolution is extremely difficult. Diastereomers, on the other hand, have different physical properties, and this property is used to achieve resolution of racemates. The reaction of a racemate with an enantiomerically pure chiral reagent gives a mixture of diastereomers, which can be separated. On reversing the first reaction, the separated enantiomers and the recovered reagent are obtained as products. Various kinds of chemical and physical reactions, including salt formation, may be used to achieve the diastereomeric intermediates needed for separation. The following diagram illustrates this general principle by showing how a nut having a right-handed thread (R) could serve as a "reagent" to discriminate and separate a mixture of right- and left-handed bolts of identical size and weight. Only the two right-handed partners can interact to give a fully-threaded intermediate; therefore, the separation is fairly simple. The resolving moiety, that is, the nut, is then removed, leaving the bolts separated into their right and left-handed forms. Chemical reactions of enantiomers are generally not so dramatically different, but a practical distinction is nevertheless possible.



Conformational Enantiomorphism

The Fischer projection formula of mesotartaric acid has a plane of symmetry bisecting the C_2–C_3 bond, as shown on the left in the diagram below, so this structure is clearly achiral. The eclipsed orientation of bonds that is assumed in the Fischer projection formula is, however, an unstable conformation, and we should, therefore, examine the stable staggered conformers that undoubtedly make up most of the sample molecules. The four structures that are shown to the right of the Fischer projection consist of the achiral Fischer conformation (A) and three staggered conformers, all shown in both sawhorse and Newman projections. The second and fourth conformations (B) and (D) are dissymmetric, and are in fact enantiomeric structures. The third conformer (C) has a center of symmetry and is achiral.



Conformations of Mesotartaric Acid

Since a significant proportion of the mesotartaric acid molecules in a given sample will have chiral conformations, the achiral properties of the sample (e.g., optical inactivity) should not be attributed to the symmetry of the

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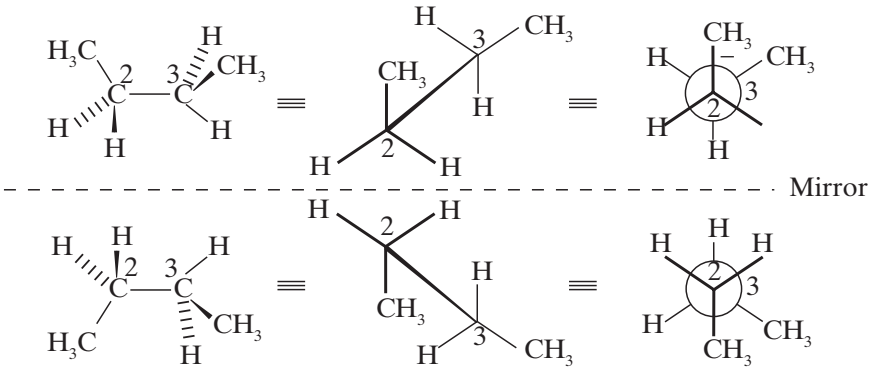
Fischer formula. Equilibria among the various conformations are rapidly established, and the proportion of each conformer present at equilibrium depends upon its relative potential energy (the most stable conformers predominate). As enantiomers have equal potential energies, they will be present in equal concentration, thus canceling their macroscopic optical activity and other chiral behavior. In other words, any chiral species that are present are racemic.

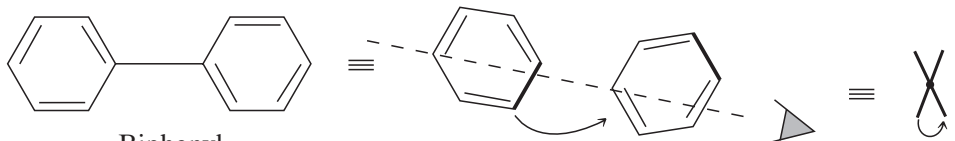


Enantiomeric gauche butane conformers

Interestingly, the chiral conformations are present in most conformationally mobile compounds, even in the absence of chiral centers. The gauche conformers of butane, for instance, are chiral and are present in equal concentration in any sample of this hydrocarbon. The following illustration shows the enantiomeric relationship of these conformers, which are an example of a chiral axis rather than a chiral center.

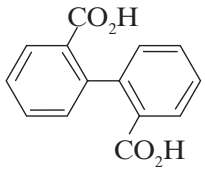
Conformations of Biphenyls

Another class of compounds that show conformational enantiomorphism are the substituted biphenyls. As shown in the following diagram, biphenyl itself is not planar. This is because one benzene ring is slightly twisted or slanted with respect to the other as a result of steric crowding. The resulting chiral conformation, having a dihedral angle of approximately 45°, equilibrates rapidly with its enantiomer via rotation about the connecting single bond. Note that a conformation having a 90° dihedral angle is achiral, as a result of a plane of symmetry.

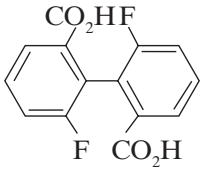


Biphenyl Dihedral angle

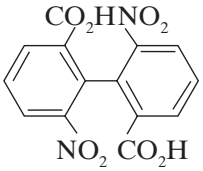
If each of the phenyl rings of a biphenyl has two different ortho or meta substituents (one may be hydrogen), then even the twisted 90° dihedral angle conformer becomes chiral. In order to interconvert such conformers with their mirror image structures, a rotation through the higher energy coplanar form must be made. The ease with which this interconversion occurs will depend upon the size of the ortho substituents, as these groups must slide past each other. The 2,2′-dicarboxylic acid (compound A) shown below cannot be resolved at room temperature, since thermal (kinetic) energy is sufficient to provide the necessary activation energy for racemization. The two additionally substituted diacids to its right have a higher activation energy for racemization, and can be resolved if care is taken to avoid heating them. *As a rule, an activation energy barrier of* 16–19 *kcal/mole is required to prevent spontaneous room temperature racemization of substituted biphenyls*. As fluorine is smaller than a nitro group, compound (B) racemizes more rapidly on heating than does the nitro compound to its right. Conformational isomers that are isolable due to high-energy barriers are called **atropisomers**.



Not resolved at room temperature



Resolved at room temperature; racemizes easily



Resolved at room temperature; racemizes slowly

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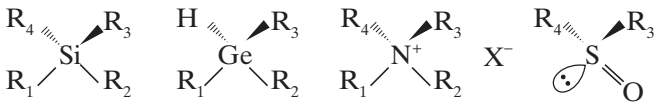
4.17 | COMPOUNDS WITH CHIRALITY CENTERS OTHER THAN CARBON

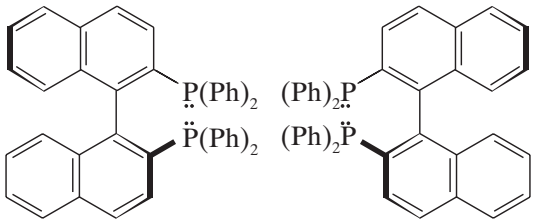
Any tetrahedral atom with four different groups attached to it is a chirality center. Shown here are general formulas of compounds whose molecules contain chirality centers other than carbon. Silicon and germanium are in the same group of the periodic table as carbon. They form tetrahedral compounds as carbon does. When four different groups are situated around the central atom in silicon, germanium, and nitrogen compounds, the molecules are chiral and the enantiomers can, in principle, be separated. Sulphoxides, like certain examples of other functional groups where one of the four groups is a nonbonding electron pair, are also chiral. This is not the case for amines, however,



4.18 | CHIRAL MOLECULES THAT DO NOT POSSESS A CHIRALITY CENTER

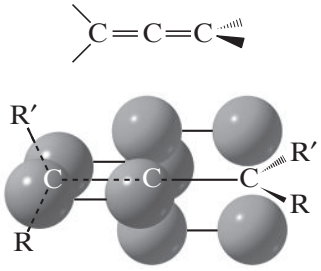
A molecule is chiral if it is not superposable on its mirror image. The presence of a tetrahedral atom with four different groups is only one type of chirality center, however. While most of the chiral molecules we shall encounter have chirality centers, there are other structural attributes that can confer chirality on a molecule. For example, there are compounds that have such large rotational barriers between conformers that individual conformational isomers can be separated and purified, and some of these conformational isomers are stereoisomers.

Conformational isomers that are stable, isolable compounds are called **atropisomers**. The existence of chiral atropisomers has been exploited to great effect in the development of chiral catalysts for stereoselective reactions. An example is BINAP, shown below in its enantiomeric forms:



(*S*)-BINAP (*R*)-BINAP

The origin of chirality in BINAP is the restricted rotation about the bond between the two nearly perpendicular naphthalene rings. This torsional barrier leads to two resolvable enantiomeric conformers, (*S*)- and (*R*)-BINAP. When each enantiomer is used as a ligand for metals such as ruthenium and rhodium (bound by unshared electron pairs on the phosphorus atoms), chiral organometallic complexes result that are capable of catalyzing stereoselective hydrogenation and other important industrial reactions. The significance of chiral ligands is highlighted by the industrial synthesis each year of approximately 3500 *tons* of (−)-menthol using an isomerization reaction involving a rhodium (*S*)-BINAP catalyst.



Allenes are compounds that also exhibit stereoisomerism. Allenes are molecules that contain the following double-bond sequence. The planes of the π bonds of allenes are perpendicular to each other.

This geometry of the π bonds causes the groups attached to the end carbon atoms to lie in perpendicular planes, and, because of this, allenes with different substituents on the end carbon atoms are chiral (Fig. 4.22). (Allenes do not show *cis–trans* isomerism.)

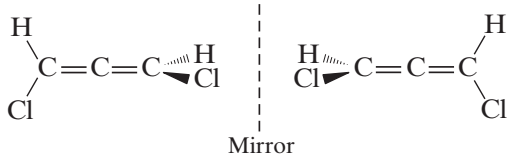


Figure 4.22 Enantiomeric forms of 1,3-dichloroallene.

These two molecules are nonsuperposable mirror images of each other and are therefore chiral. They do not possess a tetrahedral atom with four different groups, however.

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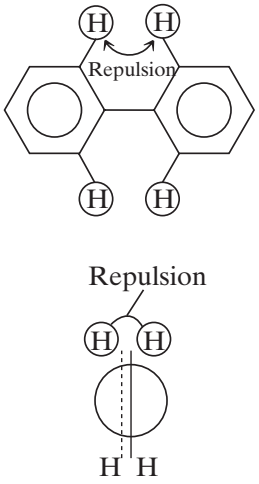
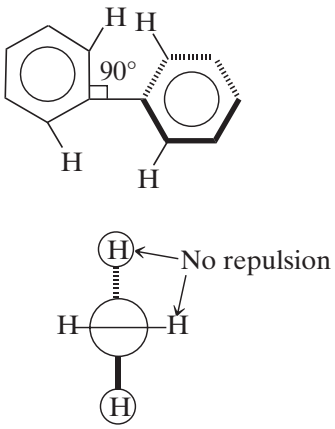
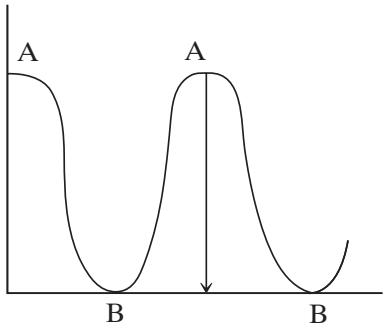
4.19 | BIPHENYL

A biphenyl unit consists of two phenyl rings attached with a σ bond or an intra-annular bond. Phenyl ring has a planar structure but it can rotate along α bond to form different conformations or rotational isomers called rotamers like staggered, eclipsed and skew.





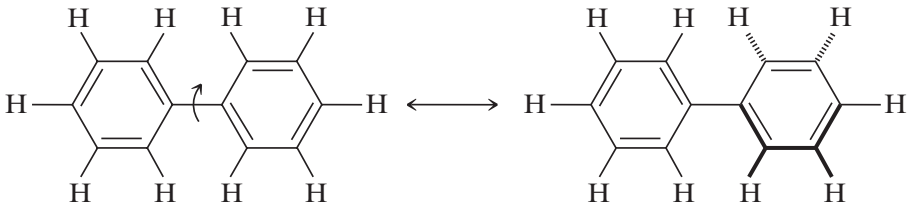


In an ortho-substituted biphenyl compound, due to steric hindrance the molecule has a large energy barrier (75–150 kJ/mol) to produce different rotational isomers which can be optically active or inactive depending on their chiral properties.

If biphenyls are optically active along Û bond then the type of isomers resulting from hindered rotation along this bond are known as atropisomers. This type of isomerism is known as atropisomerism.

4.19A Stereochemistry of Biphenyl

Benzene ring has a planar structure due to sp^2 hybridization. In case of biphenyl, the individual benzene rings are planar but the two rings are joined by a σ bond that result in conformations or rotational isomers. Therefore, biphenyls can be planar or non-planar.



Both conformations A and B shown in figure have a plane of symmetry. If the biphenyl is substituted by certain groups (given below) at the four ortho positions then structure (B) will be more contributing due to ortho hydrogen/substituent repulsion which is explained by van der Waals radii of the group.

H – 1.20 Å	Cl – 1.80 Å	Br < CH_3 > Cl > NO_2 > COOH >> OCH_3 > F > H
O – 1.40 Å	Br – 1.25 Å	
N – 1.50 Å	CH_3 – 2.00 Å	
F – 1.35 Å	I – 2.15 Å	

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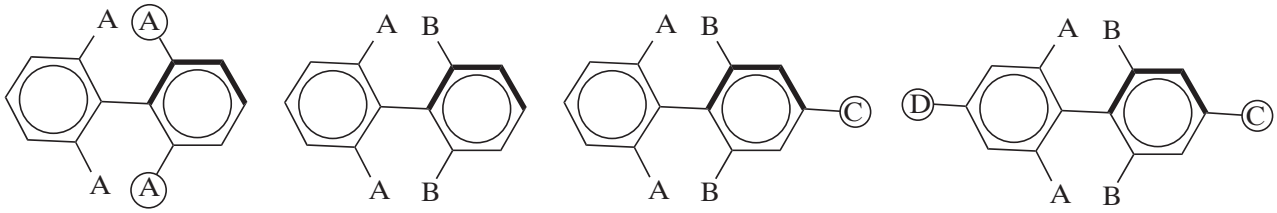
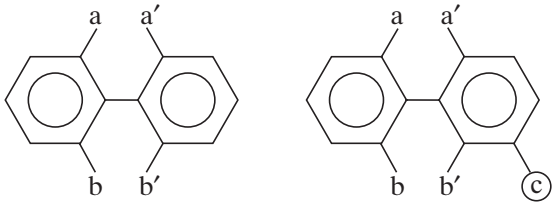
4.19B Absolute Configuration of Biphenyl

1. Biphenyl is an asymmetric compound so it must not have plane of symmetry, center of symmetry or alternate axis of symmetry to be optically active. The following types of biphenyls are optically inactive as they have a plane of symmetry.

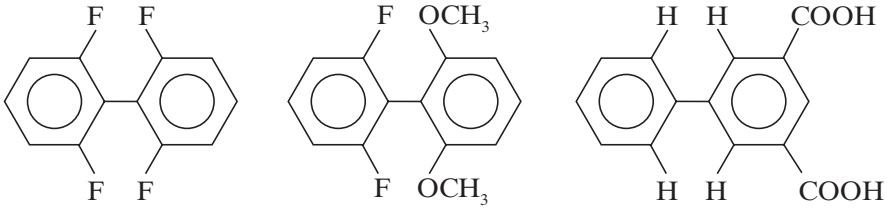


2. In a normal chiral compound, all the four groups must be different. However, in biphenyl each ring should have two different ortho-substituting groups; but, it is not necessary that 'a' should be different from 'a'' or 'b' from 'b''.

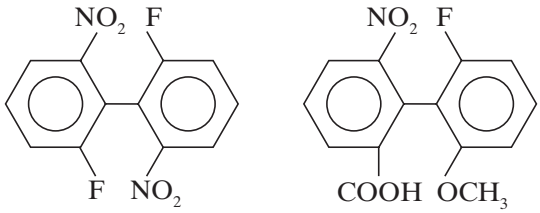


3. van der Waals radii affects racemization (nature of the substituents).

   (a) Smaller van der Waal radii groups: The substituents F, H, OCH_3, etc. have smaller van der Waal's radius. Therefore, when the four ortho-substituting groups are smaller, the rotation about single bond is free and so the compound is not resolvable.

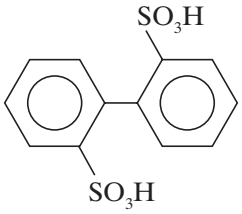


   (b) Medium-sized groups: It contains atleast amino groups, two carboxy groups or one amino and one carbon; and the remaining group may be F, OMe.



   In this situation biphenyl readily racemizes.

   (c) Bulky groups: It contains two nitro groups or sulphonic groups at ortho position and the remaining groups are F, OCH_3 then the compound will be resolvable.



   The resonance affects the rate of racemization.

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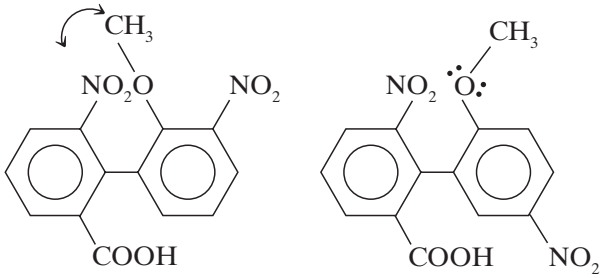
4.20 | RACEMIZATION OF BIPHENYL COMPOUNDS

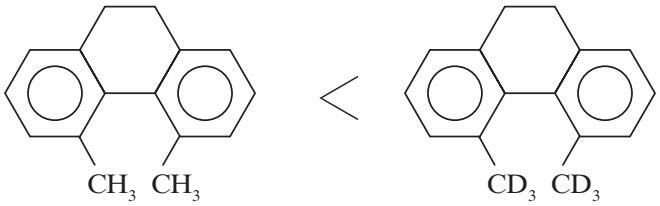
Ortho-substituted biphenyls are optically active due to restricted rotation along σ bonds, and the enantiomers can be resolved. There are several factors which govern racemization of optically active biphenyls. Some of these factors are mentioned below:

1. **Effects of substituents:** The rate of racemization of structure (A) is slower than structure (B) due to the presence of NO_2 group. In case of a methoxy (OCH_3) group, the conformation will be as follows:

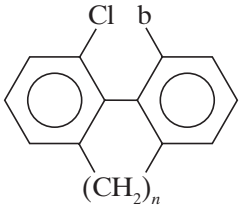


Therefore, methyl of the methoxy group will show interference by two groups (NO_2, COOH) of the other benzene ring because of which the racemization will be less. This is known as buttressing effect and the order for this effect is $NO_2 > Cl > Me$.

2. **Effect of heat:** Racemization of biphenyls is also affected by heating or irradiation in a suitable solvent. On heating, the ortho-substituted group as well as the two benzene rings will vibrate in such a way that optically active compounds get converted into equimolecular amounts of (+) and (–) isomers and racemization takes place.
3. **Secondary inverse isotope effects:** Deuterium has a smaller van der Waals radius than hydrogen; therefore, van der Waal radius CD_3 is smaller than CH_3, so the rate of racemization of the following compounds will be as shown below:



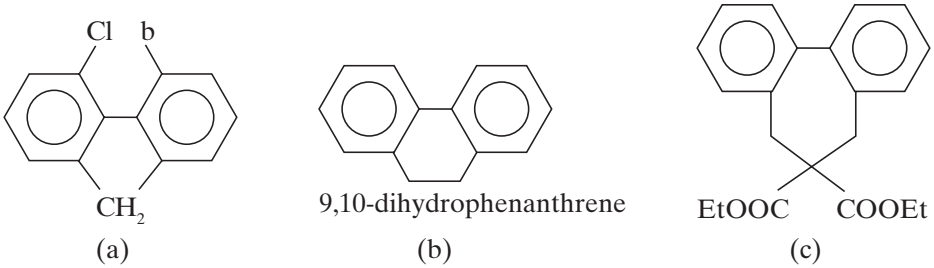
4. **Effect of a bridge in the molecular structure:**



(a) If $n = 1$ the molecule is planar having a molecular plane of symmetry, and therefore optically inactive because on the carbon bridge is tightly bound and both the rings are in one plane.

(b) If $n = 2$, the bridge is loose, and therefore the rings can move out of plane with respect to each other and optically active at low temperature.

(c) If $n = 3$, the compound is optically active and stable.



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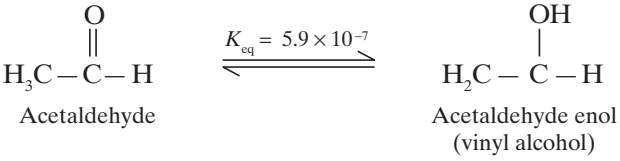
4.21 | TAUTOMERISM

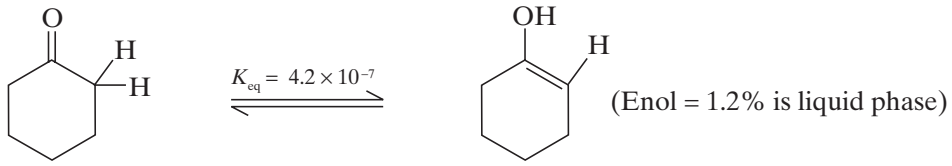
The term tautomers is used to describe the relationship between enols and their corresponding carbonyl compounds. Tautomers means 'constitutional isomers that undergo such rapid interconversion that they cannot be independently isolated'. Under the most common circumstances, carbonyl compounds and their corresponding enols are in rapid equilibrium. However, chemists are now aware that the interconversion of enols and their corresponding carbonyl compounds is catalyzed by acids and bases. This reaction can be very slow in dilute solutions in the absence of acid or base catalysts, and enols have actually been isolated under very carefully controlled conditions.

4.21A Enolization of Carbonyl Compounds

Carbonyl compounds with α-hydrogens are in equilibrium with small amounts of their enol isomers. The equilibrium constants shown in the following equations are typical.



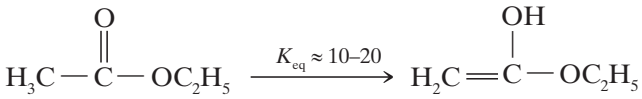
Acetaldehyde — Acetaldehyde enol (vinyl alcohol)



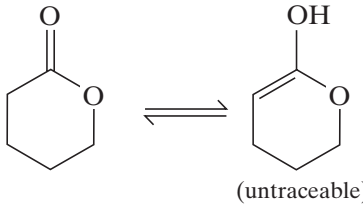
(Enol = 1.2% is liquid phase)

Cyclohexanone — Cyclohexanone enol

Unsymmetrical ketones are in equilibrium with more than one enol. Esters contain even smaller amounts of enol isomers than aldehydes or ketones.

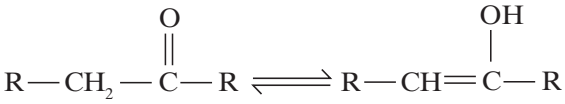


Ethyl acetate — Enol of ethyl acetate



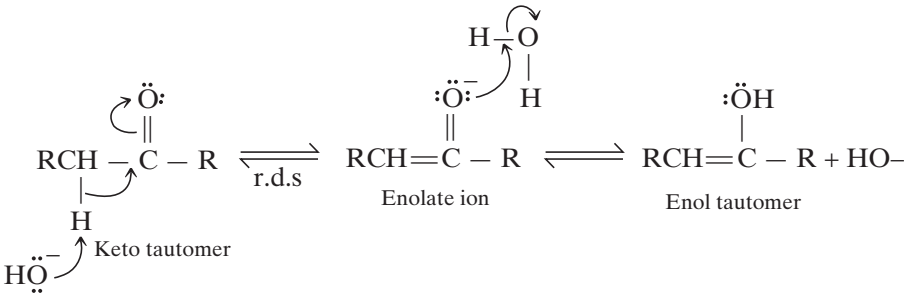
(untraceable)

The mechanism of tautomerism is as follows:



In alkaline solutions, hydroxide ion extracts a proton from the α-carbon of the keto tautomer, thus forming an enolate ion. Protonation on oxygen forms the enol tautomer, whereas protonation on the α-carbon re-forms the keto tautomer.

Base-Catalyzed Keto–Enol Interconversion



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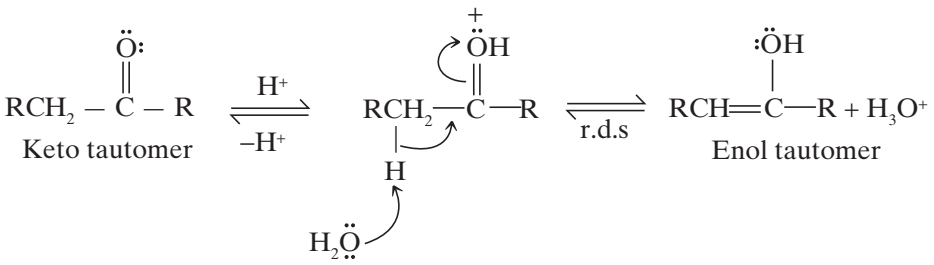
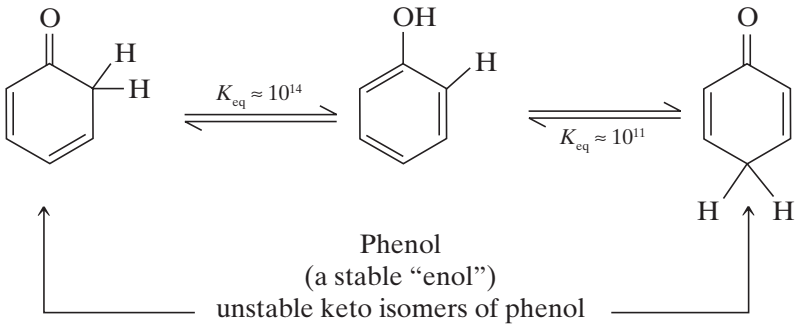
In an acidic solution, the carbonyl oxygen of the keto tautomer is protonated and water removes a proton from the α-carbon, forming the enol.

Acid-Catalyzed Keto–Enol Interconversion

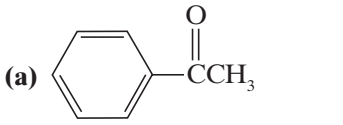


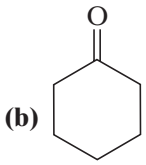
The major reason for the instability of enols is that the C=O bond of a carbonyl group is a stronger than the C=C bond of an enol. In the presence of esters and acids, the additional instability of enols results from the loss of the stabilizing resonance interaction between the carboxylate oxygen and the carbonyl p electrons, which are present in the carbonyl forms. Some enols are more stable than their corresponding carbonyl compounds. Note that phenol is actually an enol (i.e, a vinylic alcohol); however, phenol is more stable than its keto isomers because of aromaticity.

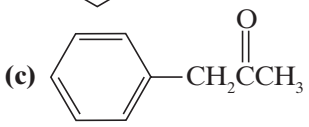


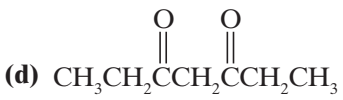
Solved Problem 4.7

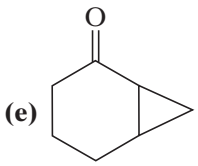
Draw the most stable enol tautomers for each of the following:



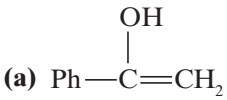


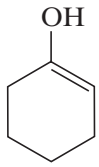


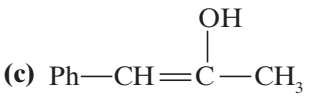


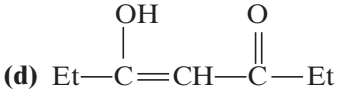


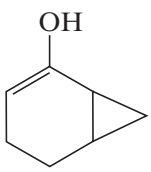
Answer











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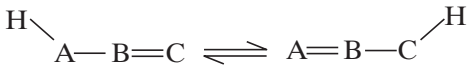
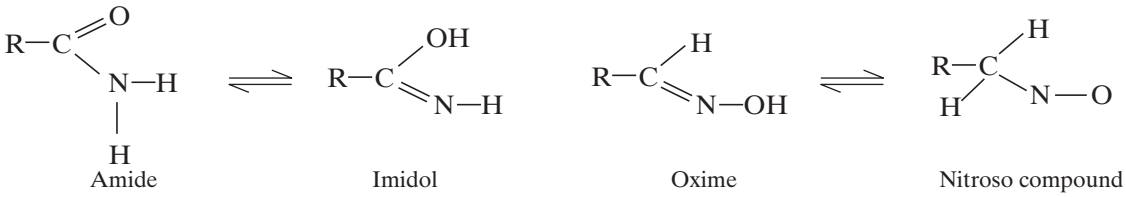
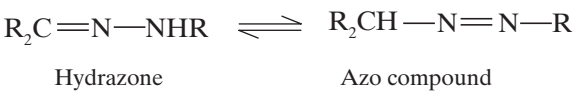
4.21B Three-Atom Tautomerism

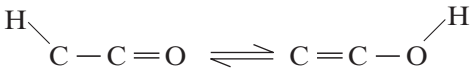


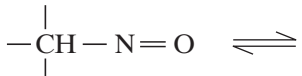
Three-atom tautomerism is very rampant, with one tautomer usually being much more stable than the other. For example, the summations of bond energies rightly predict greater stabilities of amides, oximes and aliphatic hydrazones over that of isomeric imidols, nitroso compounds and aliphatic azo compounds, respectively.

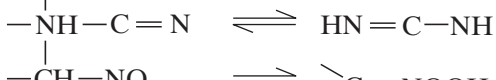




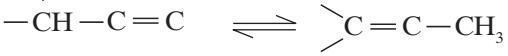
Another common pair of tautomers is the ketone–enol couple.

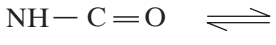


(i) Amidine system: 

(ii) Amidine system: 

(iii) Nitroso-oximino system: 

(iv) Three-carbon system: 

(v) Amido-imidol system: 

(vi) Azo-hydrazone system: 

(vii) Diazo-nitrosamine system: 

(viii) Diazo-amino (triazen) system: 

4.21C Experimental Evidence

Acetoacetic ester  was discovered first by Geuther in 1863, who prepared it by the action of sodium on ethyl acetate, and suggested the formula $CH_3C(OH) = CHCO_2C_2H_5$ (β-hydroxycrotonic ester). In 1865, Frankland and Duppa, who independently also prepared the acetoacetic ester by the action of sodium on ethyl acetate, proposed the formula $CH_3COCH_2CO_2C_2H_5$ (β-ketobutyric ester). These two formulas immediately gave rise to two schools of thought: one upholding the Geuther formula, and the other the Frankland–Duppa formula; each school bringing forward evidence to prove its own claim.

The experimental evidences favoring the two formulas are given below:

1. **Experimenal evidence for Geuther fomula:**

   (a) On treatment of acetoacetic ester with an ethanolic solution of bromine, the color of the latter is immediately discharged. This indicates the presence of an olefinic double bond.

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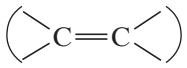
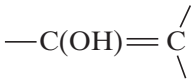


(b) On treatment of acetoacetic ester with sodium, hydrogen is evolved and the sodium derivative is formed. This indicates the presence of a hydroxyl group (—OH group).

(c) When acetoacetic ester is treated with ferric chloride, a reddish-violet color is produced. This is characteristic of compounds containing the group.



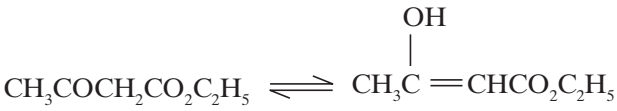
2. Experimenal evidence for the Frankland–Duppa formula:

This experiment is basically the test for enols.

(a) Acetoacetic ester forms a cyanohydrin with HCN.

(b) Acetoacetic ester forms a bisulphite compound with sodium hydrogen sulphite.

The correctness of the two formulas was a subject of debate among chemists until about 1910; it was finally concluded that the two compounds existed together in equilibrium in solution.



The direction of equilibrium in keto–enol tautomerism is as follows:

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ = -RT \ln K$$

$$\text{Keto} \rightleftharpoons \text{Enol};\ K = \frac{(\text{Enol})}{(\text{Keto})}$$

Knowing the values of the enthalpy and entropy changes would help us to compute ΔG°, from which K, the equilibrium constant of the reaction, can be calculated. The major reason for the instability of enols is that the C = O bond of a carbonyl group is stronger than the C = C bond of a enol.

If the equilibrium mixture contains 1% enol, then $\Delta G^\circ = -5.7 \log (1/99) = 11.42$ kJ.

If the equilibrium mixture contains 99 % enol, then $\Delta G^\circ = -5.7 \log (99) = -11.42$ kJ

Thus, the difference of 22.84 kJ mol^{-1} in ΔG shifts the equilibrium from 1% enol to 99% enol. Therefore, small changes in ΔG will have large effects on the position of the equilibrium. Hence, K can be calculated from estimated values of ΔH and ΔS. However, a semi-quantitative approach is instructive. Factors that affect ΔH° and ΔS° will affect the value of ΔG°. The sum of the bond energies of the $-CH_2CO-$ group is 1870 kJ and that of the $-CH{=}C(OH)-$ group is 1820 kJ.

$$2C\text{–}H\ (828.4\ kJ) + C\text{–}C\ (347.3\ kJ) + C{=}(694.5\ kJ) = 1870\ kJ$$

$$C\text{–}H\ (414.2\ kJ) + C{=}C\ (606.7\ kJ) + C\text{–}\ (334.7\ kJ) + O\text{–}H\ (464.4\ kJ) = 1820\ kJ$$

This indicates that the enthalpy of formation of the CH_2CO group is –1870 kJ and that of the CH = C(OH) group is –1820 kJ. Thus, the keto form is more stable than the enol by 50 kJ mol^{-1}; and hence there must be some driving force to bring about enolization.

4.22 | GERO ENTROPY

Gero (in 1962) has found that cyclic monoketones contain more percentage of enol than the corresponding acyclic 2-one. In the cyclic ketones, changing from keto to enol form involves a relatively small change in the strain of the ring due to the introduction of a double bond. For acyclic ketones, the introduction of the double bond has a much greater effect on the liberty to take up different conformations. The enols of β-dicarbonyl compounds are also relatively stable. (β-dicarbonyl compounds have two carbonyl groups separated by one carbon).

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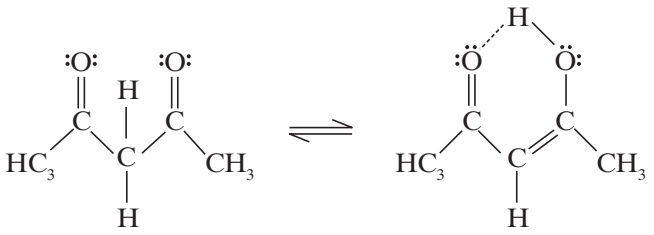
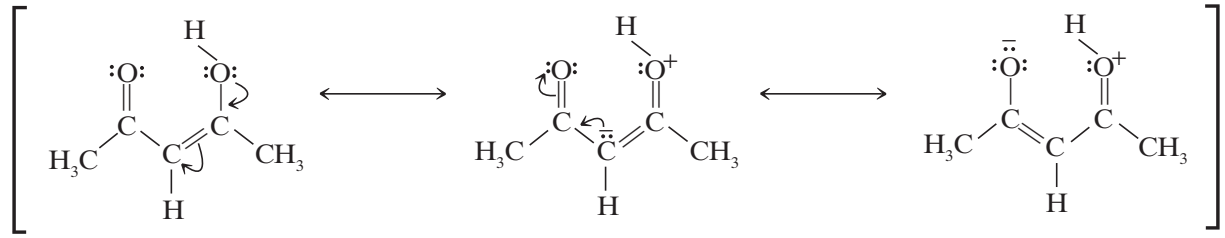


2,4-pentanedione
(acetylacetone)
(a β-dicarbonyl compound)

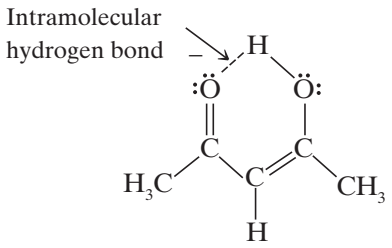
enol form
92% in hexane solution

Stability of these enols is because of two reasons:

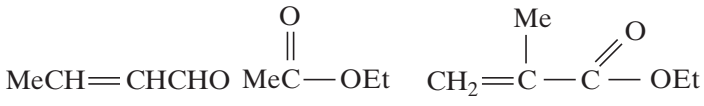
1. Enols are conjugated, however, their parent carbonyl compounds are not. The resonance stabilization (π electron overlap) associated with conjugation provides additional bonding that stabilizes the enol.



2. The intramolecular hydrogen bond present in each of these enols provides another source of increased bonding and hence, increased stabilization.

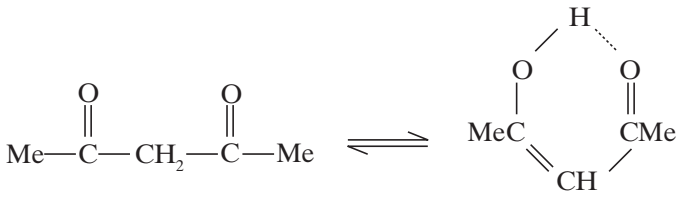


In each case, the enol form is stabilized by intramolecular hydrogen bonding (about 29.3 kJ mol^{-1}). Now, let us consider the resonance energies of crotonaldehyde (I), ethyl acetate (II) and ethyl methacrylate (III).



R.E. (kJ)	(I) 10.40	(II) 75.35	(III) 75.35

Note that in compound (III), the ethylenic bond does not enter into resonance with the CO_2Et group. Compound (III) contains crossed conjugation, and the contribution to resonance is the only path that leads to the greater resonance energy, which, in this case, is the carbethoxy group. In case of the following equilibria:



76%

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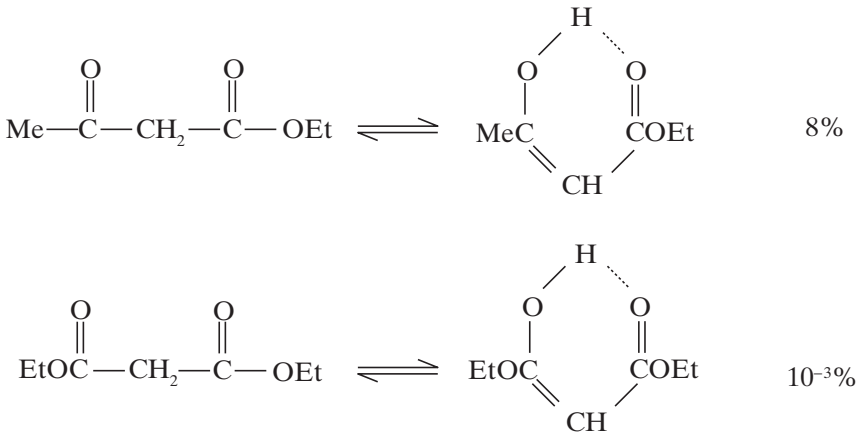
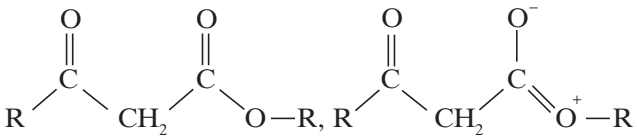
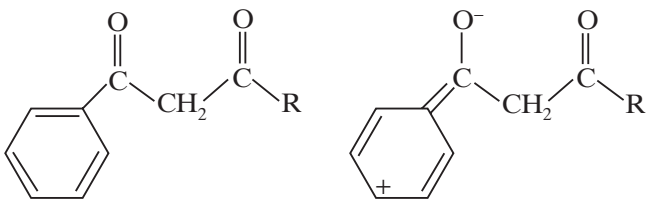


When an OR group is substituted for one of the R groups, thereby producing an acetoacetic ester, there is a decrease in the enol content. This is largely due to a cross-conjugation between the ester group and the enol structure. The resonance of the ester group takes place at the expense of the resonance of the enol group. This destabilizes the enol with respect to the keto tautomer and shifts the equilibrium toward the ketone. As expected, the diester ethyl malonate has an even smaller enol content (7.7×10^{-3}%).

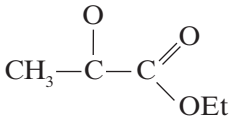


	Enol content
EtO—CO—CH_2—CO—OEt	<1%
CH_3—CO—CH_2—CO—OEt	7.7
Ph—CO—CH_2—CO—OEt	21
CH_3—CO CH_2—CO—CH_3	76
Ph—CO—CH_2—CO—CH_3	89
Ph—CO—CH_2—CO—Ph	100

Substitution of a phenyl group increases the resonance energy of the keto as well as the enol tautomer, but much more increase is found for the enol tautomer.



Consequently, diarylmethanes, $(\phi CO)_2CH_2$, are essentially 100% enolic. The effect of resonance in stabilizing the enols of α-diketones is also demonstrable. For instance, the enol content in ethyl pyruvate is too small to undergo reaction with diazomethane. However, ethyl *p*-nitropyruvate is 42% enolic in alcohol solution. Therefore, again the enol is stabilized by the cinnamoyl resonance energy. Other benzyl glyoxals have large enolic contents, too, and some range up to 100%.



Ethyl pyruvate

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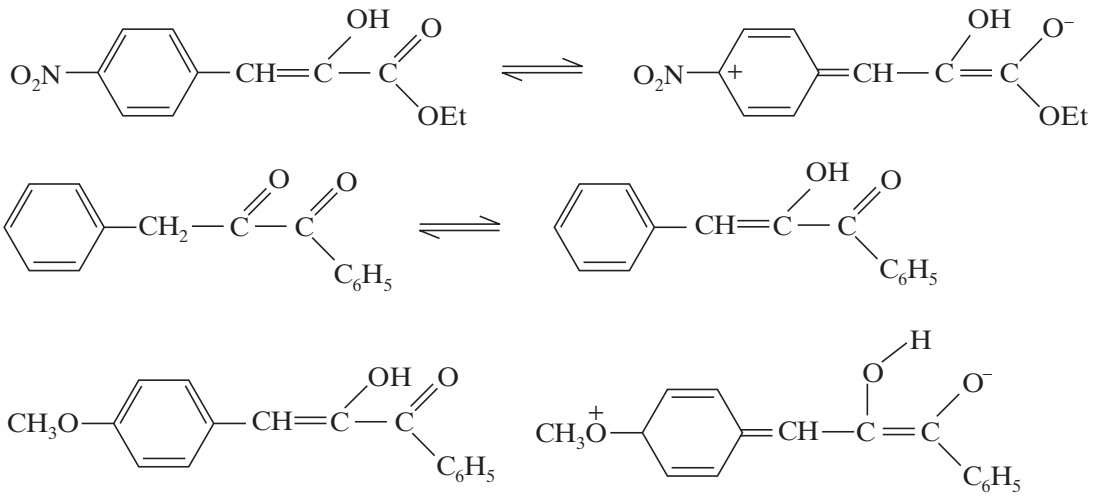
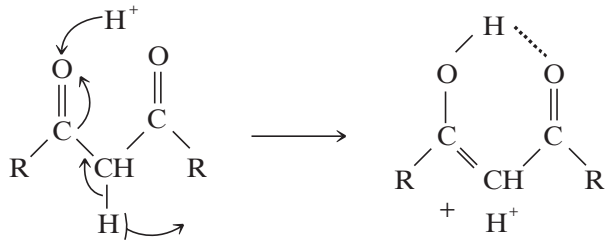


100% enolic

Tabel 4.2 Enol Content of Some 1,3-Diketones in Different Solvents

Diketone	% enol	Solvent
$C_6H_5-CS-CO-CO_2-C_2H_5$	95	Isooctane
	87	Ethanol
$CH_3-CO-CH_2-CO_2C_2H_5$	46.4	Hexane
	16.2	Benzene
	10.5	Ethanol
	10.1	Nitrobenzene
$CH_3-CO-CH_2-CO-CH_3$	92	Hexane
	15	Water
$CH_3-CO-CH\phi-CO_2C_2H_5$	67	Hexane
	31	Water

Enolization probably takes place by ionization of an α-hydrogen atom and short electron-pair shifts. Therefore, the more electronegative groups are the groups attached to the α-carbon atom, the easier it is for an α-hydrogen atom to escape in form of a proton. This expectation is fully substantiated in the substituted acetoacetic esters $CH_3CO-CHR-CO_2Et$, in which the enol content increases with increasing electronegativity of the R group.



R in $CH_3-C(=O)-CH(R)-CO_2Et$	Percent enol (liquid)
C_2H_5	3
CH_3	4
H	7.5
C_6H_5	30
CO_2Et	44

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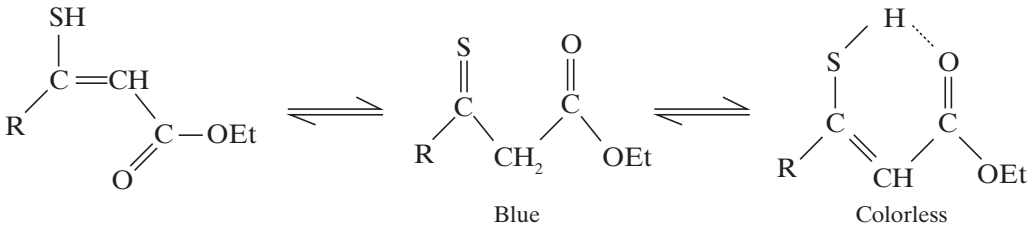
The inductive effect alone, however, is only a minor factor. For example, ethyl cyanoacetate has only a 0.25% enol content. Another illustration is provided by the ketosulfones (RSO_2CH_2COR) and β-disulfones (RSO_2–CH_2–SO_2R), which are hardly enolized and are weaker acids than the corresponding β-diketones. The sulfones do not form chelates and the ketosulfones exhibit typical C═O infrared absorption and no O–H----O bonds. On the other hand, thiobenzoylacetates are more enolic than the corresponding benzoylacetates.

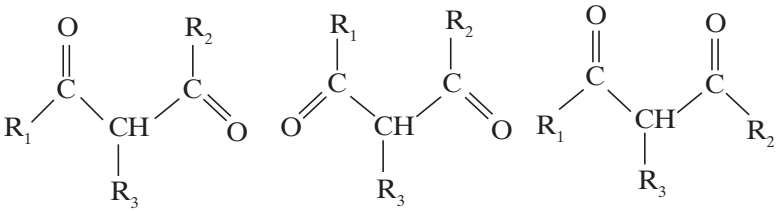


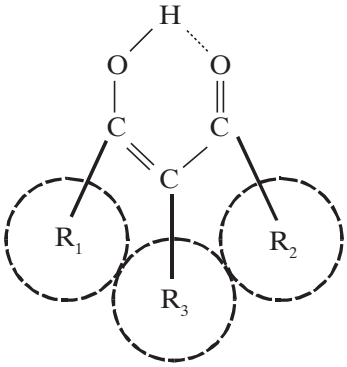
Blue Colorless

	Enol content (in alchohol)
$CH_3 - CO - CH_2 - CO_2Et$	11
$CH_3 - CS - CH_2 - CO_2Et$	41
$\phi - CO - CH_2 - CO_2Et$	29 (liq)
$\phi - CS - CH_2 - CO_2Et$	87

The weakness of the C═S bond shifts the equilibrium in favor of the thioenol. Since the S–H---O bond is not as strong as the O–H---O bond, some of the thioenol exists in a nonchelated structure.

Steric and entropy effects: Finally, it can be shown that steric requirements and entropy changes can have a profound effect upon the keto–enol equilibrium. A diketone R_1–CO–CHR_3–CO–R_2 may exist in several conformations.





R_1—CO—CH_2(—R_2)—CO—R_3	% Enol (liquid phase)
$R_1 = R_3 = CH_3$, $R_2 = -H$	76%
$R_1 = R_2 = R_3 = -CH_3$	44%
$R_1 = R_2 = R_3 =$ *tert*–Butyl	0%

Compound	% Enol content	Compound	% Enol content
2-Butanone	0.12	3-Pentanone	0.07
2-Pentanone	0.01	3-Hexanone	0.05
2-Hexanone	0.11	3-Heptanone	0.17
2-Heptanone	0.10	3-Octanone	0.01
2-Octanone	0.92		

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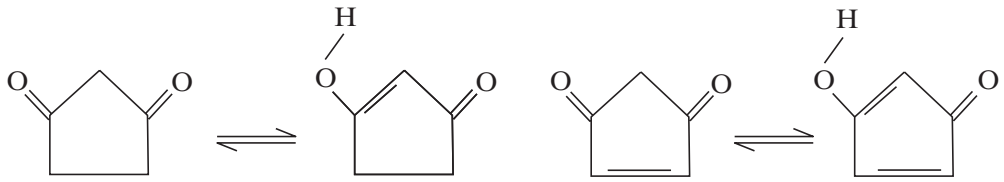
Ring size of cyclanone	% Enol content
4	0.55
5	0.09
6	1.18
7	0.56
8	9.3
9	4.0
10	6.1

It is interesting to note, in this connection, that cyclopentane-1,3-dione (I) is completely enolic while cyclopentene-3,5-dione (II) is completely ketonic. This further supports the notion that the cyclopentadienone is very unstable because of the bond-angle strain.



I II

Additional evidence for the ionization of α-hydrogen:
Acetone in deuterium oxide (D_2O) containing NaOD undergoes H–D exchange and is *trans*formed in successive steps into CD_3COCD_3:

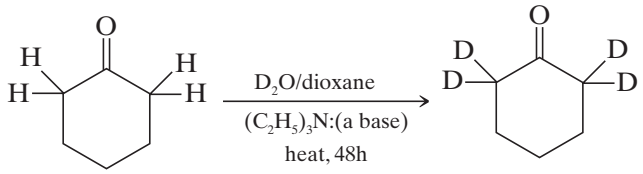
$$CH_3COCH_3 + DO^- \rightleftharpoons CH_3COCH_2:^- + HOD$$

$$CH_3COCH_2:^- + D_2O \rightleftharpoons CH_3COCH_2D + DO^- : \text{etc.}$$

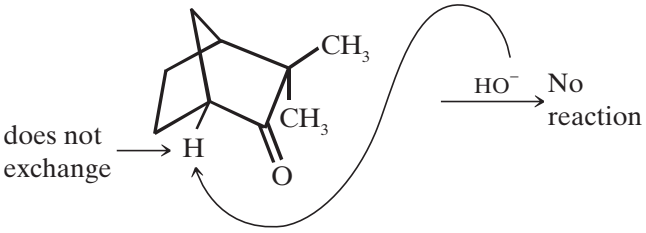
This exchange reaction is often of diagnostic value in determining the number of (replaceable) hydrogen atoms in an unknown carbonyl compound. Exchange of this kind, followed by analysis of the recovered compound for its deuterium content, shows the number of α-hydrogen atoms. The acidities of aldehydes, ketones and esters are particularly important because enolate ions are the key reactive intermediates in many important reactions of carbonyl compounds.

Enolate ions are Bronsted bases, and they react with Bronsted acids. The formation of enolate ions and their reactions with Bronsted acids have two simple but important consequences:

1. The α-hydrogens of only aldehydes or ketones can be exchanged by treating the carbonyl compound with a base D_2O.



The following compound does not undergo base-catalyzed exchange in D_2O even though it has an α-hydrogen because α-hydrogen is less acidic – Bredt's rule is violated.



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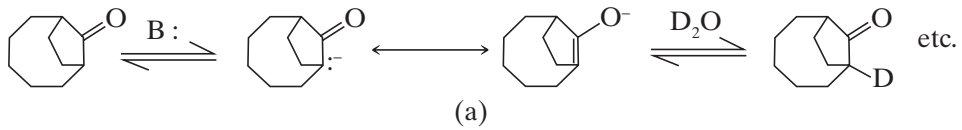
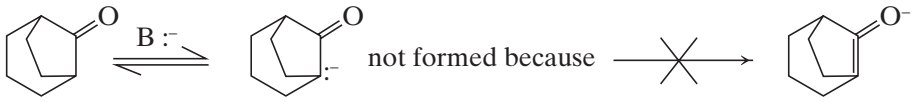
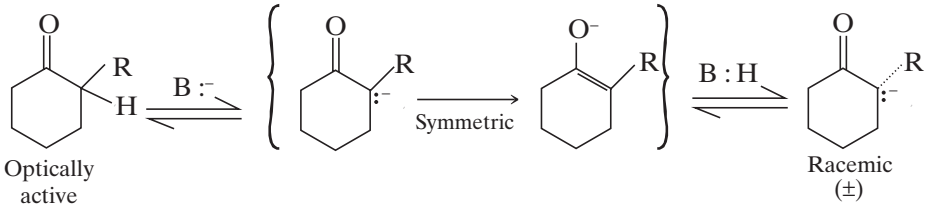


(a)



(b)

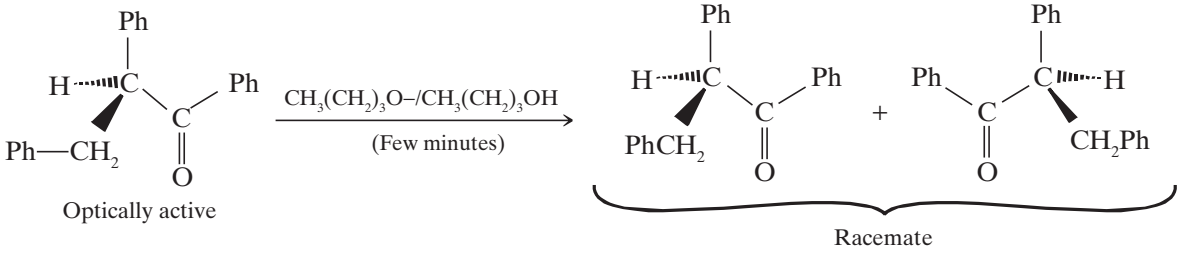
The non-exchangeability of the hydrogens in (b) is expressed in Bredt's rule, which states that a bicyclic compound cannot contain a double bond at a bridgehead. It is apparent that the rule does not apply when the ring system is large enough to accommodate the double bond, as in compound (a). When the ketone (or aldehyde or ester) possesses an asymmetric α-carbon atom, the formation of the enolate anion destroys this asymmetry, with the result that optically active carbonyl compounds of this type are racemized by bases:



The symmetrical enolate anion can be reprotonated with equal probability to give either enantiomer.

The equilibrium between the keto and enol forms is established by a deprotonation–protonation reaction that, when base catalyzed, can be regarded as proceeding via the enolate anion.

2. The second consequence of enolate ion formation and protonation is that of an optically active aldehyde or ketone owes its chirality solely to an asymmetric α-carbon, and if this carbon bears a hydrogen, the compound will be racemized by a base.

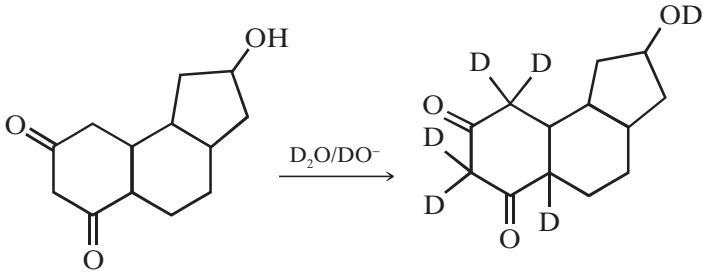


Solved Problem 4.8

Provide an example indicating which of the hydrogen(s) would be exchanged for deuterium following base treatment in D_2O.

Answer

The example is as follows:



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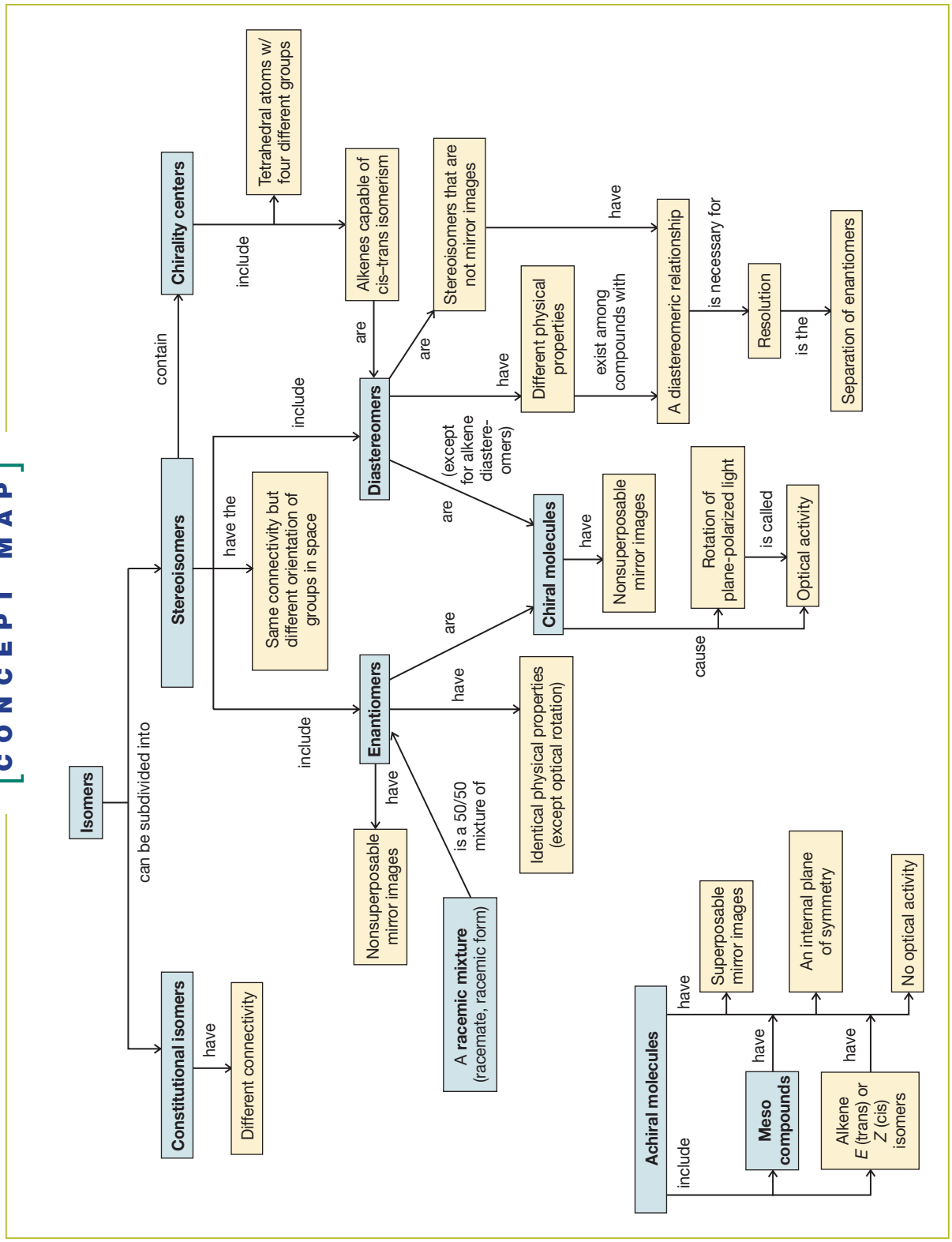
[CONCEPT MAP]



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REVIEW PROBLEMS

Chirality and Stereoisomerism

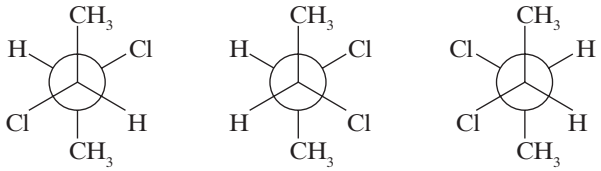
4.27 Which of the following are chiral and, therefore, capable of existing as enantiomers?

(a) 1,3-Dichlorobutane
(b) 1,2-Dibromopropane
(c) 1,5-Dichloropentane
(d) 3-Ethylpentane
(e) 2-Bromobicyclo[1.1.0]butane
(f) 2-Fluorobicyclo[2.2.2]octane
(g) 2-Chlorobicyclo[2.1.1]hexane
(h) 5-Chlorobicyclo[2.1.1]hexane

4.28 **(a)** How many carbon atoms does an alkane (not a cycloalkane) need before it is capable of existing in enantiomeric forms? **(b)** Give correct names for two sets of enantiomers with this minimum number of carbon atoms.

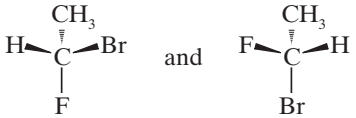
4.29 **(a)** Write the structure of 2,2-dichlorobicyclo[2.2.1]heptane. **(b)** How many stereogenic carbon atoms does it contain? **(c)** How many stereoisomers are predicted by the 2n rule? **(d)** Only one pair of enantiomers is possible for 2,2-dichlorobicyclo[2.2.1]heptane. Explain.

4.30 Shown below are Newman projection formulas for (*R,R*)-, (*S,S*)-, and (*R,S*)-2,3-dichlorobutane. **(a)** Which is which? **(b)** Which formula is a meso compound?



4.31 Write appropriate structural formulas for **(a)** a cyclic molecule that is a constitutional isomer of cyclohexane, **(b)** molecules with the formula C_6H_{12} that contain one ring and that are enantiomers of each other, **(c)** molecules with the formula C_6H_{12} that contain one ring and that are diastereomers of each other, **(d)** molecules with the formula C_6H_{12} that contain no ring and that are enantiomers of each other, and **(e)** molecules with the formula C_6H_{12} that contain no ring and that are diastereomers of each other.

4.32 Consider the following pairs of structures. Identify the relationship between them by describing them as representing enantiomers, diastereomers, constitutional isomers, or two molecules of the same compound. Use hand-held molecular models to check your answers.

(a)


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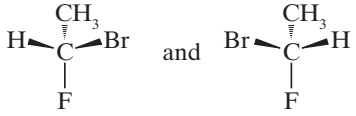
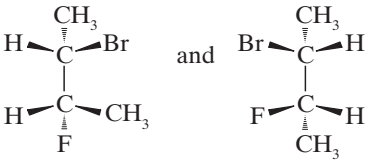
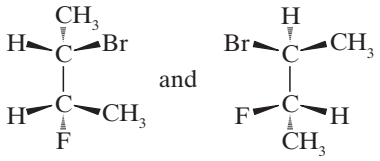


(c)


(d)


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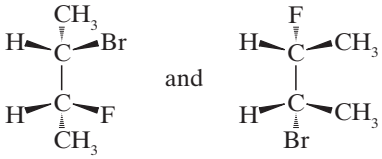

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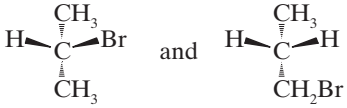

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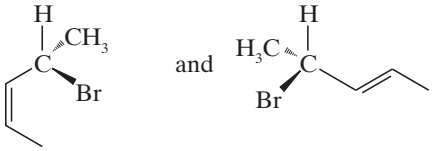

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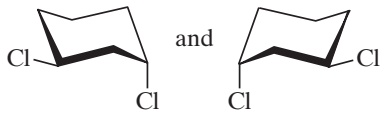
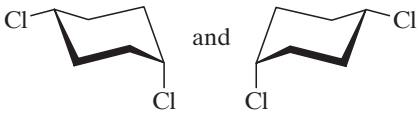


(i)


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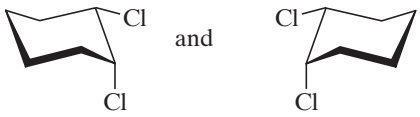
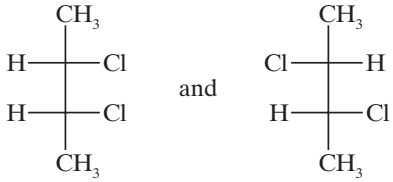
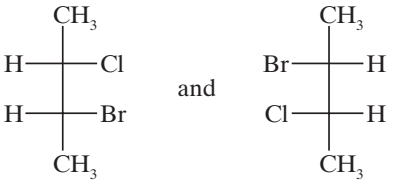


(k)


(l)


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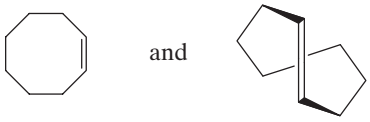

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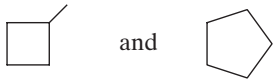
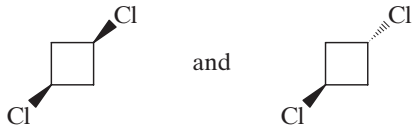
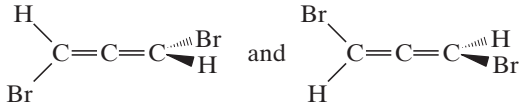
(n)  and

(o)  and

(p)  and

(q)  and

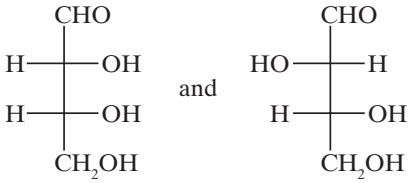
4.33 Discuss the anticipated stereochemistry of each of the following compounds.

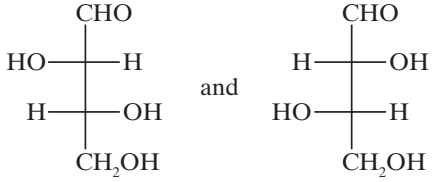
(a) $ClCH=C=C=CHCl$

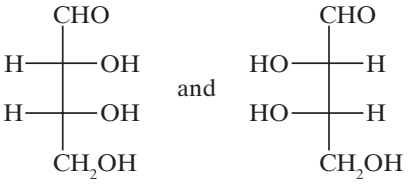
(b) $CH_2=C=C=CHCl$

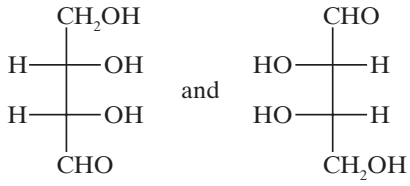
(c) $ClCH=C=C=CCl_2$

4.34 Tell whether the compounds of each pair are enantiomers, diastereomers, constitutional isomers, or not isomeric.

(a) 

(b) 

(c) 

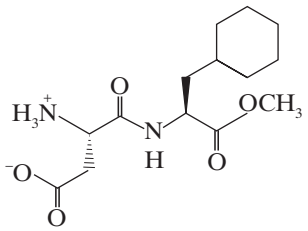
(d) 

4.35 A compound **D** with the molecular formula C_6H_{12} is optically inactive but can be resolved into enantiomers. On catalytic hydrogenation, **D** is converted to **E** (C_6H_{14}) and **E** is optically inactive. Propose structures for **D** and **E**.

4.36 Compound **F** has the molecular formula C_5H_8 and is optically active. On catalytic hydrogenation **F** yields **G** (C_5H_{12}) and **G** is optically inactive. Propose structures for **F** and **G**.

4.37 Compound **H** is optically active and has the molecular formula C_6H_{10}. On catalytic hydrogenation **H** is converted to **I** (C_6H_{12}) and **I** is optically inactive. Propose structures for **H** and **I**.

4.38 Aspartame is an artificial sweetener. Give the (*R,S*) designation for each chirality center of aspartame.



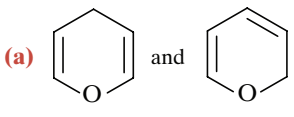
Aspartame

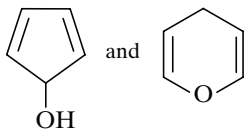
4.39 There are four dimethylcyclopropane isomers. **(a)** Write three-dimensional formulas for these isomers. **(b)** Which of the isomers are chiral? **(c)** If a mixture consisting of 1 mol of each of these isomers were subjected to simple gas chromatography (an analytical method that can separate compounds according to boiling point), how many fractions would be obtained and which compounds would each fraction contain? **(d)** How many of these fractions would be optically active?

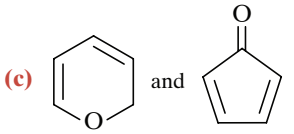
ADDITIONAL OBJECTIVE QUESTIONS

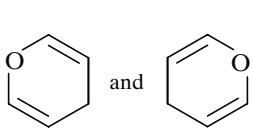
Single Correct Choice Type

1. Which of the following pairs of structures do not represent isomers?

(a) 

(b) 

(c) 

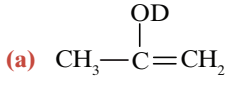
(d) 

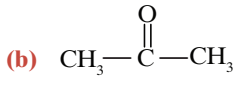
2. Only two isomers of monochloro product is possible for

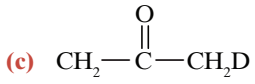
(a) *n*-butane. **(b)** 2,4-dimethyl pentane.

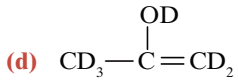
(c) benzene. **(d)** 1-methyl propane.

3. The enol form of acetone, after prolonged treatment with D_2O, gives

(a) 

(b) 

(c) 

(d) 

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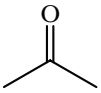
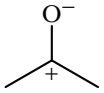
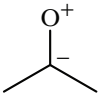
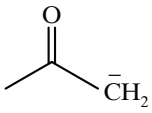
4. Which of the following is formed as intermediate in keto-enol isomerism?

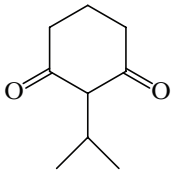
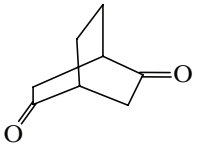
(a)  **(b)** 

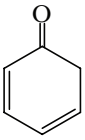
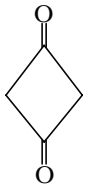
(c)  **(d)** 

5. How many optically active stereoisomers are possible for butane-2,3-diol?

(a) 1 **(b)** 2 **(c)** 3 **(d)** 4

6. Which of the following compound have almost 100% enol content?

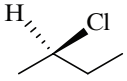
(a)  **(b)** 

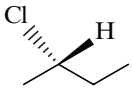
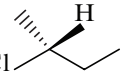
(c)  **(d)** 

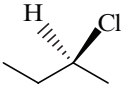
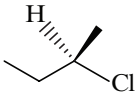
7. The number of isomers for the compound with molecular formula $C_2BrClFI$ is

(a) 3 **(b)** 4 **(c)** 5 **(d)** 6

8. Choose those structures that have the same configuration as the following compound.

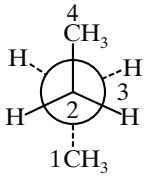


(i)  **(ii)** 

(iii)  **(iv)** 

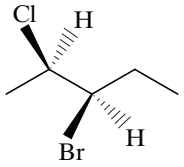
(a) (i) + (ii) **(b)** (ii) + (iii) **(c)** (iv) **(d)** (ii)

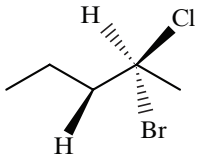
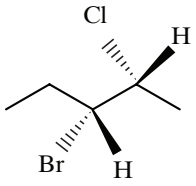
9. In the given conformation, if C2 is rotated about C2–C3 bond anticlockwise by an angle of 120° then the conformation obtained is

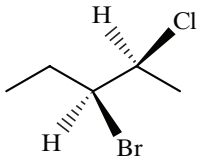
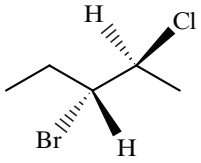


(a) fully eclipsed. **(b)** partially eclipsed.
(c) gauche. **(d)** staggered

10. Which of the following structures is an enantiomer of molecule?



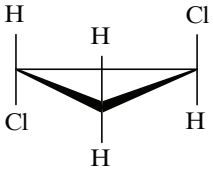
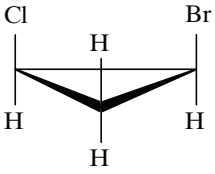
(a)  **(b)** 

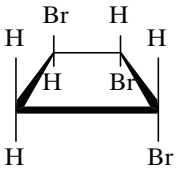
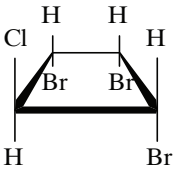
(c)  **(d)** 

11. On monochlorination of 2–methylbutane, the total number of chiral compounds formed is

(a) 2 **(b)** 4 **(c)** 6 **(d)** 8

12. Which of the following compound is not optically active?

(a)  **(b)** 

(c)  **(d)** 

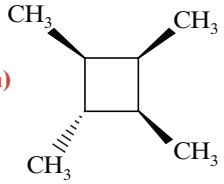
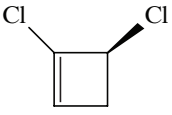
13. The number of structural isomers for C_6H_{14} is

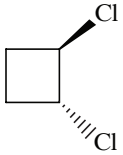
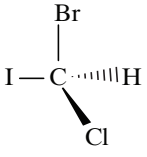
(a) 3 **(b)** 4 **(c)** 5 **(d)** 6

14. The process of separation of (*d*,*l*)-mixture into its constituents is referred to as

(a) fractional distillation. **(b)** resolution.
(c) fragmentation. **(d)** sedimentation.

15. Which of the following compounds have plane of symmetry?

(a)  **(b)** 

(c)  **(d)** 

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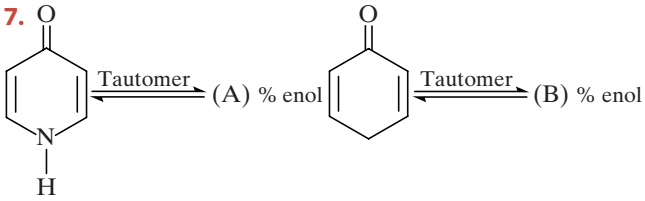
16. Which of the following will have *meso*-isomer also?

(a) 2-Chlorobutane **(b)** 2-Hydroxy propanoic acid

(c) 2,3-Dichloropentane **(d)** 2,3-Dichlorobutane

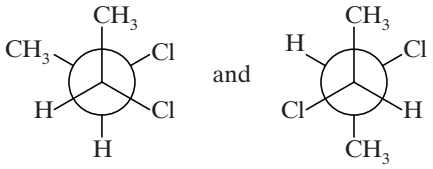
17.



In the above reaction

(a) A > B **(b)** B > A **(c)** A = B **(d)** A >> B

18. Relationship in between

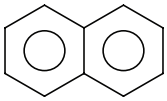


(a) diastereomer. **(b)** meso.

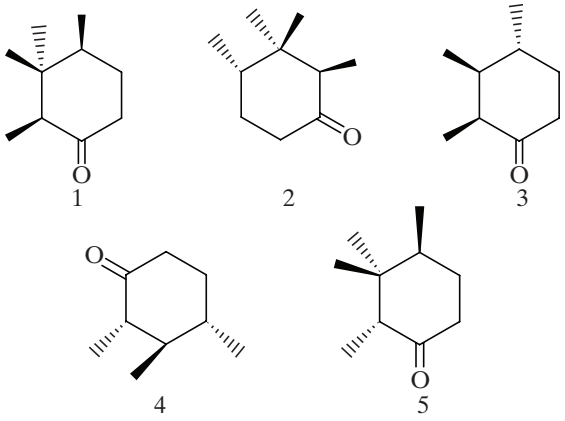
(c) enantiomer. **(d)** structural isomer.

19. The number of planes of symmetry in this compound is

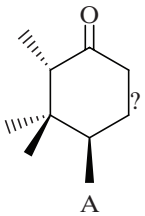
(a) 1 **(b)** 2 **(c)** 3 **(d)** 4



20.



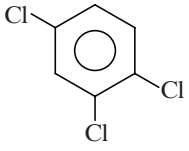
Which of the above structures is a diastereomer of



(a) 3 **(b)** 1 and 4 **(c)** 4 **(d)** 5

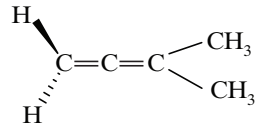
21. Number of plane of symmetry in below compound is

(a) 0 **(b)** 1 **(c)** 2 **(d)** 3

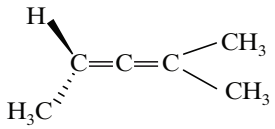


22. The molecule that has formula C_5H_8 with 2 sp^3 C's, 2 sp^2 C's, and 1 *sp* C and chiral isomer is

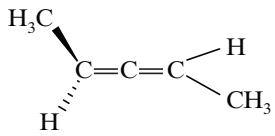
(a)



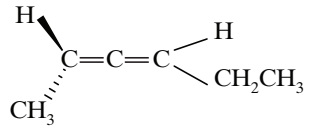
(b)



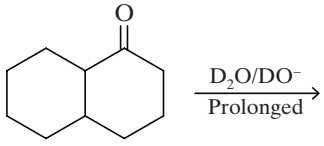
(c)



(d)



23. How many hydrogens are replaced by deuterium?



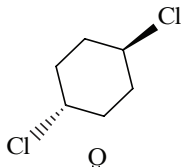
(a) 1 **(b)** 2 **(c)** 3 **(d)** 4

24. In which of the following compounds plane of symmetry and center of symmetry both are present?

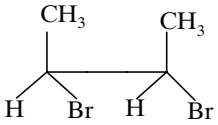
(a)



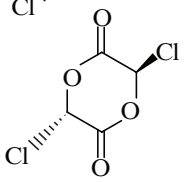
(b)



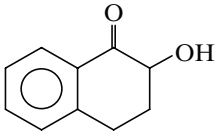
(c)



(d)



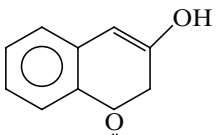
25.



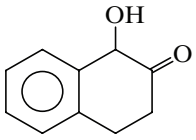
(A)

(A) and **(B)** are isomers. The product **(B)** is

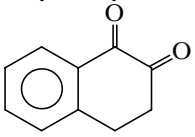
(a)



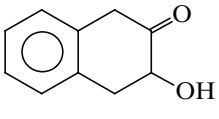
(b)



(c)



(d)



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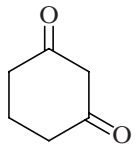
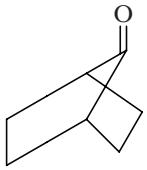
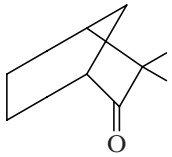
26. Which of the following compound does not undergo base-catalyzed exchange in D_2O even though it has an α-hydrogen?

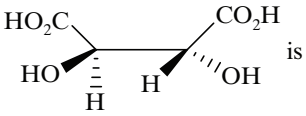
(a) 

(b) 

(c) 

(d) Both (b) and (c)

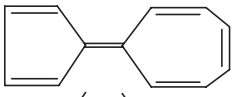
27. The absolute configuration of

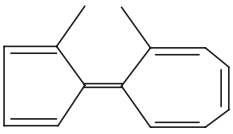


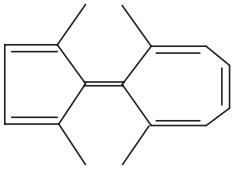
is

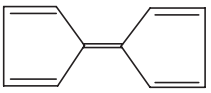
(a) S, S **(b)** R, R **(c)** R, S **(d)** S, R

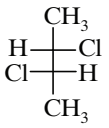
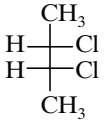
28. Which of following compound will rotate the plane polarized light at room temperature?

(a) 

(b) 

(c) 

(d) 

29. Optical rotation produced by  which results into the product  is

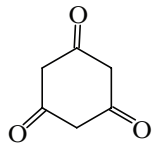
(a) $-36°$ **(b)** $0°$ **(c)** $+36°$ **(d)** unpredictable

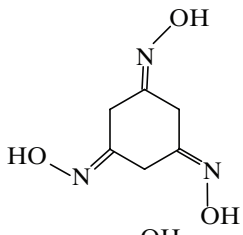
30. The number of stereoisomers possible for the following compound is

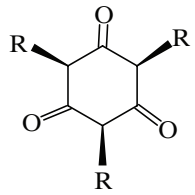
$$CH_3-CH=CH-CH(OH)-Me$$

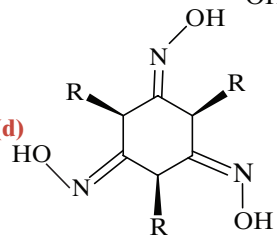
(a) 3 **(b)** 2 **(c)** 4 **(d)** 6

31. Which of following compounds is chiral?

(a) 

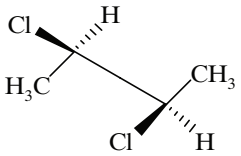
(b) 

(c) 

(d) 

Multiple Correct Choice Type

1. The correct statement(s) about the compound given below is (are)

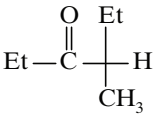


(a) The compound is optically active.
(b) The compound possesses center of symmetry.
(c) The compound possesses plane of symmetry.
(d) The compound possesses axis of symmetry.

Integer Type

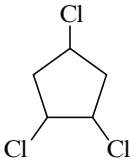
1. The number of possible alkynes with molecular formula C_5H_8 is _____.

2. The total number of possible isomeric structures for trimethyl benzene is _____.

3. How many enol forms are possible for  (including stereoisomers)?

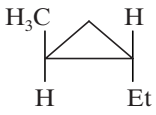
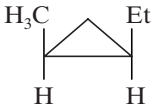
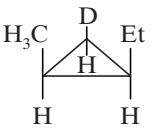
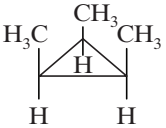
4. What is the total number of stereoisomers that can exist for the molecule 2,6-dichlorocyclohexanol?

5. How many meso isomers are possible for the following compound?



Matrix Match Type

1.

Column I (Compound)	Column II (Isomerism)
(a) 	**(p)** Geometrical isomerism
(b) 	**(q)** Optical isomerism
(c) 	**(r)** Compound containing plane of symmetry
(d) 	**(s)** Compound containing center of symmetry

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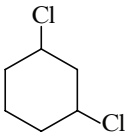
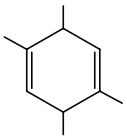
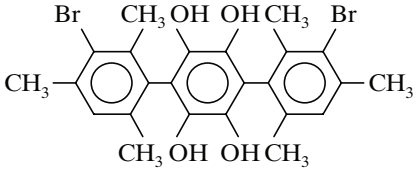
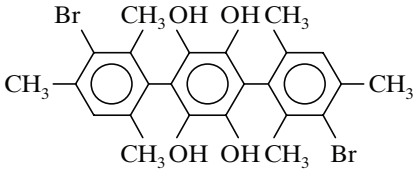
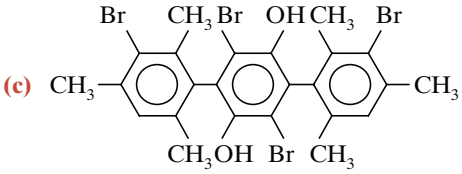
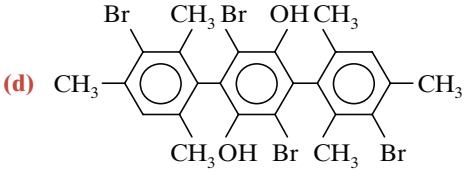
2.

Column I (Number of carbon atoms)	Column II (Number of structural isomers)
(a) C_4H_{10}	(p) 2
(b) C_5H_{12}	(q) 3
(c) C_6H_{14}	(r) 5
(d) C_7H_{16}	(s) 9

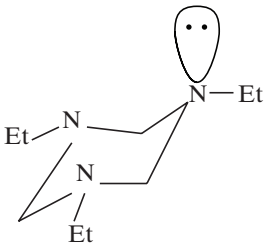
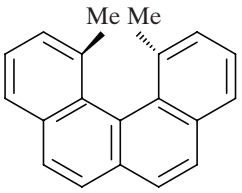
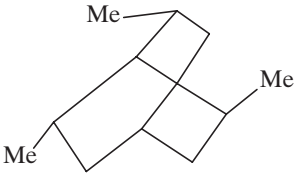
3.

Column I	Column II
(a) 2,3–Dihydroxybutane–1,4–dioic acid.	(p) Number of meso stereoisomer is odd.
(b) 2,3,4–Trichloropentane	(q) Number of meso stereoisomer is even.
(c) 	(r) Number of optically active isomer is even.
(d) 	(s) Number of optically active isomer is odd.
	(t) Total number of stereoisomer is odd.

4.

Column I	Column II
(a) 	(p) C_2 (Axis of symmetry)
(b) 	(q) POS (Plane of symmetry)
(c) 	(r) COS (Center of symmetry)
(d) 	(s) Optically inactive

5.

Column I	Column II
(a) 	(p) COS (Center of symmetry)
(b) 	(q) POS (Plane of symmetry)
(c) 	(r) AOS (Axis of symmetry)
(d) 2,2,3,3-Tetramethly butane in staggered state	(s) Optically active

ANSWER KEY

Single Correct Choice Type

1. (d)	**2.** (a)	**3.** (d)	**4.** (d)
5. (b)	**6.** (c)	**7.** (d)	**8.** (c)
9. (d)	**10.** (c)	**11.** (b)	**12.** (d)
13. (c)	**14.** (b)	**15.** (a)	**16.** (d)
17. (b)	**18.** (b)	**19.** (c)	**20.** (b)

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21. (b) **22.** (c) **23.** (c) **24.** (b)
25. (b) **26.** (d) **27.** (b) **28.** (b)
29. (b) **30.** (c) **31.** (c)

Multiple Correct Choice Type

1. (a), (d)

Integer Type

1. (3) **2.** (3) **3.** (4) **4.** (4) **5.** (2)

Matrix Match Type

1. a → (p, q); b → (p, q); c → (p, q); d → (p, r)
2. a → (p); b → (q); c → (r); d → (s)
3. a → (p, r, t); b → (q, r); c → (p, r, t); d → (p, r, t)
4. a → (p, q, s); b → (p, q, r, s); c → (p); d → (r, s)
5. a → (q, r); b → (r, s); c → (r, s); d → (p, q, r)

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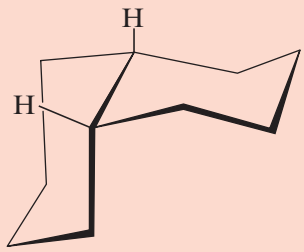
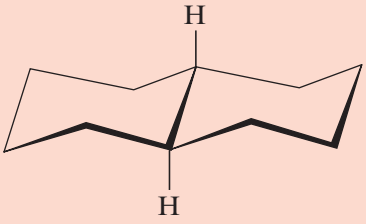
5

Nomenclature and Conformations of Alkanes and Cycloalkanes



cis-Decalin



trans-Decalin

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5.2 | Shapes of Alkanes
5.3 | HOW TO Name Alkanes, Alkyl Halides, and Alcohols: The IUPAC System
5.4 | HOW TO Name Cycloalkanes
5.5 | HOW TO Name Alkenes and Cycloalkenes
5.6 | HOW TO Name Alkynes
5.7 | Physical Properties of Alkanes and Cycloalkanes
5.8 | Sigma Bonds and Bond Rotation
5.9 | Conformational Analysis of Butane
5.10 | The Relative Stabilities of Cycloalkanes: Ring Strain
5.11 | Conformations of Cyclohexane: The Chair and the Boat
5.12 | Substituted Cyclohexanes: Axial and Equatorial Hydrogen Groups
5.13 | Disubstituted Cycloalkanes: *Cis–Trans* Isomerism
5.14 | Bicyclic and Polycyclic Alkanes
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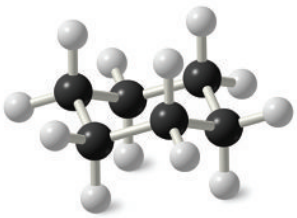
5.18 | Applications of Basic Principles

5.1 | INTRODUCTION TO ALKANES AND CYCLOALKANES

We noted earlier that the family of organic compounds called hydrocarbons can be divided into several groups on the basis of the type of bond that exists between the individual carbon atoms. Those hydrocarbons in which all of the carbon–carbon bonds are single bonds are called **alkanes**, those hydrocarbons that contain a carbon–carbon double bond are called **alkenes**, and those with a carbon–carbon triple bond are called **alkynes**.

Cycloalkanes are alkanes in which all or some of the carbon atoms are arranged in a ring. Alkanes have the general formula C_nH_{2n+2}; cycloalkanes containing a single ring have two fewer hydrogen atoms and thus have the general formula C_nH_{2n}.



Cyclohexane

5.1A Sources of Alkanes: Petroleum

The primary source of alkanes is petroleum. Petroleum is a complex mixture of organic compounds, most of which are alkanes and aromatic compounds (cf. Chapter 13). It also contains small amounts of oxygen-, nitrogen-, and sulfur-containing compounds.

Some of the molecules in petroleum are clearly of biological origin. Most scientists believe that petroleum originated with accumulation of dead microorganisms that settled to the bottom of the sea and that were entombed in sedimentary rock. These microbial remains eventually were *trans*formed into oil by the heat radiating from Earth's core.

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Hydrocarbons are also found in outer space. Asteroids and comets contain a variety of organic compounds. Methane and other hydrocarbons are found in the atmospheres of Jupiter, Saturn, and Uranus. Saturn's moon Titan has a solid form of methane–water ice at its surface and an atmosphere rich in methane. Whether of terrestrial or celestial origin, we need to understand the properties of alkanes. We begin with a consideration of their shapes and how we name them.

5.2 | SHAPES OF ALKANES

A general tetrahedral orientation of groups—and thus sp^3 hybridization—is the rule for the carbon atoms of all alkanes and cycloalkanes. We can represent the shapes of **alkanes** as shown in Fig. 5.1.

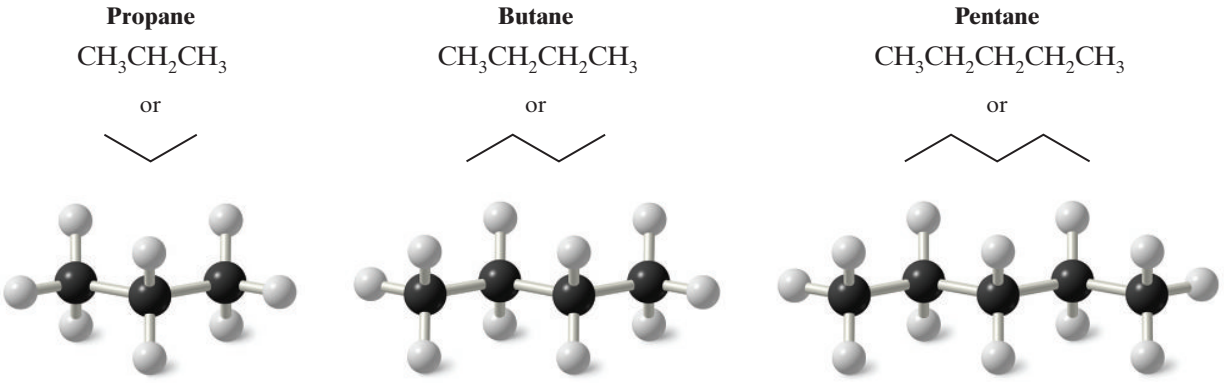

Figure 5.1 Ball-and-stick models for three simple alkanes.

Butane and pentane are examples of alkanes that are sometimes called "straight-chain" alkanes. One glance at three-dimensional models, however, shows that because of their tetrahedral carbon atoms the chains are zigzagged and not at all straight. Indeed, the structures that we have depicted in Fig. 5.1 are the straightest possible arrangements of the chains because rotations about the carbon–carbon single bonds produce arrangements that are even less straight. A better description is **unbranched**. This means that each carbon atom within the chain is bonded to no more than two other carbon atoms and that unbranched alkanes contain only primary and secondary carbon atoms. Primary, secondary, and tertiary carbon atoms were defined in Section 2.5.

Isobutane, isopentane, and neopentane (Fig. 5.2) are examples of branched-chain alkanes. In neopentane the central carbon atom is bonded to four carbon atoms.

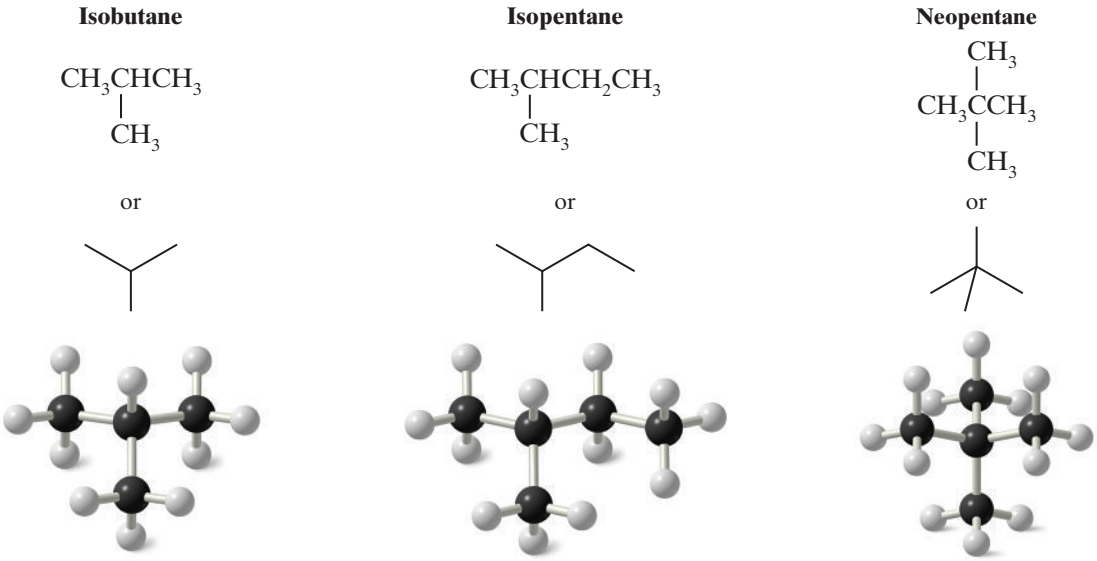

Figure 5.2 Ball-and-stick models for three branched-chain alkanes. In each of the compounds one carbon atom is attached to more than two other carbon atoms.

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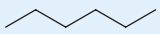
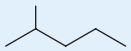
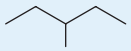
Butane and isobutane have the same molecular formula: C_4H_{10}. The two compounds have their atoms connected in a different order and are, therefore, **constitutional isomers** (Section 1.3). Pentane, isopentane, and neopentane are also constitutional isomers. They, too, have the same molecular formula (C_5H_{12}) but have different structures.

Practice Problem 5.1

Write condensed and bond-line structural formulas for all of the constitutional isomers with the molecular formula C_7H_{16}. (There are a total of nine constitutional isomers.)

Constitutional isomers, as stated earlier, have different physical properties. The differences may not always be large, but constitutional isomers are always found to have different melting points, boiling points, densities, indexes of refraction, and so forth. Table 5.1 gives some of the physical properties of the C_6H_{14} isomers, of which there are only five. Note that the number of constitutional isomers that is possible increases dramatically as the number of carbon atoms in the alkane increases.

Table 5.1 Physical Constants of the Hexane Isomers

Molecular Formula	Condensed Structural Formula	Bond-Line Formula	mp (°C)	bp (°C)[a] (1 atm)	Density (g mL^{-1}) at 20 °C	Index of Refraction[b] (n_D 20 °C)
C_6H_{14}	$CH_3CH_2CH_2CH_2CH_2CH_3$		–95	68.7	0.6594	1.3748
C_6H_{14}	$CH_3CH(CH_3)CH_2CH_2CH_3$		–153.7	60.3	0.6532	1.3714
C_6H_{14}	$CH_3CH_2CH(CH_3)CH_2CH_3$		–118	63.3	0.6643	1.3765
C_6H_{14}	$CH_3CH(CH_3)CH(CH_3)CH_3$		–128.8	58	0.6616	1.3750
C_6H_{14}	$CH_3C(CH_3)_2CH_2CH_3$		–98	49.7	0.6492	1.3688

[a]Unless otherwise indicated, all boiling points given in this book are at 1 atm or 760 torr.
[b]The index of refraction is a measure of the ability of the alkane to bend (refract) light rays. The values reported are for light of the D line of the sodium spectrum (n_D).

Prior to the development near the end of the nineteenth century of a formal system for naming organic compounds, many organic compounds had already been discovered or synthesized. Early chemists named these compounds, often on the basis of the source of the compound. Acetic acid (systematically called ethanoic acid) is an example; it was obtained by distilling vinegar, and it got its name from the Latin word for vinegar, *acetum*. Formic acid (systematically called methanoic acid) had been obtained by the distillation of the bodies of ants, so it got the name from the Latin word for ants, *formicae*. Many of these older names for compounds, called common or trivial names, are still in wide use today.

Today, chemists use a systematic nomenclature developed and updated by the International Union of Pure and Applied Chemistry (IUPAC). Underlying the IUPAC system is a fundamental principle: **each different compound should have a different and unambiguous name.***

*The complete IUPAC rules for nomenclature can be found through links at the IUPAC website.

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5.3 | HOW TO NAME ALKANES, ALKYL HALIDES, AND ALCOHOLS: THE IUPAC SYSTEM

The **IUPAC system** for naming **alkanes** is not difficult to learn, and the principles involved are used in naming compounds in other families as well. For these reasons we begin our study of the IUPAC system with the rules for naming alkanes and then study the rules for alkyl halides and alcohols.

The names for several of the unbranched alkanes are listed in Table 5.2. The ending for all of the names of alkanes is *-ane*. The stems of the names of most of the alkanes (above C_4) are of Greek and Latin origin. Learning the stems is like learning to count in organic chemistry. Thus, one, two, three, four, and five become meth-, eth-, prop-, but-,and pent-.

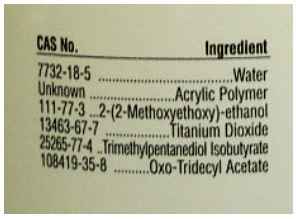


Photo by Lisa Gee

The Chemical Abstracts Service assigns a CAS Registry Number to every compound. CAS numbers make it easy to find information about a compound in the chemical literature. The CAS numbers for ingredients in a can of latex paint are shown here.

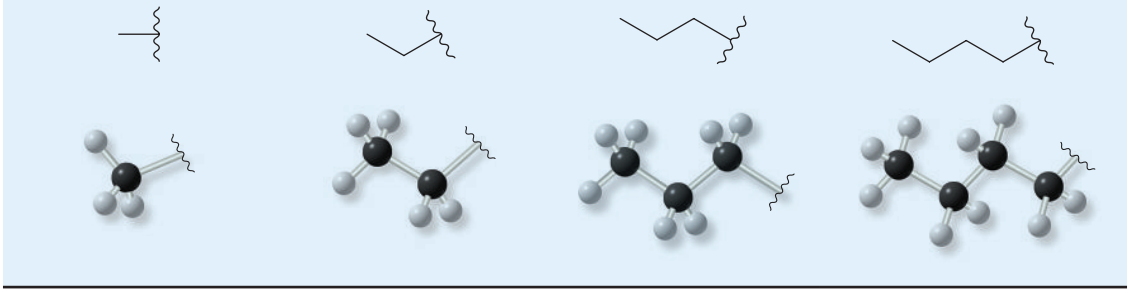
Table 5.2 The Unbranched Alkanes

Name	Number of Carbon Atoms	Structure	Name	Number of Carbon Atoms	Structure
Methane	1	CH_4	Undecane	11	$CH_3(CH_2)_9CH_3$
Ethane	2	CH_3CH_3	Dodecane	12	$CH_3(CH_2)_{10}CH_3$
Propane	3	$CH_3CH_2CH_3$	Tridecane	13	$CH_3(CH_2)_{11}CH_3$
Butane	4	$CH_3(CH_2)_2CH_3$	Tetradecane	14	$CH_3(CH_2)_{12}CH_3$
Pentane	5	$CH_3(CH_2)_3CH_3$	Pentadecane	15	$CH_3(CH_2)_{13}CH_3$
Hexane	6	$CH_3(CH_2)_4CH_3$	Hexadecane	16	$CH_3(CH_2)_{14}CH_3$
Heptane	7	$CH_3(CH_2)_5CH_3$	Heptadecane	17	$CH_3(CH_2)_{15}CH_3$
Octane	8	$CH_3(CH_2)_6CH_3$	Octadecane	18	$CH_3(CH_2)_{16}CH_3$
Nonane	9	$CH_3(CH_2)_7CH_3$	Nonadecane	19	$CH_3(CH_2)_{17}CH_3$
Decane	10	$CH_3(CH_2)_8CH_3$	Eicosane	20	$CH_3(CH_2)_{18}CH_3$

5.3A HOW TO Name Unbranched Alkyl Groups

If we remove one hydrogen atom from an alkane, we obtain what is called an **alkyl group**. These alkyl groups have names that end in **-yl**. When the alkane is **unbranched**, and the hydrogen atom that is removed is a **terminal** hydrogen atom, the names are straightforward:

$CH_3—H$	$CH_3CH_2—H$	$CH_3CH_2CH_2—H$	$CH_3CH_2CH_2CH_2—H$
Methane	**Ethane**	**Propane**	**Butane**
$CH_3—$	$CH_3CH_2—$	$CH_3CH_2CH_2—$	$CH_3CH_2CH_2CH_2—$
Methyl	**Ethyl**	**Propyl**	**Butyl**
Me-	**Et-**	**Pr-**	**Bu-**



5.3B HOW TO Name Branched-Chain Alkanes

Branched-chain alkanes are named according to the following rules:

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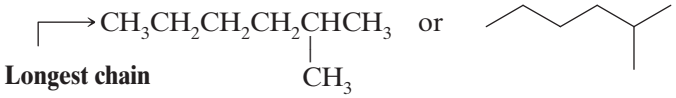
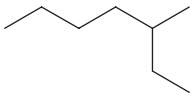
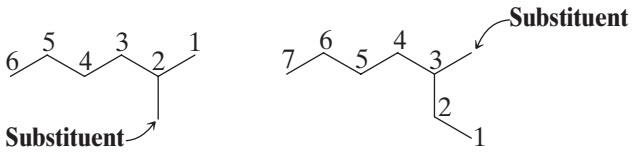
1. **Locate the longest continuous chain of carbon atoms; this chain determines the parent name for the alkane.** We designate the following compound, for example, as a *hexane* because the longest continuous chain contains six carbon atoms:



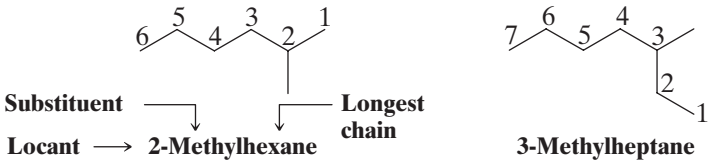
The longest continuous chain may not always be obvious from the way the formula is written. Notice, for example, that the following alkane is designated as a *heptane* because the longest chain contains seven carbon atoms:



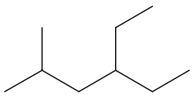
2. **Number the longest chain beginning with the end of the chain nearer the substituent.** Applying this rule, we number the two alkanes that we illustrated previously in the following way:



3. **Use the numbers obtained by application of rule 2 to designate the location of the substituent group.** The parent name is placed last, and the substituent group, preceded by the number designating its location on the chain, is placed first. Numbers are separated from words by a hyphen. Our two examples are 2-methylhexane and 3-methylheptane, respectively:



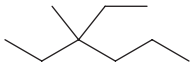
4. **When two or more substituents are present, give each substituent a number corresponding to its location on the longest chain**. For example, we designate the following compound as 4-ethyl-2-methylhexane:



4-Ethyl-2-methylhexane

The substituent groups should be listed *alphabetically* (i.e., ethyl before methyl).* In deciding on alphabetical order, disregard multiplying prefixes such as "di" and "tri."

5. **When two substituents are present on the same carbon atom, use that number twice:**



3-Ethyl-3-methylhexane

6. **When two or more substituents are identical, indicate this by the use of the prefixes di-, tri-, tetra-,** and so on. Then make certain that each and every substituent has a number. Commas are used to separate numbers from each other:

*Some handbooks also list the groups in order of increasing size or complexity (i.e., methyl before ethyl). An alphabetical listing, however, is now by far the most widely used system.

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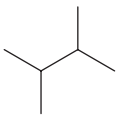
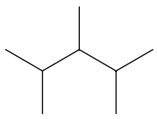


2,3-Dimethylbutane



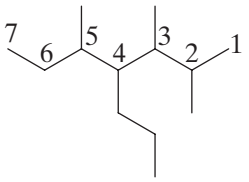
2,3,4-Trimethylpentane



2,2,4,4-Tetramethylpentane

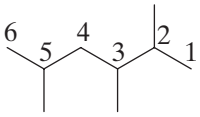
Application of these six rules allows us to name most of the alkanes that we shall encounter. Two other rules, however, may be required occasionally:

7. **When two chains of equal length compete for selection as the parent chain, choose the chain with the greater number of substituents:**



2,3,5-Trimethyl-4-propylheptane
(four substituents)

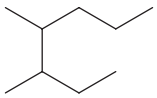
8. **When branching first occurs at an equal distance from either end of the longest chain, choose the name that gives the lower number at the first point of difference:**



2,3,5-Trimethylhexane
(*not* 2,4,5-trimethylhexane)

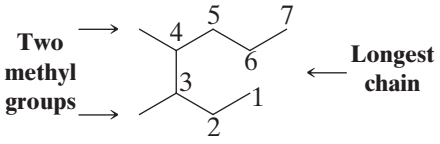
Solved Problem 5.1

Provide an IUPAC name for the following alkane.



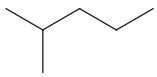
Answer

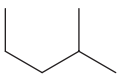
We find the longest chain (shown in blue) to be seven carbons; therefore the parent name is heptane. There are two methyl substituents (shown in red). We number the chain so as to give the first methyl group the lower number. The correct name, therefore, is 3,4-dimethylheptane. Numbering the chain from the other end to give 4,5-dimethylheptane would have been incorrect.

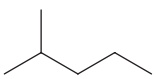


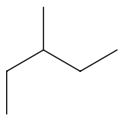
Practice Problem 5.2

Which structure does not represent 2-methylpentane?

(a) 

(b) 

(c) 

(d) 

Practice Problem 5.3

Write the structure and give the IUPAC name for an alkane with formula C_6H_{14} that has only primary and secondary carbon atoms.

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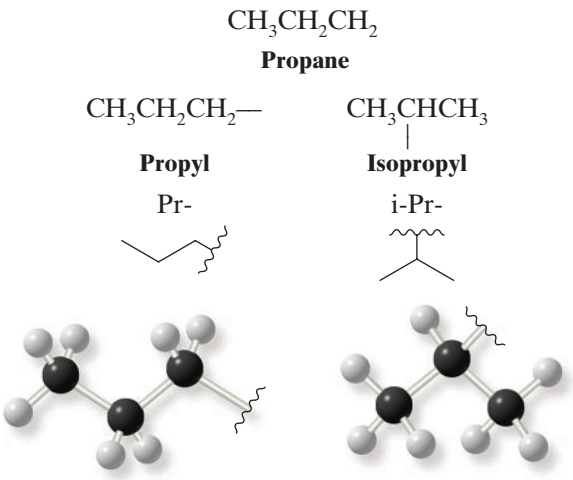
Practice Problem 5.4

Draw bond-line formulas for all of the isomers of C_8H_{18} that have **(a)** methyl substituents, and **(b)** ethyl substituents.

5.3C HOW TO Name Branched Alkyl Groups

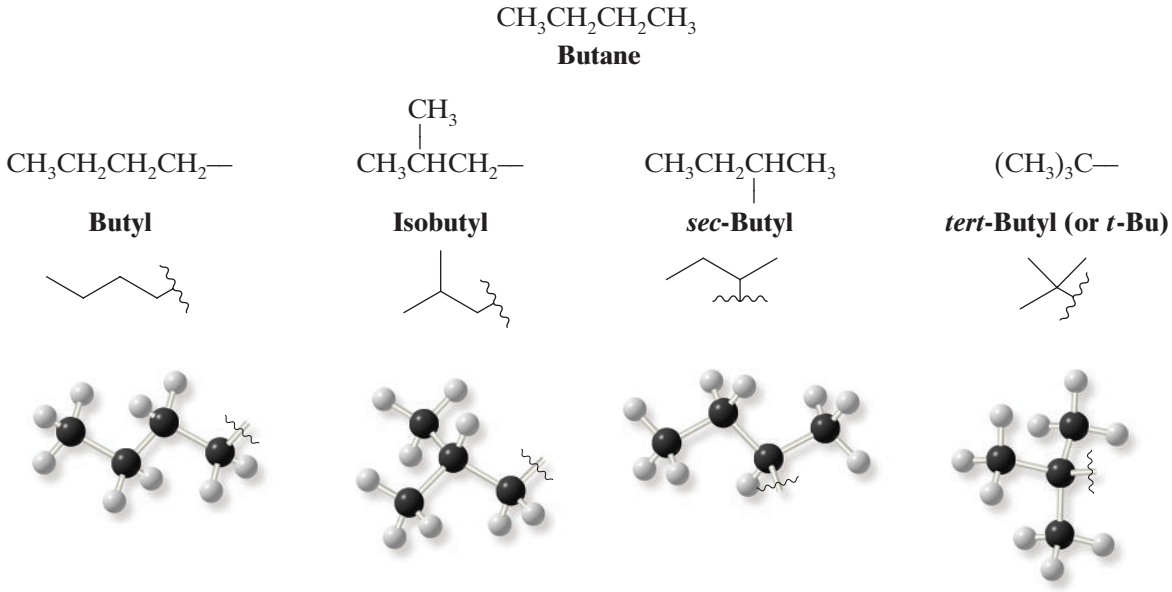
In Section 5.3A you learned the names for the unbranched alkyl groups such as methyl, ethyl, propyl, and butyl, groups derived by removing a terminal hydrogen from an alkane. For alkanes with more than two carbon atoms, more than one derived group is possible. Two groups can be derived from propane, for example; the **propyl group** is derived by removal of a terminal hydrogen, and the **1-methylethyl** or **isopropyl group** is derived by removal of a hydrogen from the central carbon:

Three-Carbon Groups



1-Methylethyl is the systematic name for this group; isopropyl is a common name. Systematic nomenclature for alkyl groups is similar to that for branched-chain alkanes, with the provision that *numbering always begins at the point where the group is attached to the main chain*. There are four C_4 groups.

Four-Carbon Groups



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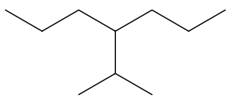
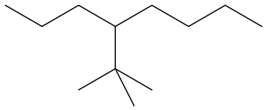
The following examples show how the names of these groups are employed:



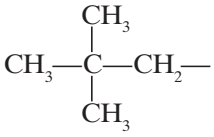
4-(1-Methylethyl)heptane or **4-isopropylheptane**

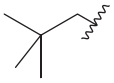


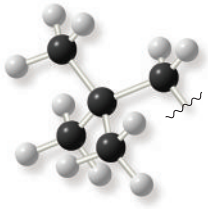
4-(1,1-Dimethylethyl)octane or **4-*tert*-butyloctane**

The common names **isopropyl**, **isobutyl**, ***sec*-butyl**, and ***tert*-butyl** are approved by the IUPAC for the unsubstituted groups, and they are still very frequently used. You should learn these groups so well that you can recognize them any way they are written. In deciding on alphabetical order for these groups you should disregard structure-defining prefixes that are written in italics and separated from the name by a hyphen. Thus *tert*-butyl precedes ethyl, but ethyl precedes isobutyl.*

There is one five-carbon group with an IUPAC approved common name that you should also know: the 2,2-dimethylpropyl group, commonly called the **neopentyl group**.







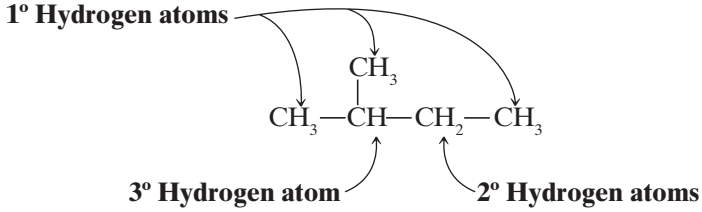
2,2-Dimethylpropyl or neopentyl group

Practice Problem 5.5

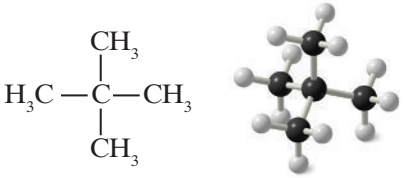
(a) In addition to the 2,2-dimethylpropyl (or neopentyl) group just given, there are seven other five-carbon groups. Draw bond-line formulas for their structures and give each structure its systematic name. **(b)** Draw bond-line formulas and provide IUPAC names for all of the isomers of C_7H_{16}.

5.3D HOW TO Classify Hydrogen Atoms

The hydrogen atoms of an alkane are classified on the basis of the carbon atom to which they are attached. A hydrogen atom attached to a primary carbon atom is a primary (1°) hydrogen atom, and so forth. The following compound, 2-methylbutane, has primary, secondary (2°), and tertiary (3°) hydrogen atoms:



On the other hand, 2,2-dimethylpropane, a compound that is often called **neopentane**, has only primary hydrogen atoms:



2,2-Dimethylpropane (neopentane)

*The abbreviations *i*-, *s*-, and *t*- are sometimes used for iso-, *sec*-, and *tert*-, respectively.

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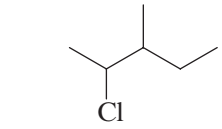
5.3E HOW TO Name Alkyl Halides

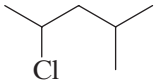
Alkanes bearing halogen substituents are named in the IUPAC substitutive system as haloalkanes:

CH_3CH_2Cl	$CH_3CH_2CH_2F$	$CH_3CHBrCH_3$
Chloroethane	**1-Fluoropropane**	**2-Bromopropane**

- When the parent chain has both a halo and an alkyl substituent attached to it, number the chain from the end nearer the first substituent, regardless of whether it is halo or alkyl. If two substituents are at equal distance from the end of the chain, then number the chain from the end nearer the substituent that has alphabetical precedence:

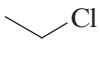


2-Chloro-3-methylpentane



2-Chloro-4-methylpentane

Common names for many simple haloalkanes are still widely used, however. In this common nomenclature system, called **functional class nomenclature**, haloalkanes are named as alkyl halides. (The following names are also accepted by the IUPAC.)



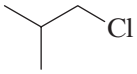
Ethyl chloride



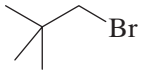
Isopropyl bromide



***tert*-Butyl bromide**



Isobutyl chloride



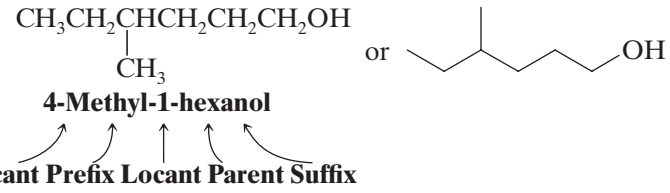
Neopentyl bromide

Practice Problem 5.6

Draw bond-line formulas and give IUPAC substitutive names for all of the isomers of **(a)** C_4H_9Cl and **(b)** $C_5H_{11}Br$.

5.3F HOW TO Name Alcohols

In what is called IUPAC **substitutive nomenclature**, a name may have as many as four features: **locants, prefixes, parent compound,** and **suffixes**. Consider the following compound as an illustration without, for the moment, being concerned as to how the name arises:



The *locant* **4-** tells that the substituent **methyl** group, named as a *prefix*, is attached to the *parent compound* at C4. The parent compound contains six carbon atoms and no multiple bonds, hence the parent name **hexane**, and it is an alcohol; therefore it has the *suffix* **-ol**. The locant **1-** tells that C1 bears the hydroxyl group. **In general, numbering of the chain always begins at the end nearer the group named as a suffix**.

The locant for a suffix (whether it is for an alcohol or another functional group) may be placed before the parent name as in the above example or, according to a 1993 IUPAC revision of the rules, immediately before the suffix. Both methods are IUPAC approved. Therefore, the above compound could also be named **4-methylhexan-1-ol**.

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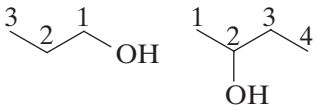
The following procedure should be followed in giving alcohols IUPAC substitutive names:

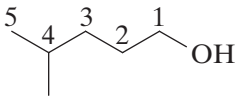
1. Select the longest continuous carbon chain *to which the hydroxyl is directly attached*. Change the name of the alkane corresponding to this chain by dropping the final *-e* and adding the suffix *-ol*.
2. Number the longest continuous carbon chain so as to give the carbon atom bearing the hydroxyl group the lower number. Indicate the position of the hydroxyl group by using this number as a locant; indicate the positions of other substituents (as prefixes) by using the numbers corresponding to their positions along the carbon chain as locants.

The following examples show how these rules are applied:

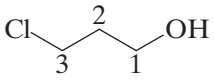


1-Propanol

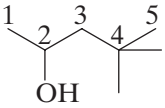
2-Butanol



4-Methyl-1-pentanol or 4-methylpentan-1-ol (*not* 2-methyl-5-pentanol)



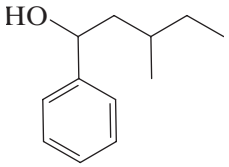
3-Chloro-1-propanol or 3-chloropropan-1-ol



4,4-Dimethyl-2-pentanol or 4,4-dimethylpentan-2-ol

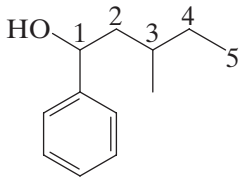
Solved Problem 5.2

Give an IUPAC name for the compound shown.



Answer

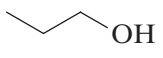
We find that the longest carbon chain (in red at right) has five carbons and it bears a hydroxyl group on the first carbon. So we name this part of the molecule as a 1-pentanol. There is a phenyl group on carbon-1 and a methyl group on carbon-3, so the full name is 3-methyl-1-phenyl-1-pentanol.



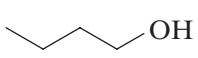
Practice Problem 5.7

Draw bond-line formulas and give IUPAC substitutive names for all of the isomeric alcohols with the formulas **(a)** $C_4H_{10}O$ and **(b)** $C_5H_{12}O$.

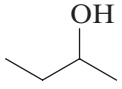
Simple alcohols are often called by *common* functional class names that are also approved by the IUPAC. We have seen several examples already (Section 2.6). In addition to *methyl alcohol, ethyl alcohol, and isopropyl alcohol*, there are several others, including the following:



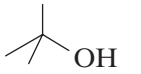
Propyl alcohol



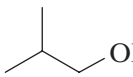
Butyl alcohol



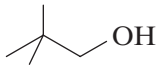
***sec*-Butyl alcohol**



***tert*-Butyl alcohol**



Isobutyl alcohol



Neopentyl alcohol

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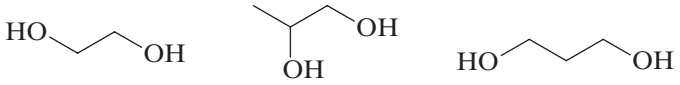
Alcohols containing two hydroxyl groups are commonly called **glycols**. In the IUPAC substitutive system they are named as **diols**:



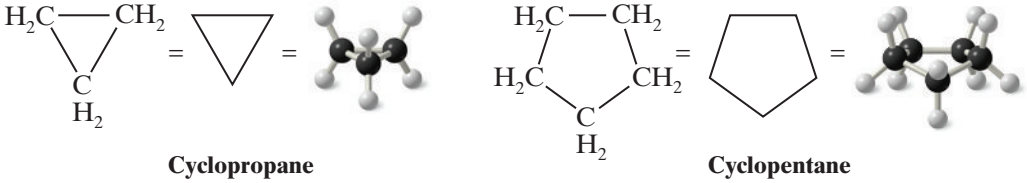
Substitutive	**1,2-Ethanediol or ethane-1,2-diol**	**1,2-Propanediol or propane-1,2-diol**	**1,3-Propanediol or propane-1,3-diol**
Common	***Ethylene glycol***	***Propylene glycol***	***Trimethylene glycol***

5.4 | HOW TO NAME CYCLOALKANES

5.4A HOW TO Name Monocyclic Cycloalkanes

Cycloalkanes are named by adding "cyclo" before the parent name.

1. *Cycloalkanes with one ring and no substituents:* Count the number of carbon atoms in the ring, then add "cyclo" to the beginning of the name of the alkane with that number of carbons. For example, cyclopropane has three carbons and cyclopentane has five carbons.



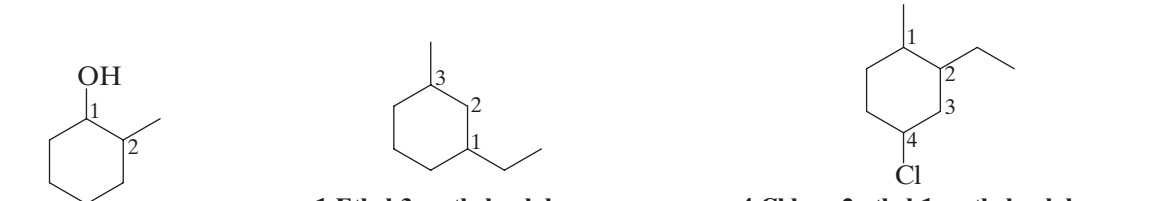
Cyclopropane **Cyclopentane**

2. *Cycloalkanes with one ring and one substituent:* Add the name of the substituent to the beginning of the parent name. For example, cyclohexane with an attached isopropyl group is isopropylcyclohexane. For compounds with only one substituent, it is not necessary to specify a number (locant) for the carbon bearing the substituent.



Isopropylcyclohexane **Chlorocyclopentane**

3. *Cycloalkanes with one ring and two or more substituents:* For a ring with two substituents, begin by numbering the carbons in the ring, starting at the carbon with the substituent that is first in the alphabet and number in the direction that gives the next substituent the lower number possible. When there are three or more substituents, begin at the substituent that leads to the lowest set of numbers (locants). The substituents are listed in alphabetical order, not according to the number of their carbon atom.

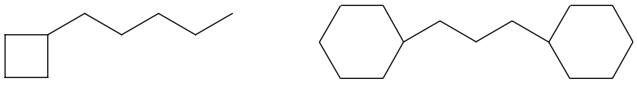


2-Methylcyclohexanol

1-Ethyl-3-methylcyclohexane (not 1-ethyl-5-methylcyclohexane)

4-Chloro-2-ethyl-1-methylcyclohexane (not 1-chloro-3-ethyl-4-methylcyclohexane)

4. When a single ring system is attached to a single chain with a greater number of carbon atoms, or when more than one ring system is attached to a single chain, then it is appropriate to name the compounds as *cycloalkylalkanes*. For example.



1-Cyclobutylpentane **1,3-Dicyclohexylpropane**

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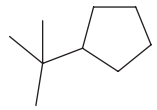
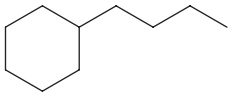
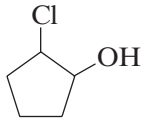
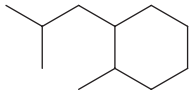
Practice Problem 5.8

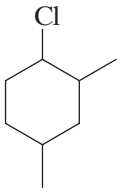
Give names for the following substituted alkanes:

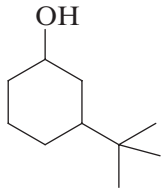
(a) 

(c) 

(e) 

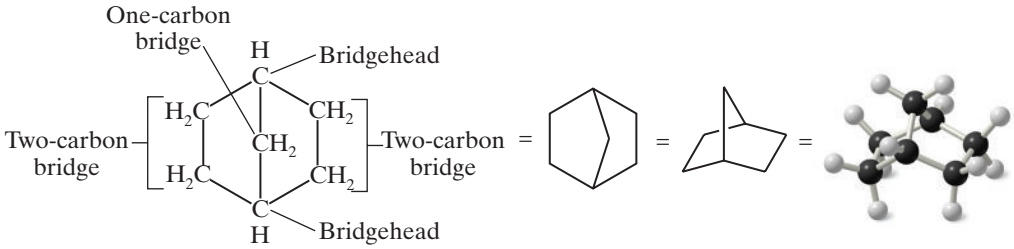
(b) 

(d) 

(f) 

5.4B HOW TO Name Bicyclic Cycloalkanes

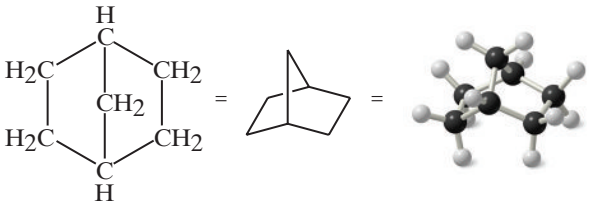
1. We name compounds containing two fused or bridged rings as bicycloalkanes and we use the name of the alkane corresponding to the total number of carbon atoms in the rings as the parent name. The following compound, for example, contains seven carbon atoms and is, therefore, a bicycloheptane. The carbon atoms common to both rings are called bridgeheads, and each bond, or each chain of atoms connecting the bridgehead atoms, is called a bridge.



A bicycloheptane

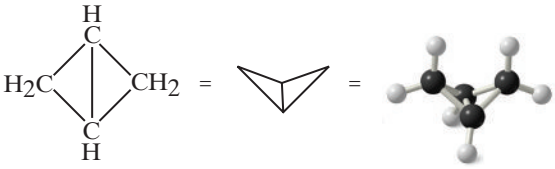
2. We then interpose an expression in brackets within the name that denotes the number of carbon atoms in each bridge (in order of decreasing length). Fused rings have zero carbons in their bridge. For example,

Bridged



Bicyclo[2.2.1]heptane
(also called norbornane)

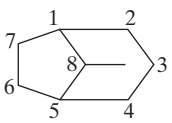
Fused



Bicyclo[1.1.0]butane

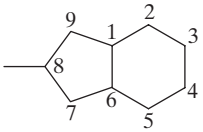
3. In bicycloalkanes with substituents, we number the bridged ring system beginning at one bridgehead, proceeding first along the longest bridge to the other bridgehead, then along the next longest bridge back to the first bridgehead; the shortest bridge is numbered last.

Bridged



8-Methylbicyclo[3.2.1]octane

Fused



8-Methylbicyclo[4.3.0]nonane

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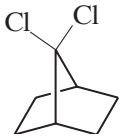
Solved Problem 5.3

Write a structural formula for 7,7-dichlorobicyclo[2.2.1]heptane.

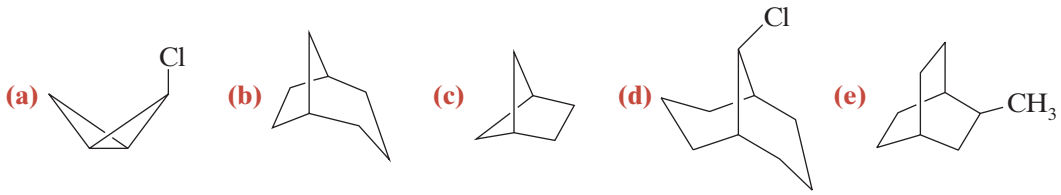
Answer

First we write a bicyclo[2.2.1]heptane ring and number it. Then we add the substituents (two chlorine atoms) to the proper carbon.



Practice Problem 5.9

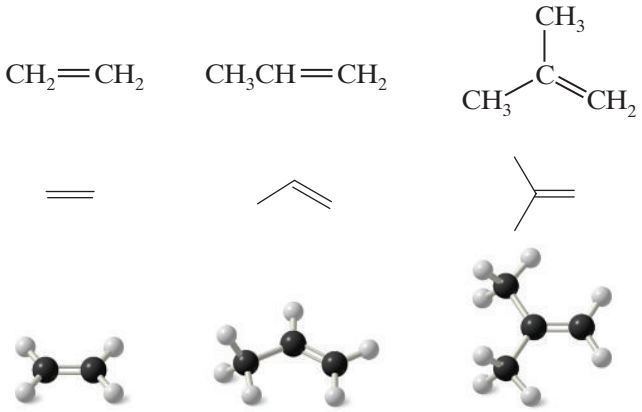
Give names for each of the following bicyclic alkanes:



(f) Write the structure of a bicyclic compound that is a constitutional isomer of bicyclo[2.2.0]hexane and give its name.

5.5 | HOW TO NAME ALKENES AND CYCLOALKENES

Many older names for **alkenes** are still in common use. Propene is often called propylene, and 2-methylpropene frequently bears the name isobutylene:



IUPAC:	**Ethene**	**Propene**	**2-Methylpropene**
Common:	***Ethylene***	***Propylene***	***Isobutylene***

The IUPAC rules for naming alkenes are similar in many respects to those for naming alkanes:

1. **Determine the parent name by selecting the longest chain that contains the double bond and change the ending of the name of the alkane of identical length from -ane to -ene.** Thus, if the longest chain contains five carbon atoms, the parent name for the alkene is *pentene*; if it contains six carbon atoms, the parent name is *hexene*, and so on.
2. **Number the chain so as to include both carbon atoms of the double bond, and begin numbering at the end of the chain nearer the double bond. Designate the location of the double bond by using the number of the first atom of the double bond as a prefix. The locant for the alkene suffix may precede the parent name or be placed immediately before the suffix.** We will show examples of both styles:



1-Butene (*not* 3-butene) **2-Hexene** (*not* 4-hexene)

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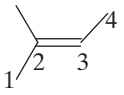
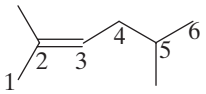
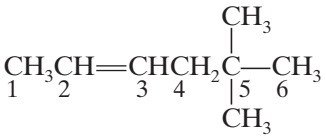
3. Indicate the locations of the substituent groups by the numbers of the carbon atoms to which they are attached:



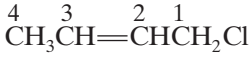
2-Methyl-2-butene
or 2-methylbut-2-ene



2,5-Dimethyl-2-hexene
or 2,5-dimethylhex-2-ene

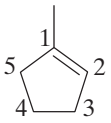


5,5-Dimethyl-2-hexene
or 5,5-dimethylhex-2-ene

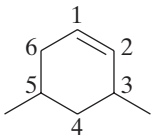


1-Chloro-2-butene
or 1-chlorobut-2-ene

4. Number substituted cycloalkenes in the way that gives the carbon atoms of the double bond the 1 and 2 positions and that also gives the substituent groups the lower numbers at the first point of difference. With substituted cycloalkenes it is not necessary to specify the position of the double bond since it will always begin with C1 and C2. The two examples shown here illustrate the application of these rules:

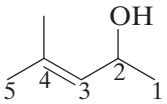


1-Methylcyclopentene
(*not* 2-methylcyclopentene)

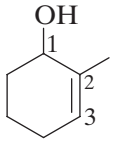


3,5-Dimethylcyclohexene
(*not* 4,6-dimethylcyclohexene)

5. Name compounds containing a double bond and an alcohol group as alkenols (or cycloalkenols) and give the alcohol carbon the lower number:



4-Methyl-3-penten-2-ol
or 4-methylpent-3-en-2-ol

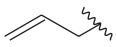


2-Methyl-2-cyclohexen-1-ol
or 2-methylcyclohex-2-en-1-ol

6. Two frequently encountered alkenyl groups are the **vinyl group** and the **allyl group**:

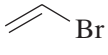


The vinyl group



The allyl group

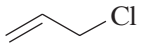
Using substitutive nomenclature, the vinyl and allyl groups are called *ethenyl* and *prop-2-en-1-yl*, respectively. The following examples illustrate how these names are employed:



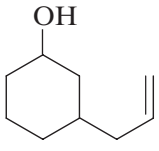
Bromoethene
or
vinyl bromide
(common)



Ethenylcyclopropane
or
vinylcyclopropane



3-Chloropropene
or
allyl chloride
(common)



3-(Prop-2-en-1-yl)cyclohexan-1-ol
or
3-allylcyclohexanol

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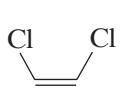
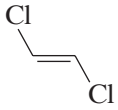
7. If two identical or substantial groups are on the same side of the double bond, the compound can be designated *cis*; if they are on opposite sides it can be designated *trans*:



***cis*-1,2-Dichloroethene**

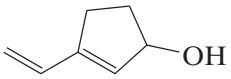


***trans*-1,2-Dichloroethene**

(In Section 7.2 we shall see another method for designating the geometry of the double bond.)

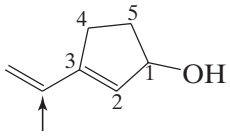
Solved Problem 5.4

Give an IUPAC name for the molecule shown.



Answer

We number the ring as shown below starting with the hydroxyl group so as to give the double bond the lower possible number. We include in the name the substituent (an ethenyl group) and the double bond (*-ene-*), and the hydroxyl group (*-ol*) with numbers for their respective positions. Hence the IUPAC name is 3-ethenyl-2-cyclopenten-1-ol.

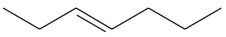


Ethenyl group

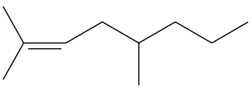
Practice Problem 5.10

Give IUPAC names for the following alkenes:

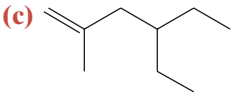
(a)



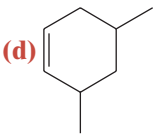
(b)



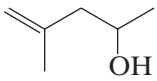
(c)



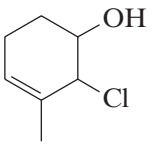
(d)



(e)



(f)



Practice Problem 5.11

Write bond-line formulas for the following:

(a) *cis*-3-Octene
(b) *trans*-2-Hexene
(c) 2,4-Dimethyl-2-pentene
(d) *trans*-1-Chlorobut-2-ene
(e) 4,5-Dibromo-1-pentene
(f) 1-Bromo-2-methyl-1-(prop-2-en-1-yl)cyclopentane
(g) 3,4-Dimethylcyclopentene
(h) Vinylcyclopentane
(i) 1,2-Dichlorocyclohexene
(j) *trans*-1,4-Dichloro-2-pentene

5.6 | HOW TO NAME ALKYNES

Alkynes are named in much the same way as alkenes. Unbranched alkynes, for example, are named by replacing the **-ane** of the name of the corresponding alkane with the ending **-yne**. The chain is numbered to give the carbon atoms of the triple bond the lower possible numbers. The lower number of the two carbon atoms of the

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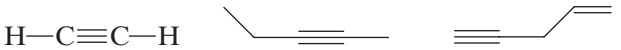
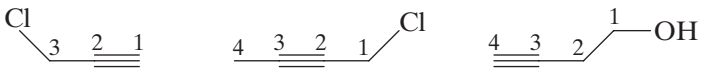
triple bond is used to designate the location of the triple bond. The IUPAC names of three unbranched alkynes are shown here:

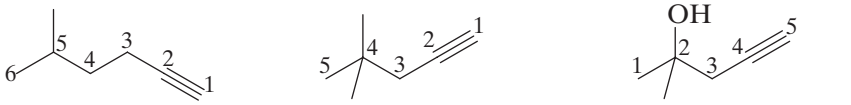


Ethyne or acetylene* | **2-Pentyne** | **1-Penten-4-yne† or pent-1-en-4-yne**

The locations of substituent groups of branched alkynes and substituted alkynes are also indicated with numbers. An —OH group has priority over the triple bond when numbering the chain of an alkynol:



3-Chloropropyne | **1-Chloro-2-butyne or 1-chlorobut-2-yne** | **3-Butyn-1-ol or but-3-yn-1-ol**



5-Methyl-1-hexyne or 5-methylhex-1-yne | **4,4-Dimethyl-1-pentyne or 4,4-dimethylpent-1-yne** | **2-Methyl-4-pentyn-2-ol or 2-methylpent-4-yn-2-ol**

Practice Problem 5.12

Give the structures and IUPAC names for all the alkynes with the formula C_6H_{10}.

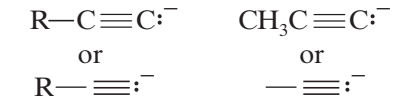
Monosubstituted acetylenes or 1-alkynes are called **terminal alkynes**, and the hydrogen attached to the carbon of the triple bond is called the **acetylenic hydrogen atom:**



A terminal alkyne

When named as a substituent, the HC≡C— group is called the ethynyl group.

The anion obtained when the acetylenic hydrogen is removed is known as an *alkynide ion* or an acetylide ion. As we shall see in Section 7.11, these ions are useful in synthesis:



An alkynide ion (an acetylide ion) | **The propynide ion**

5.7 | PHYSICAL PROPERTIES OF ALKANES AND CYCLOALKANES

If we examine the unbranched **alkanes** in Table 5.2, we notice that each alkane differs from the preceding alkane by one —CH_2— group. Butane, for example, is $CH_3(CH_2)_2CH_3$ and pentane is $CH_3(CH_2)_3CH_3$. A series of compounds like this, where each member differs from the next member by a constant unit, is called a **homologous series.** Members of a homologous series are called **homologues**.

At room temperature (25 °C) and 1 atm pressure the first four members of the homologous series of unbranched alkanes are gases (Fig. 5.3), the C_5 —C_{17} unbranched alkanes (pentane to heptadecane) are liquids, and the unbranched alkanes with 18 and more carbon atoms are solids.

*The name acetylene is retained by the IUPAC system for the compound HC≡CH and is used frequently.

†When double and triple bonds are present, the direction of numbering is chosen so as to give the lowest overall set of locants. In the face of equivalent options, then preference is given to assigning lowest numbers to the double bonds.

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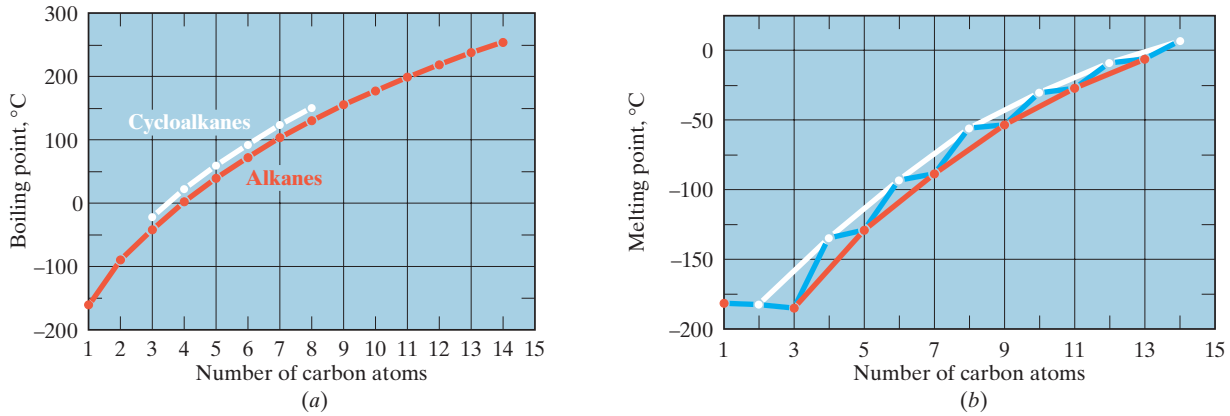
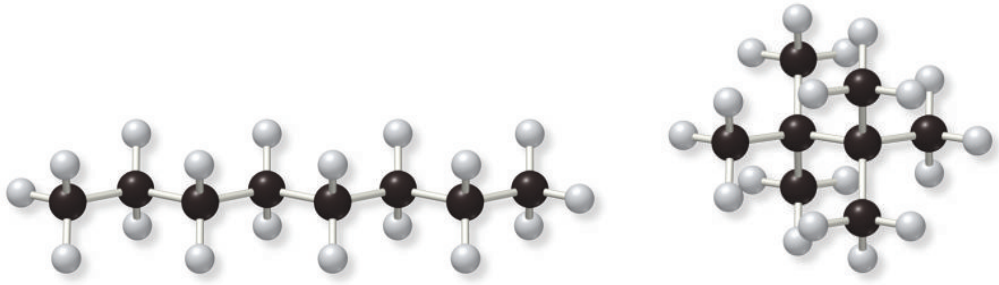


Figure 5.3 (*a*) Boiling points of unbranched alkanes (in grey) and cycloalkanes (in white). (*b*) Melting points of unbranched alkanes.

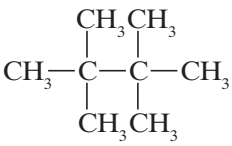
Boiling Points

The boiling points of the unbranched alkanes show a regular increase with increasing molecular weight (Fig. 5.3*a*) in the homologous series of straight-chain alkanes. Branching of the alkane chain, however, lowers the boiling point. The hexane isomers in Table 5.1 examplify this trend.

Part of the explanation for these effects lies in the dispersion forces that we studied in Section 2.13B. With unbranched alkanes, as molecular weight increases, so too do molecular size and, even more importantly, molecular surface area. With increasing surface area, the dispersion forces between molecules increase; therefore, more energy (a higher temperature) is required to separate molecules from one another and produce boiling. Chain branching, on the other hand, makes a molecule more compact, reducing its surface area and with it the strength of the dispersion forces operating between it and adjacent molecules; this has the effect of lowering the boiling point. Figure 5.4 illustrates this for two C_8 isomers.



$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_3$



(*a*) **Octane (bp 125.6 °C)**

(*b*) **2,2,3,3-Tetramethylbutane (bp 106.3 °C)**

Figure 5.4 Chain-branching decreases the contact surface area between molecules, as for the branched C8 isomer in (*b*), lessening the dispersion forces between them and leading to a lower boiling point than for the unbranched C8 isomer (*a*).

Melting Points

The unbranched alkanes do not show the same smooth increase in melting points with increasing molecular weight (blue line in Fig. 5.3*b*) that they show in their boiling points. There is an alternation as one progresses from an unbranched alkane with an even number of carbon atoms to the next one with an odd number of carbon atoms. If, however, the even- and odd-numbered alkanes are plotted on *separate* curves (white and red lines in Fig. 5.3*b*), there *is* a smooth increase in melting point with increasing molecular weight.

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X-ray diffraction studies, which provide information about molecular structure, have revealed the reason for this apparent anomaly. Alkane chains with an even number of carbon atoms pack more closely in the crystalline state. As a result, attractive forces between individual chains are greater and melting points are higher.

Cycloalkanes also have much higher melting points than their open-chain counterparts (Table 5.3).

Table 5.3 Physical Constants of Cycloalkanes

Number of Carbon Atoms	Name	bp (°C) (1 atm)	mp (°C)	Density at 20 °C (9 mL^{-1})	Refractive Index (n_D^{20})
3	Cyclopropane	–33	–126.6	—	—
4	Cyclobutane	13	–90	—	1.4260
5	Cyclopentane	49	–94	0.751	1.4064
6	Cyclohexane	81	6.5	0.779	1.4266
7	Cycloheptane	118.5	–12	0.811	1.4449
8	Cyclooctane	149	13.5	0.834	—

Density

As a class, the alkanes and cycloalkanes are the least dense of all groups of organic compounds. All alkanes and cycloalkanes have densities considerably less than 1.00 g mL^{-1} (the density of water at 4 °C). As a result, petroleum (a mixture of hydrocarbons rich in alkanes) floats on water.

Solubility

Alkanes and cycloalkanes are almost totally insoluble in water because of their very low polarity and their inability to form hydrogen bonds. Liquid alkanes and cycloalkanes are soluble in one another, and they generally dissolve in solvents of low polarity. Good solvents for them are benzene, carbon tetrachloride, chloroform, and other hydrocarbons.

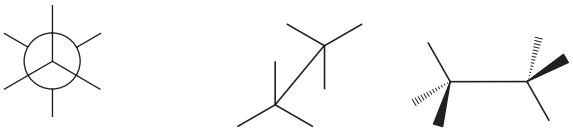
5.8 | SIGMA BONDS AND BOND ROTATION

Two groups bonded by only a single bond can undergo rotation about that bond with respect to each other.

- The temporary molecular shapes that result from such a rotation are called **conformations** of the molecule.
- Each possible structure is called a **conformer**.
- An analysis of the energy changes that occur as a molecule undergoes rotations about single bonds is called a **conformational analysis**.

5.8A Newman Projections and HOW TO Draw Them

When we do conformational analysis, we will find that certain types of structural formulas are especially convenient to use. One of these types is called a **Newman projection formula** and another type is a **sawhorse formula**. Sawhorse formulas are much like dash–wedge three-dimensional formulas we have used so far. In conformational analyses, we will make substantial use of Newman projections.



Newman projection formula **Sawhorse formula**

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To write a Newman projection formula:

- We imagine ourselves taking a view from one atom (usually a carbon) directly along a selected bond axis to the next atom (also usually a carbon atom).
- The front carbon and its other bonds are represented as  .
- The back carbon and its bonds are represented as  .

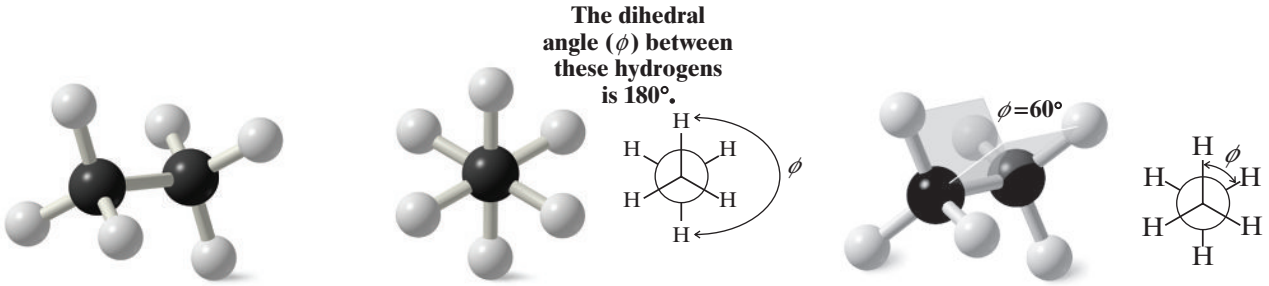

Figure 5.5 (*a*) The staggered conformation of ethane. (*b*) The Newman projection formula for the staggered conformation. (*c*) The dihedral angle between these hydrogen atoms is 60°.

In Figs. 5.5*a*, *b* we show ball-and-stick models and a Newman projection formula for the staggered conformation of ethane. The **staggered conformation** of a molecule is that conformation where the **dihedral angle** between the bonds at each of the carbon—carbon bonds is 180° and where atoms or groups bonded to carbons at each end of a carbon—carbon bond arc as far apart as possible. The 180° dihedral angle in the staggered conformation of ethane is indicated in Fig. 5.5*b*.

The eclipsed conformation of ethane is shown in Fig. 5.6 using ball-and-stick models and a Newman projection. In an **eclipsed conformation** the atoms bonded to carbons at each end of a carbon—carbon bond are directly opposed to one another. The dihedral angle between them is 0°.

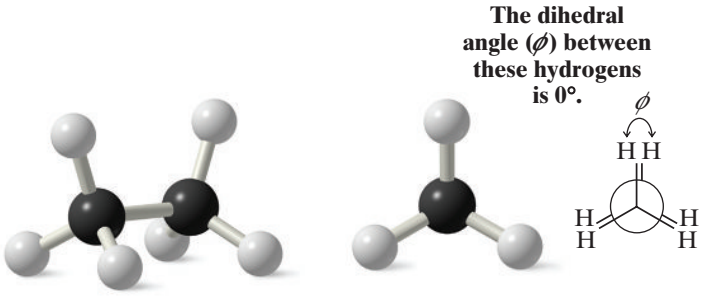

Figure 5.6 (*a*) The eclipsed conformation of ethane. (*b*) The Newman projection formula for the eclipsed conformation.

5.8B HOW TO Do a Conformational Analysis

Now let us consider a conformational analysis of ethane. Clearly, infinitesimally small changes in the dihedral angle between C—H bonds at each end of ethane could lead to an infinite number of conformations, including, of course, the staggered and eclipsed conformations. These different conformations are not all of equal stability, however, and it is known that the staggered conformation of ethane is the most stable conformation (i.e., it is the conformation of lowest potential energy). The explanation for greater stability of the staggered conformation relates mainly to steric

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replusion between bonding pairs of electrons. In the eclipsed conformation electron clouds from the C—H bonds are closer and repel one another. The staggered conformation allows the maximum possible separation of the electron pairs in the C—H bonds. In addition, there is a phenomenon called **hyperconjugation** that involves favorable overlap between filled and unfilled sigma orbitals in the staggered conformation. Hyperconjugation helps to stabilize the staggered conformation. The more important factor, however, is the minimization of steric repulsions in the staggered form. In later chapters we shall explain hyperconjugation further and the role it plays in relative stability of reactive species called carbocations.

- The energy difference between the conformations of ethane can be represented graphically in a **potential energy diagram**, as shown in Figure 5.7.

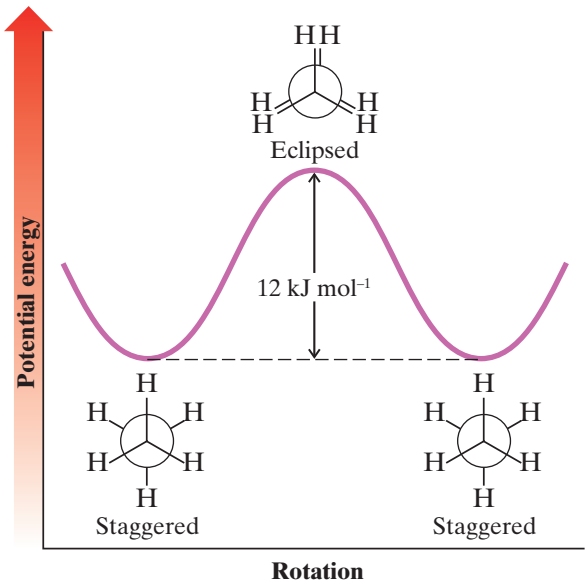


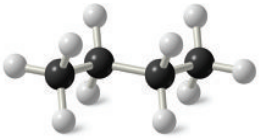
Figure 5.7 Potential energy changes that accompany rotation of groups about the carbon–carbon bond of ethane.

In ethane the energy difference between the staggered and eclipsed conformations is about 12 kJ mol^{-1}. This small barrier to rotation is called the **torsional barrier** of the single bond. Because of this barrier, some molecules will wag back and forth with their atoms in staggered or nearly staggered conformations, while others with slightly more energy will rotate through an eclipsed conformation to another staggered conformation. At any given moment, unless the temperature is extremely low (–250 °C), most ethane molecules will have enough energy to undergo bond rotation from one conformation to another.

What does all this mean about ethane? We can answer this question in two different ways. If we consider a single molecule of ethane, we can say, for example, that it will spend most of its time in the lowest energy, staggered conformation, or in a conformation very close to being staggered. Many times every second, however, it will acquire enough energy through collisions with other molecules to surmount the torsional barrier and it will rotate through an eclipsed conformation. If we speak in terms of a large number of ethane molecules (a more realistic situation), we can say that at any given moment most of the molecules will be in staggered or nearly staggered conformations.

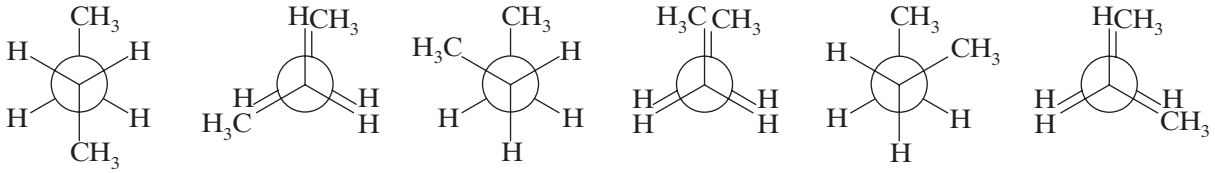
5.9 | CONFORMATIONAL ANALYSIS OF BUTANE

Now let us consider rotation about the C2—C3 bond of butane. The barriers to rotation about the C2—C3 bond in butane are larger than for rotation about the C—C bond in ethane, but still not large enough to prevent the rotations that lead to all possible butane conformers.


Butane

- The factors involved in barriers to bond rotation are together called **torsional strain** and include the repulsive interactions called **steric hindrance** between electron clouds of the bonded groups.

In butane, torsional strain results from steric hindrance between the terminal methyl groups and hydrogen atoms at C-2 and C-3 and from steric hindrance directly between the two methyl groups. These interactions result in six important conformers of butane, shown as **I–VI** below.



I An anti conformation | **II** An eclipsed conformation | **III** A gauche conformation | **IV** An eclipsed conformation | **V** A gauche conformation | **VI** An eclipsed conformation

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The **anti conformation (I)** does not have torsional strain from steric hindrance because the groups are staggered and the methyl groups are far apart. The anti conformation is the most stable. The methyl groups in the **gauche conformations III** and **V** are close enough to each other that the dispersion forces between them are *repulsive*; the electron clouds of the two groups are so close that they repel each other. This repulsion causes the gauche conformations to have approximately 3.8 kJ mol^{-1} more energy than the anti conformation.

The eclipsed conformations (**II, IV**, and **VI**) represent energy maxima in the potential energy diagram (Fig. 5.8). Eclipsed conformations **II** and **VI** have repulsive dispersion forces arising from the eclipsed methyl groups and hydrogen atoms. Eclipsed conformation **IV** has the greatest energy of all because of the added large repulsive dispersion forces between the eclipsed methyl groups as compared to **II** and **VI**.

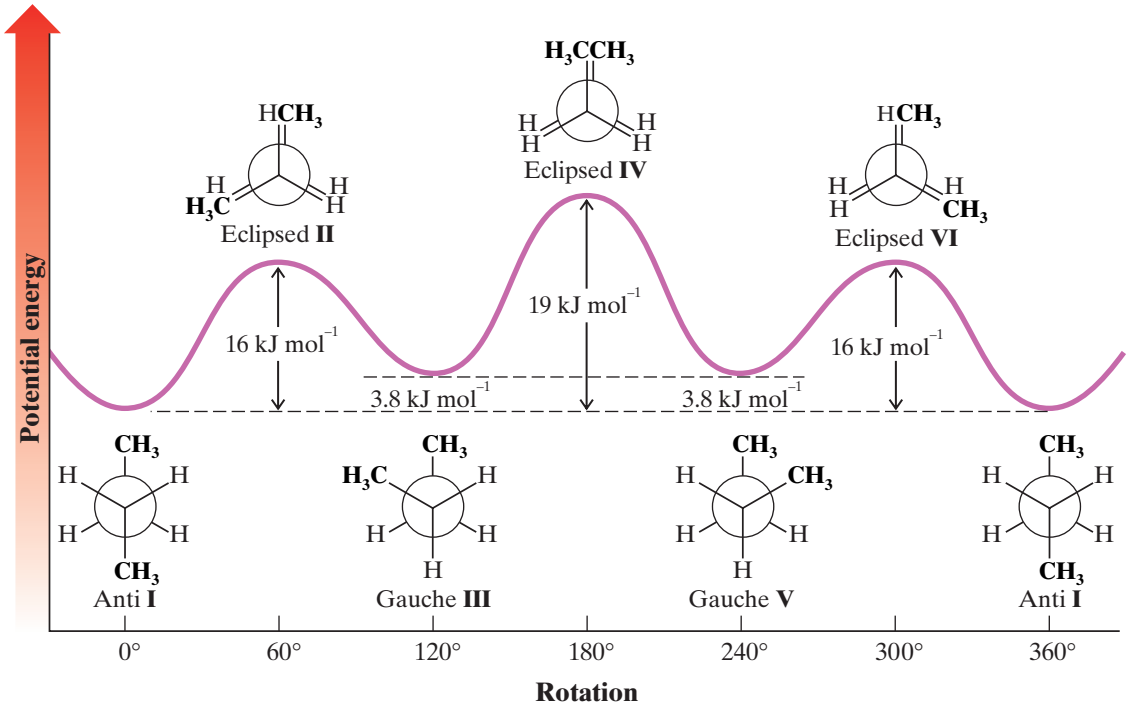

Figure 5.8 Energy changes that arise from rotation about the C2—C3 bond of butane.

Although the barriers to rotation in a butane molecule are larger than those of an ethane molecule (Section 5.8), they are still far too small to permit isolation of the gauche and anti conformations at normal temperatures. Only at extremely low temperatures would the molecules have insufficient energies to surmount these barriers.

We saw earlier (Section 2.16C) that dispersion forces can be *attractive*. Here, however, we find that they can also be *repulsive*, leading to steric hindrance. Whether dispersion interactions lead to attraction or to repulsion depends on the distance that separates the two groups. As two nonpolar groups are brought closer and closer together, the first effect is one in which a momentarily unsymmetrical distribution of electrons in one group induces an opposite polarity in the other. The opposite charges induced in those portions of the two groups that are in closest proximity lead to attraction between them. This attraction increases to a maximum as the internuclear distance of the two groups decreases. The internuclear distance at which the attractive force is at a maximum is equal to the sum of what are called the *van der Waals radii* of the two groups. The van der Waals radius of a group is, in effect, a measure of its size. If the two groups are brought still closer—closer than the sum of their van der Waals radii—their electron clouds begin to penetrate each other, and strong electron–electron repulsion occurs.

Gauche conformers **III** and **V** of butane are examples of stereoisomers.

- **Stereoisomers,** we have learnt that they have the same molecular formula and connectivity but different arrangements of atoms in three-dimensional space.
- **Conformational stereoisomers** are related to one another by bond rotations.

Conformational analysis is but one of the ways in which we will consider the three-dimensional shapes and stereochemistry of molecules.

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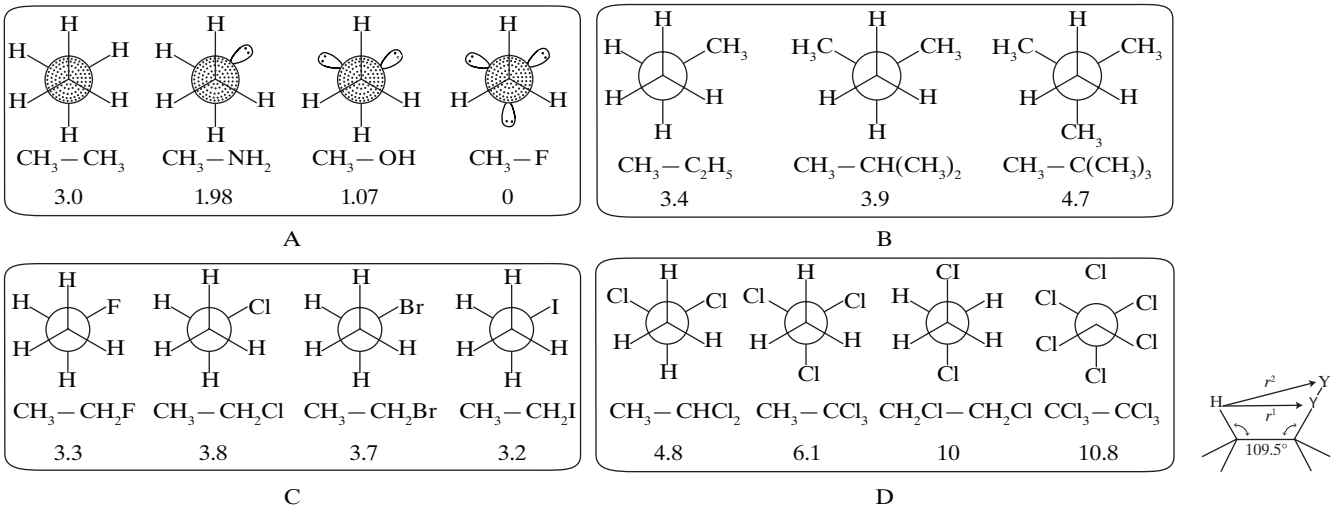
5.9A Rotamer Barriers in Saturated Compounds

We have seen that staggered conformers of small hydrocarbons (e.g., ethane and butane) are more stable than eclipsed conformers and generally predominate at equilibrium. This structural preference is usually attributed to steric effects, and has been termed torsional strain (or Pitzer strain). In the case of ethane, rotation toward an eclipsed structure brings the electrons in C—H bonds on the different C atoms closer to each other, thereby increasing repulsion. The distance between the nearest hydrogen atoms in ethane is roughly 2.5 Å in the staggered form as compared to 2.3 Å in the eclipsed rotamer. This latter distance is comparable to known instances of steric hindrance, such as the hydrogens in *axialmethylcyclohexane* and *ortho hydrogens in biphenyl*. However, since the bond vectors in ethane are diverging by nearly 40°, this comparison may not be compelling.

Since the eclipsed conformer of ethane has three eclipsed C—H bonds, it is tempting to attribute 1.0 kcal/mol of strain to each, resulting in a total of 3 kcal/mol torsion strain. It has been noted that the rotational energy barriers in methyl amine and methanol are lower by 1 kcal/mol for each eclipsed C—H bond that is missing, as shown in group (A) of the following diagram. Although the non-bonding electron pair(s) in these compounds are shown in spatially directed sp^3 orbitals, the exact location is a subject of debate and they do not appear to offer any significant steric hindrance. It might be argued that the C—X bond length is shortened and the C—X—H bond angle narrowed in the alcohol and amine; but molecular structure calculations indicate that the eclipsed H—H distance remains the same.

The second group of structures (B) shows the influence of one or more methyl substituents on one of the ethane carbons. Each methyl increases the rotational barrier by about 0.5 kcal/mol, although the effect of the third substituent (neopentane) is somewhat greater. Because a methyl group is substantially larger than a hydrogen, one might have expected a greater barrier to rotation; however, the C—C bond is more than 40% longer than the C—H bond, thereby reducing the overall steric crowding. The following diagram illustrates this feature, which is amplified by the divergent vectors of the C—H and C—Y bonds. Consequently, the relative distance $r2$ is greater than $r1$. As it takes less energy to bend a covalent bond than to stretch or shorten it, some of the crowding strain in propane and isobutene might be relieved by opening the C—C—C bond angle. However, this would not be effective in neopentane (the last structure in group B), hence this barrier is slightly higher than expected.

Rotational barriers (kcal/mol)



The influence of bond length on steric hindrance is dramatically demonstrated by the group of compounds labeled D. The covalent radii of substituent atoms increases in the order H < F < Cl < Br < I, with F being less than twice as large as H, Cl being three times as large and Br and I being roughly 3.5 and 4 times the size of hydrogen. The C—X bond lengths also increase in the same order, with C—F being 25% longer than C—H, C—Cl being 62% longer and the Br and I bonds longer still. The result of these opposing factors is apparent in the barriers. Additional chlorine substituents increase the rotational barrier, with the 1,1,1-trichloro compound having a greater than expected effect, similar to the neopentane case. Stretching the C—C bond would also reduce the steric hindrance to rotation. Although this is not normally possible, an approximation is found in the two C—Si compounds listed in group F.

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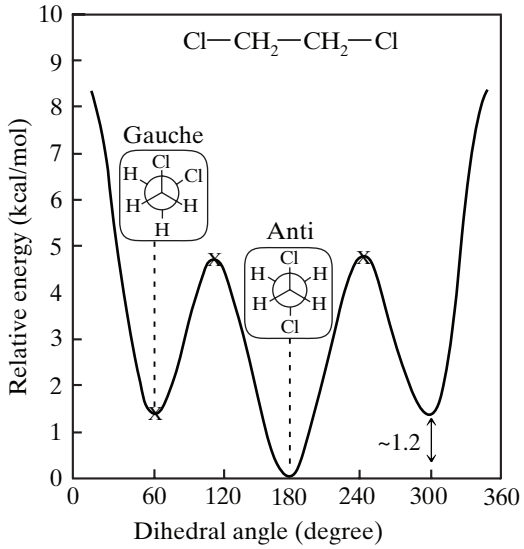
Since the C—Si bond is 21% longer than C—C, and Si—H is over 35% longer than C—H, the barrier in CH_3—SiH_3 is nearly half of that in ethane. Remarkably, the barrier in tetramethylsilane is even lower. Measurements on eclipsed conformers of these compounds indicate the H:Y distance (noted in the above diagram) is 2.74 Å when Y 5 H and 2.94 Å when Y 5CH_3. The barriers in dimethyl ether and trimethylamine are unexpectedly high, as shown in group C. Each methyl group seems to add 1.2–1.6 kcal/mol to the barrier. For example, the barrier in dimethyl amine is 3.6 kcal/mol, which agrees well with the methyl component in dimethyl ether (1.6 kcal/mol in both cases). However, the second methyl in trimethylamine then adds only 0.8 kcal/mol. The shorter bond lengths and smaller bond angles in these compounds may contribute to these variations, which are poorly understood.

Finally the presence of a polar substituent **on each ethane carbon** often results in a relatively high barrier, as shown by the compounds in group (E). It is instructive to compare 1,2-dichloroethane with butane. From the previous discussion, one might anticipate a lower barrier for the former, as a consequence of the longer C—Cl bond. However, the full barrier for the dichloro compound is roughly twice as high, and may be attributed to dipole repulsion between the polar C—Cl bonds as they approach each other. The energy difference between the anti and gauche staggered conformers of 1,2-dichloroethane is approximately 45% higher than the difference in butane, and the lower barrier between these conformers is 25% higher.



Unexpectedly, hexachloroethane has a barrier of only about 20% higher than 1,2-dichlorooethane. This may be due in part to a 0.03 Å increase in the C—C bond length (about 2%), caused by the extensive dipole repulsion. The rotational energy diagram (see above) reflects enthalpy measurements made in the gas phase. In solution or as the pure liquid, the magnitude of the barriers often decreases, and the energy difference between anti and gauche conformers changes in favor of the latter. For butane, the anti–gauche difference drops from 0.85 to 0.55 kcal/mol in the liquid. In the case of 1,2-dichloroethane solutions, polar solvents lower the energy of the gauche conformer to such a degree that it becomes favored at equilibrium.

Recent studies of rotational barriers in substituted ethanes suggest that a significant contribution comes from sigma bond–antibond interactions which stabilize an anti configuration of W and Z groups in W–C–C–Z constitutions, relative to their gauche orientation. This stereoelectronic factor, which is similar to *hyperconjugation*, becomes larger as the electronegativity difference between W and Z increases. The conformational preferences of 1,2-difluoroethane and 1-fluoropropane provide instructive examples, as shown in the following diagram. Although 1,2-difluoroethane should suffer dipole repulsion as the fluorine atoms approach each other, the gauche form is more stable than the anti-conformer ($\Delta H^\circ = 50.6$ kcal/mol). This surprising fact may be explained by the two hyperconjugative bond interactions in the gauche form. These act to stabilize the gauche rotamer, and do not exist in the anti-conformer. The overall barrier to rotation in this compound is about 6 kcal/mol, significantly lower than the dichloro analog discussed above. A comparison of 1,2-difluoroethane and 1,2-dichloroethane is informative. The bond dipoles of C—F and C—Cl are similar, with the latter being slightly larger because of its longer bond. The hyperconjugative interactions that stabilize the gauche rotamer are stronger for fluorine than for chlorine, due to the former's greater electronegativity relative to hydrogen. Taken together, these differences shift the conformational equilibria of 1,2-dihaloethanes from preferentially anti in the chloro, bromo and iodo compounds to gauche for the difluoride.

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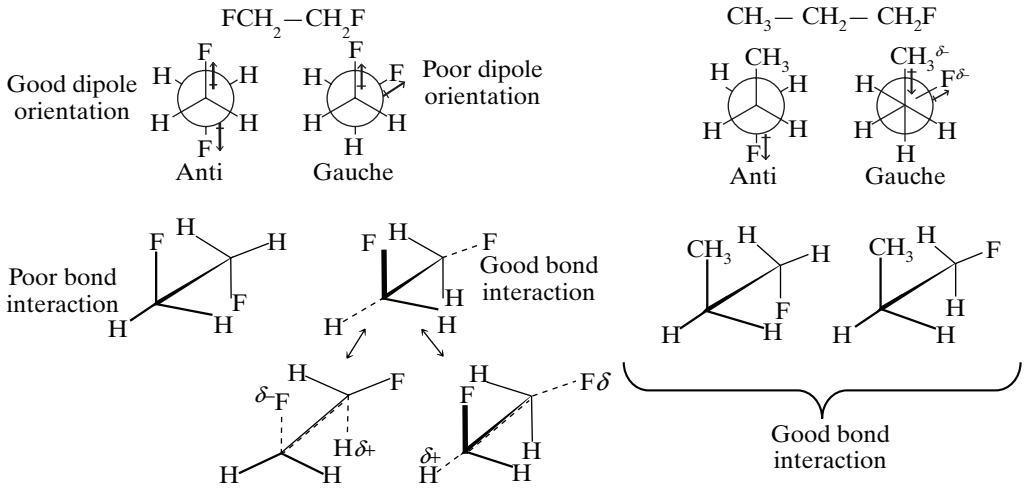
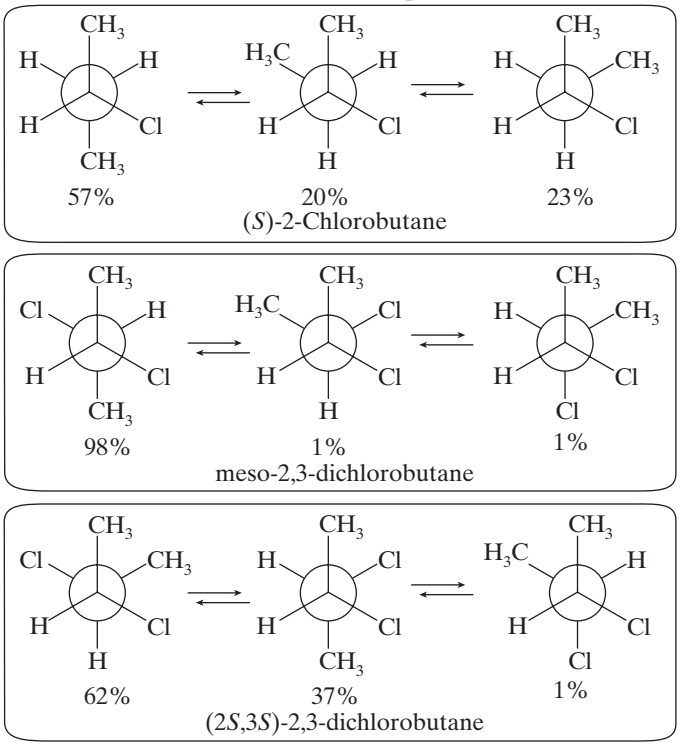


The case of 1-fluoropropane demonstrates another factor. The C2–C3 rotational barrier is about 1 kcal/mol less than that of butane, and the gauche conformer is slightly favored ($\Delta H°$= 0.09 kcal/mol). A similar behavior is observed for 1-chloropropane. Hyperconjugative stabilization is possible for all staggered conformations; and it is probably not a determining factor. When the strong C—F bond dipole rotates to approach the CH_3—CH_2 bond, it induces an opposite dipole in that bond. As shown above, this may actually result in an attractive interaction between the methyl and fluorine substituents (as well as methyl and chlorine in 1-chloropropane). The concepts described above are used to explain and predict many other cases of conformational isomerism. Three such examples are shown below, all measured in the gas phase. The rotational barriers of the two 2,3-dichlorobutane diastereomers are significantly different, the meso isomer being $\Delta H°$= 12.5 kcal/mol, and the racemic compound being $\Delta H°$= 9.5 kcal/mol.

Conformational equilibria



5.9B Rotamer Barriers in Unsaturated Compounds

Alkenes: The rotation of a methyl group (or any alkyl group) relative to a double bond is an important conformational event. A simple example of propene is shown below. In the course of the methyl rotation a C—H bond eclipses either an sp^2 hybrid C—H bond or the C═CH_2 bond, but not simultaneously. The energy of this rotation follows a simple sine curve

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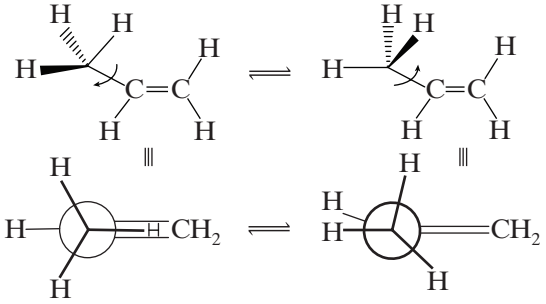
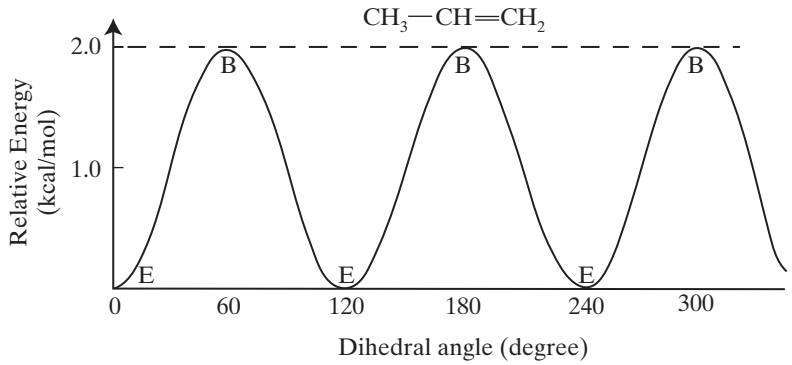
similar to the rotational barrier of ethane, with a smaller amplitude (ca. 2 kcal/mol). The conformer in which the C═CH_2 bond is eclipsed is the lower energy rotamer, possibly reflecting a stabilizing interaction between σ-C—H bonds of methyl and the π^*-antibonding orbital. This conformer will be termed *eclipsed*, and the higher energy alternative *bisected*.

Adding a methyl group to propene, as in 1-butene, doubles the number of eclipsed and bisected conformers. Interestingly, the overall rotational barrier is reduced, and the energy difference between the two eclipsed rotamers is over 20 times greater than the difference between the two bisected forms. This is illustrated in the following diagram. The eclipsing shown by magenta colored arrows in conformer B2 is referred to as allylic 1,2-strain (A 1,2-strain). If the vinyl hydrogen is replaced by a larger methyl group, as in 2-methyl-1-butene, this strain adds about 1.3 kcal/mol to the rotational barrier.

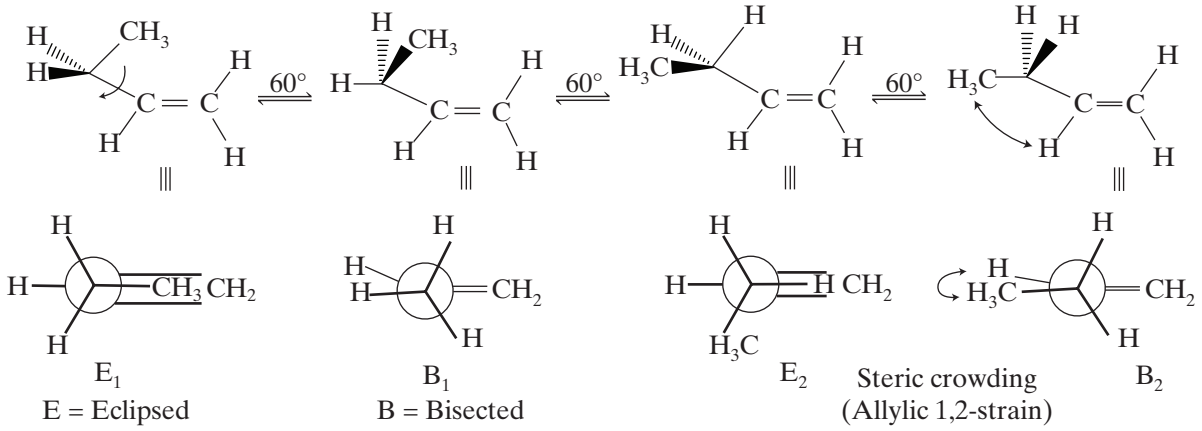
Propene rotamers





A larger substituent, such as *tert*-butyl in 3,3-dimethyl-1-butene, does not change significantly the stability order of eclipsed relative to bisected rotamers.

Rotamers of 1-butene



Double bond stereoisomers, such as (*E*) and (*Z*)-2-pentene have very different rotational energy barriers. The *E* isomer, shown below, has a rotational profile very similar to that of 1-butene (above). Since the C_1 methyl is directed away from the ethyl group, this is not surprising.

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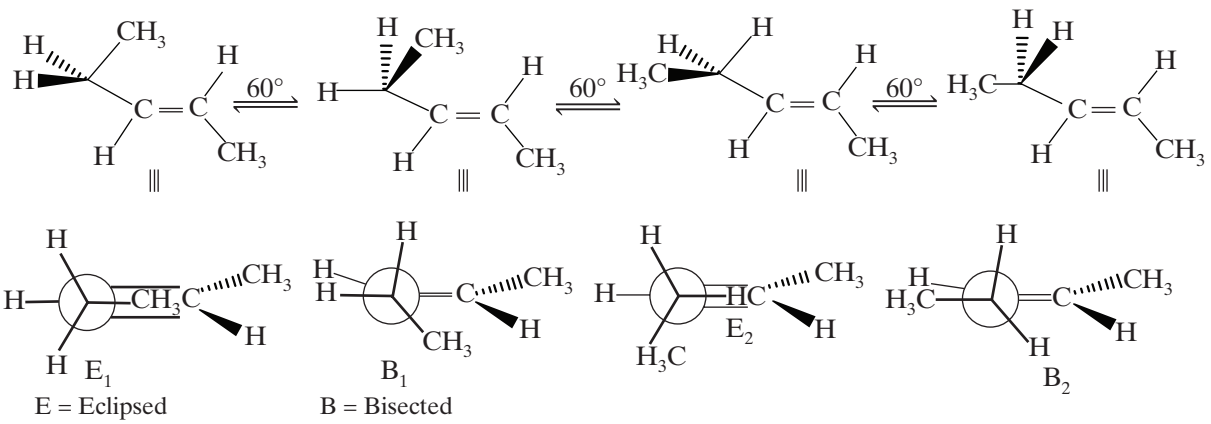
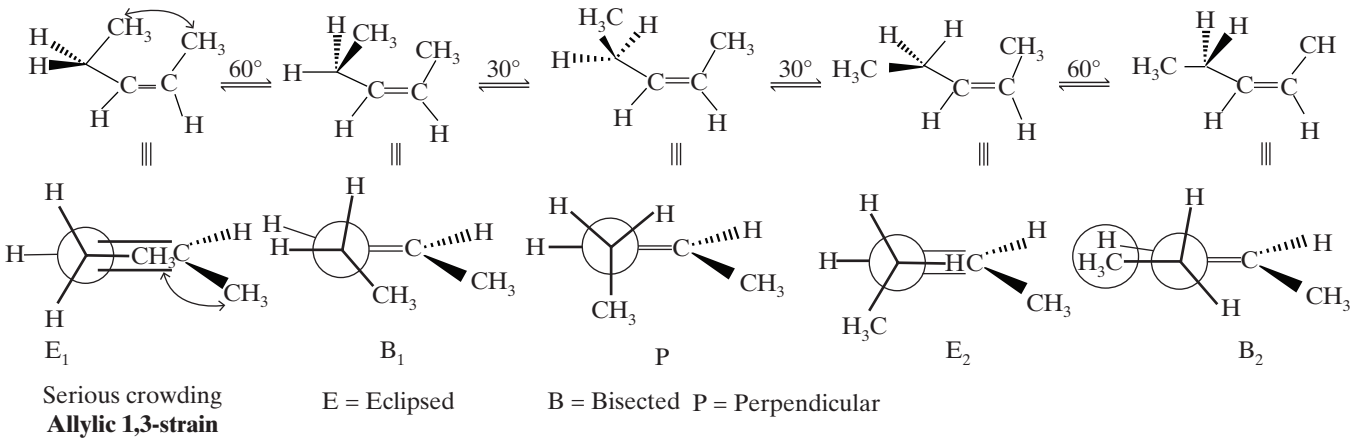
Rotamers of (*E*)-2-pentene



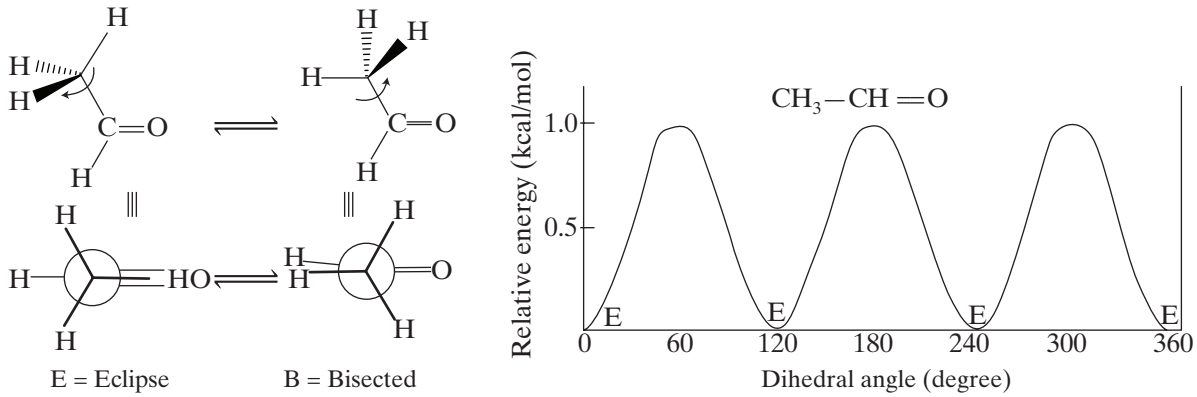
For the *Z*-isomer, the C_1 methyl is *cis* to the ethyl group, leading to severe steric crowding in the E_1 and B_1 conformers, shown again by arrows. This destabilizing hindrance is called allylic 1,3-strain (A 1,3-strain). Unexpectedly, a 1,3-strain renders eclipsed conformer E_2 slightly higher in energy than bisected conformer. The perpendicular conformation, P, is lower in energy than either E_2 or B_2.

Rotamers of (Z)-2-pentene



On comparison, the conformational energy profile of propanal differs significantly from that of 1-*butene*. As shown below, conformer E_1 is more stable than E_2 by roughly 0.8 kcal/mol, reflecting the relatively small size of oxygen. Even the larger substituent in 3-methylbutanal prefers this conformation. Furthermore, the activation energy for interconversion of the chiral eclipsed E_2 conformers is very small, and it is not possible to relate experimental behavior to a preferred conformer. Ketones, of course, will exhibit a 1,2-strain in conformer B_2.

Acetaldehyde rotamers



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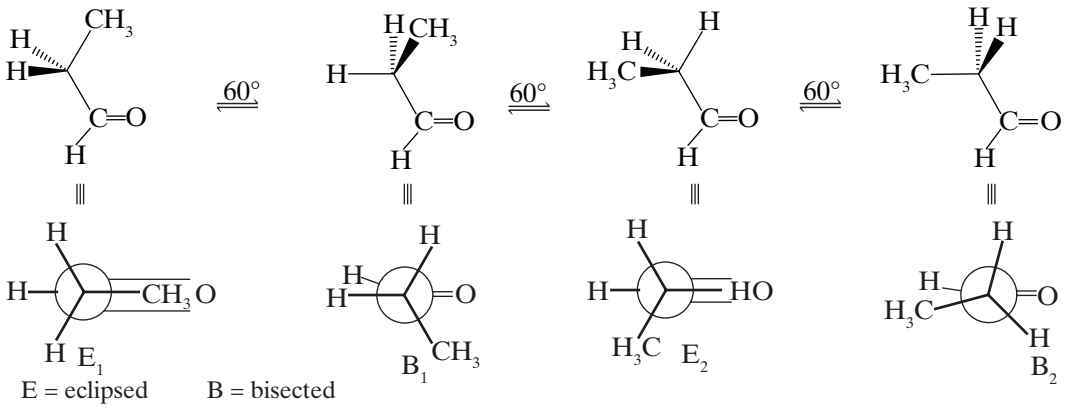
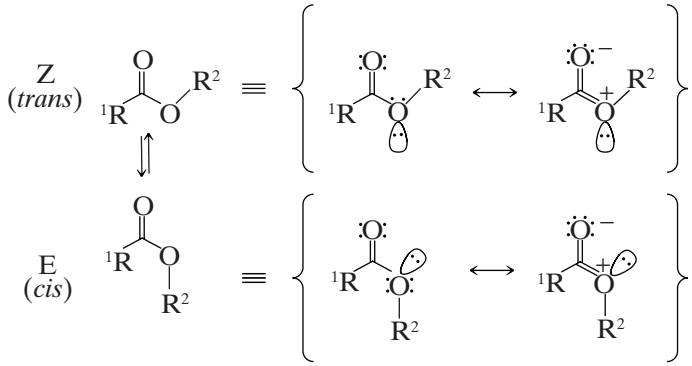
Although the conformational differences shown here are not large, addition reactions to aldehydes and ketones are sensitive to the configuration of substituents on the α-carbon atom. Due to the importance of such asymmetric induction in the stereoselective formation of new stereogenic centers, it has been extensively studied.

Rotamers of propanal



Esters and Amides: The contribution of n–π conjugation to the structure of amides is even greater than that observed in esters, as is indicated by their lower C═O *stretching frequency*. Thus, the barrier to rotation about the NH_2—CHO bond in formamide is over 18 kcal/mol, and the CH_3NH—CHO bond in *N*-methylformamide is more than 1 kcal/mol greater. Such barriers permit the observation of conformational isomers of amides by room temperature NMR. For simple amides like *N*-methylacetamide and the formamides noted above, the *trans* conformer is more stable than the *cis* by more than 1.5–2.5 kcal/mol.



Practice Problem 5.13

Sketch a curve similar to that in Fig. 5.8 showing in general terms the energy changes that arise from rotation about the C2—C3 bond of 2-methylbutane. You need not concern yourself with the actual numerical values of the energy changes, but you should label all maxima and minima with the appropriate conformations.

5.10 | THE RELATIVE STABILITIES OF CYCLOALKANES: RING STRAIN

Cycloalkanes do not all have the same relative stability. Experiments have shown that cyclohexane is the most stable cycloalkane and that, in comparison, cyclopropane and cyclobutane are much less stable. This difference in relative stability is due to **ring strain**, which comprises **angle strain** and **torsional strain**.

- **Angle strain** is the result of deviation from ideal bond angles caused by inherent structural constraints (such as ring size).
- **Torsional strain** is the result of repulsive dispersion forces that cannot be relieved due to restricted conformational mobility.

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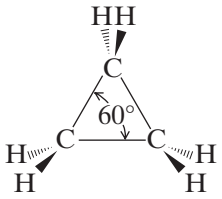
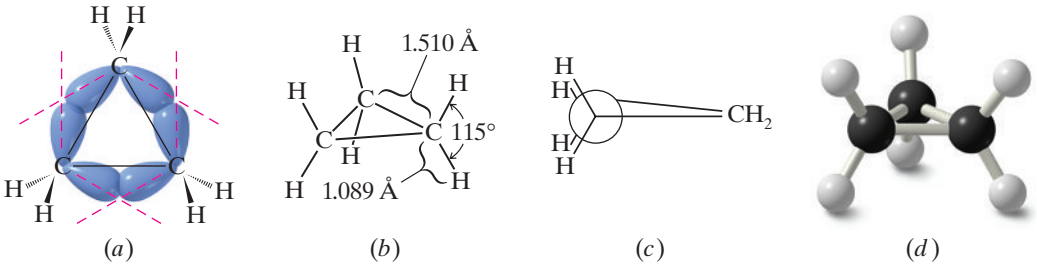
5.10A Cyclopropane

The carbon atoms of alkanes are sp^3 hybridized. The normal tetrahedral bond angle of an sp^3-hybridized atom is 109.5°. In cyclopropane (a molecule with the shape of a regular triangle), the internal angles must be 60° and therefore they must depart from this ideal value by a very large amount—by 49.5°:



Angle strain exists in a cyclopropane ring because the sp^3 orbitals comprising the carbon–carbon σ bonds cannot overlap as effectively (Fig. 5.9*a*) as they do in alkanes (where perfect end-on overlap is possible). The carbon–carbon bonds of cyclopropane are often described as being "bent." Orbital overlap is less effective. (The orbitals used for these bonds are not purely sp^3; they contain more *p* character.) The carbon–carbon bonds of cyclopropane are weaker, and as a result the molecule has greater potential energy.

While angle strain accounts for most of the ring strain in cyclopropane, it does not account for it all. Because the ring is (of necessity) planar, the C—H bonds of the ring are all *eclipsed* (Figs. 5.9*b*,*c*), and the molecule has torsional strain from repulsive dispersion forces as well.

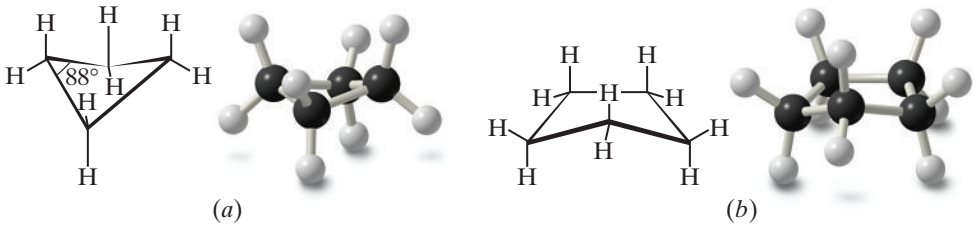


(*a*) (*b*) (*c*) (*d*)

Figure 5.9 (*a*) Orbital overlap in the carbon–carbon bonds of cyclopropane cannot occur perfectly end-on. This leads to weaker "bent" bonds and to angle strain. (*b*) Bond distances and angles in cyclopropane. (*c*) A Newman projection formula as viewed along one carbon–carbon bond shows the eclipsed hydrogens. (Viewing along either of the other two bonds would show the same picture.) (*d*) Ball-and-stick model of cyclopropane.

5.10B Cyclobutane

Cyclobutane also has considerable angle strain. The internal angles are 88°—a departure of more than 21° from the normal tetrahedral bond angle. The cyclobutane ring is not planar but is slightly "folded" (Fig. 5.10*a*). If the cyclobutane ring were planar, the angle strain would be somewhat less (the internal angles would be 90° instead of 88°), but torsional strain would be considerably larger because all eight C—H bonds would be eclipsed. By folding or bending slightly the cyclobutane ring relieves more of its torsional strain than it gains in the slight increase in its angle strain.



(*a*) (*b*)

Figure 5.10 (*a*) The "folded" or "bent" conformation of cyclobutane. (*b*) The "bent" or "envelope" form of cyclopentane. In this structure the front carbon atom is bent upward. In actuality, the molecule is flexible and shifts conformations constantly.

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5.10C Cyclopentane

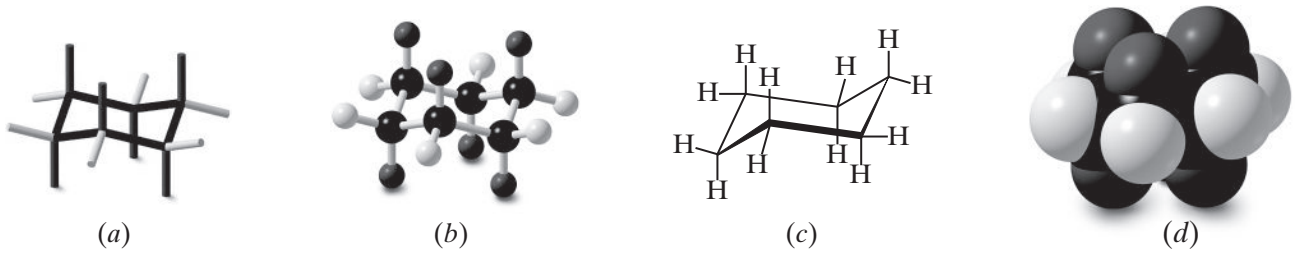
The internal angles of a regular pentagon are 108°, a value very close to the normal tetrahedral bond angles of 109.5°. Therefore, if cyclopentane molecules were planar, they would have very little angle strain. Planarity, however, would introduce considerable torsional strain because all ten C—H bonds would be eclipsed. Consequently, like cyclobutane, cyclopentane assumes a slightly bent conformation in which one or two of the atoms of the ring are out of the plane of the others (Fig. 5.10*b*). This relieves some of the torsional strain. Slight twisting of carbon–carbon bonds can occur with little change in energy and causes the out-of-plane atoms to move into plane and causes others to move out. Therefore, the molecule is flexible and shifts rapidly from one conformation to another. With little torsional strain and angle strain, cyclopentane is almost as stable as cyclohexane.

5.11 | CONFORMATIONS OF CYCLOHEXANE: THE CHAIR AND THE BOAT

Cyclohexane is more stable than the other **cycloalkanes** we have discussed, and it has several conformations that are important for us to consider.

- The most stable **conformation of cyclohexane** is the **chair conformation**.
- There is no angle or torsional strain in the chair form of cyclohexane.

In a chair conformation (Fig. 5.11), all of the carbon–carbon bond angles are 109.5°, and are thereby free of angle strain. The chair conformation is free of torsional strain, as well. When viewed along any carbon–carbon bond (viewing the structure from an end, Fig. 5.12), the bonds are seen to be perfectly staggered. Moreover, the hydrogen atoms at opposite corners of the cyclohexane ring are maximally separated.

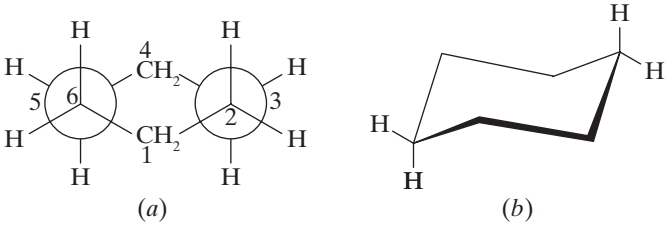


(*a*) (*b*) (*c*) (*d*)

Figure 5.11 Representations of the chair conformation of cyclohexane: (*a*) tube format; (*b*) ball-and-stick format; (*c*) line drawing; (*d*) space-filling model of cyclohexane. Notice that there are two orientations for the hydrogen substituents—those that project obviously up or down (shown in red) and those that lie around the perimeter of the ring in more subtle up or down orientations (shown in black or gray). We shall discuss this further in Section 5.12.

- By partial rotations about the carbon–carbon single bonds of the ring, the chair conformation can assume another shape called the **boat conformation** (Fig. 5.13).
- The boat conformation has no angle strain, but it does have torsional strain.

When a model of the boat conformation is viewed down carbon–carbon bond axes along either side (Fig. 5.14*a*), the C—H bonds at those carbon atoms are found to be eclipsed, causing torsional strain. Additionally, two of the hydrogen atoms on C1 and C4 are close enough to each other to cause van der Waals repulsion (Fig. 5.14*b*). This latter effect has been called the "flagpole" interaction of the boat conformation. Torsional strain and flagpole interactions cause the boat conformation to have considerably higher energy than the chair conformation.



(*a*) (*b*)

Figure 5.12 (*a*) A Newman projection of the chair conformation of cyclohexane. (Comparisons with an actual molecular model will make this formulation clearer and will show that similar staggered arrangements are seen when other carbon–carbon bonds are chosen for sighting.) (*b*) Illustration of large separation between hydrogen atoms at opposite corners of the ring (designated C1 and C4) when the ring is in the chair conformation.

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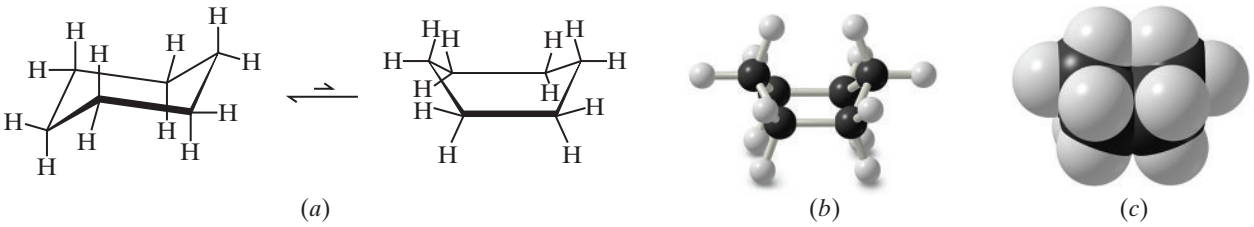
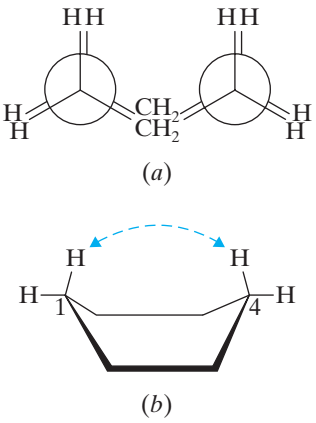


(*a*) (*b*) (*c*)

Figure 5.13 (*a*) The boat conformation of cyclohexane is formed by "flipping" one end of the chair form up (or down). This flip requires only rotations about carbon–carbon single bonds. (*b*) Ball-and-stick model of the boat conformation. (*c*) A space-filling model of the boat conformation.



(*a*) (*b*)

Figure 5.14 (*a*) Illustration of the eclipsed conformation of the boat conformation of cyclohexane. (*b*) Flagpole interaction of the C1 and C4 hydrogen atoms of the boat conformation. The C1—C4 flagpole interaction is also readily apparent in Fig. 5.13*c*.

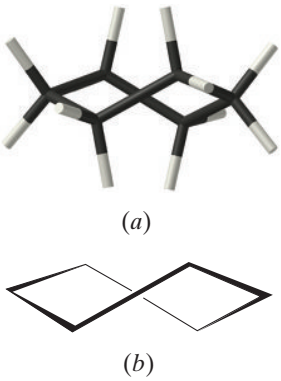
Although it is more stable, the chair conformation is much more rigid than the boat conformation. The boat conformation is quite flexible. By flexing to a new form—the twist conformation (Fig. 5.15)—the boat conformation can relieve some of its torsional strain and, at the same time, reduce the flagpole interactions.

- The twist boat conformation of cyclohexane has a lower energy than the pure boat conformation, but is not as stable as the chair conformation.

The stability gained by flexing is insufficient, however, to cause the twist conformation to be more stable than the chair conformation. The chair conformation is estimated to be lower in energy than the twist conformation by approximately 23 kJ mol^{-1}.

The energy barriers between the chair, boat, and twist conformations of cyclohexane are low enough (Fig. 5.16) to make separation of the conformers impossible at room temperature. At room temperature the thermal energies of the molecules are great enough to cause approximately 1 million interconversions to occur each second.

- *Because of the greater stability of the chair, more than 99% of the molecules are estimated to be in a chair conformation at any given moment.*



(*a*) (*b*)

Figure 5.15 (*a*) Tube model and (*b*) line drawing of the twist conformation of cyclohexane.

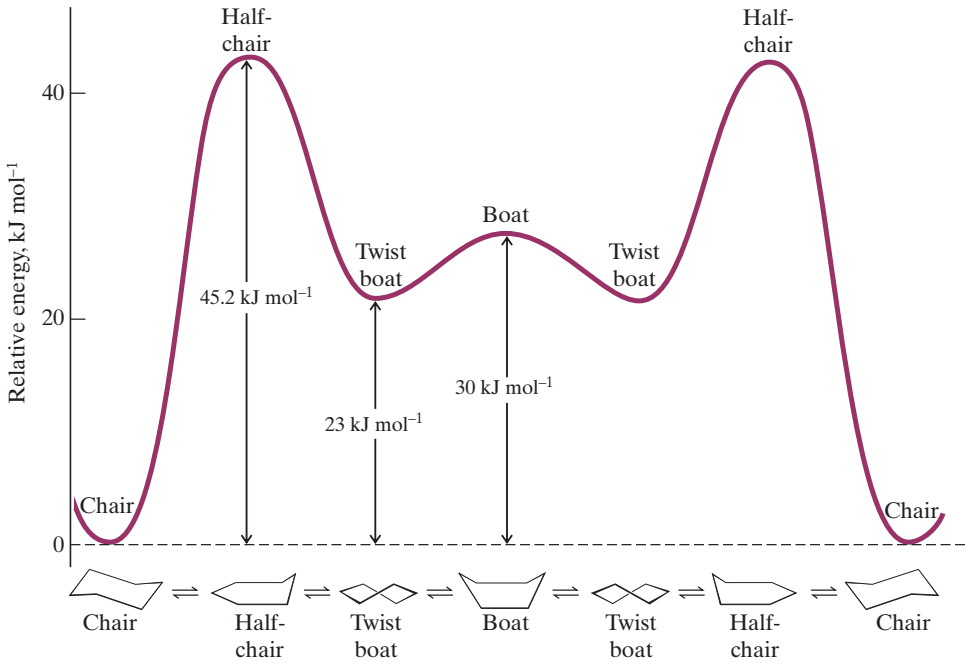


Figure 5.16 The relative energies of the various conformations of cyclohexane. The positions of maximum energy are conformations called half-chair conformations, in which the carbon atoms of one end of the ring have become coplanar.

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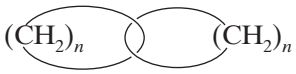
5.11A Conformations of Higher Cycloalkanes

Cycloheptane, cyclooctane, and cyclononane and other higher cycloalkanes also exist in nonplanar conformations. The small instabilities of these higher cycloalkanes appear to be caused primarily by torsional strain and repulsive dispersion forces between hydrogen atoms across rings, called *transannular strain*. The nonplanar conformations of these rings, however, are essentially free of angle strain.

X-ray crystallographic studies of cyclodecane reveal that the most stable conformation has carbon–carbon–carbon bond angles of 117°. This indicates some angle strain. The wide bond angles apparently allow the molecules to expand and thereby minimize unfavorable repulsions between hydrogen atoms across the ring.

There is very little free space in the center of a cycloalkane unless the ring is quite large. Calculations indicate that cyclooctadecane, for example, is the smallest ring through which a $—CH_2CH_2CH_2—$ chain can be threaded. Molecules have been synthesized, however, that have large rings threaded on chains and that have large rings that are interlocked like links in a chain. These latter molecules are called **catenanes**:



A catenane ($n \geq 18$)

In 1994 J. F. Stoddart and co-workers, then at the University of Birmingham (England), achieved a remarkable synthesis of a catenane containing a linear array of five interlocked rings. Because the rings are interlocked in the same way as those of the olympic symbol, they named the compound **olympiadane**.

5.12 | SUBSTITUTED CYCLOHEXANES: AXIAL AND EQUATORIAL HYDROGEN GROUPS

The six-membered ring is the most common ring found among nature's organic molecules. For this reason, we shall give it special attention. We have already seen that the chair conformation of cyclohexane is the most stable one and that it is the predominant conformation of the molecules in a sample of cyclohexane.

The chair conformation of a cyclohexane ring has two distinct orientations for the bonds that project from the ring. These positions are called axial and equatorial, as shown for cyclohexane in Fig. 5.17.

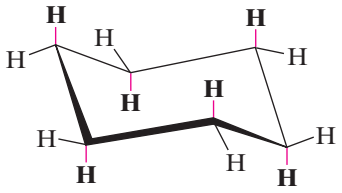
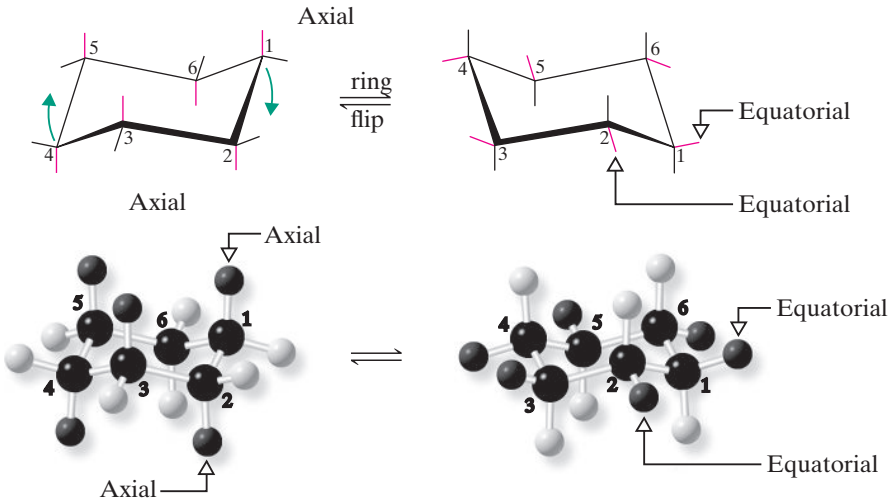


Figure 5.17 The chair conformation of cyclohexane. Axial hydrogen atoms are shown in red, equatorial hydrogens are shownin black.

- The **axial bonds** of cyclohexane are those that are perpendicular to the average plane of the ring. There are three axial bonds on each face of the cyclohexane ring, and their orientation (up or down) alternates from one carbon to the next.
- The **equatorial bonds** of cyclohexane are those that extend from the perimeter of the ring. The equatorial bonds alternate from slightly up to slightly down in their orientation from one carbon to the next.
- When a cyclohexane ring undergoes a chair–chair conformational change (a **ring flip**), all of the bonds that were axial become equatorial, and all bonds that were equatorial become axial.



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5.12A HOW TO Draw Chair Conformational Structures

A set of guidelines will help you draw chair conformational structures that are clear and that have unambiguous axial and equatorial bonds.

- Notice in Fig. 5.18*a* that sets of parallel lines define opposite sides of the chair. Notice, too, that equatorial bonds are parallel to ring bonds that are one bond away from them in either direction. When you draw chair conformational structures, try to make the corresponding bonds parallel in your drawings.
- When a chair formula is drawn as shown in Fig. 5.18, the axial bonds are all either up or down, in a vertical orientation (Fig. 5.18*b*). When a vertex of bonds in the ring points up, the axial bond at that position is also up, and the equatorial bond at the same carbon is angled slightly down. When a vertex of ring bonds is down, the axial bond at that position is also down, and the equatorial bond is angled slightly upward.

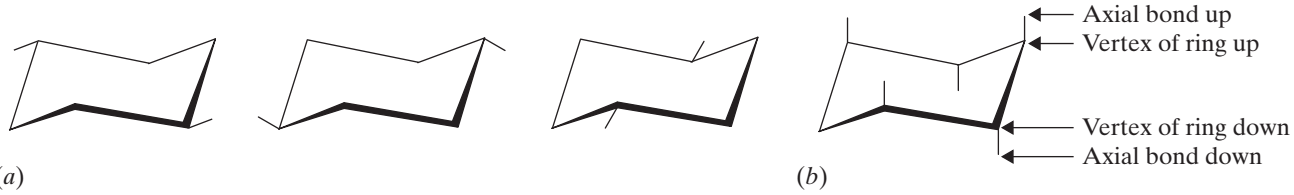

Figure 5.18 (*a*) Sets of parallel lines that constitute the ring and equatorial C—H bonds of the chair conformation. (*b*) The axial bonds are all vertical. When the vertex of the ring points up, the axial bond is up and vice versa.

Now, try to draw some chair conformational structures for yourself that include the axial and equatorial bonds. Then, compare your drawings with those here and with actual models. You will see that with a little practice your chair conformational structures can be perfect.

5.12B A Conformational Analysis of Methylcyclohexane

Now let us consider methylcyclohexane. Methylcyclohexane has two possible chair conformations (Fig. 5.19, **I** and **II**), and these are interconvertible through the bond rotations that constitute a ring flip. In conformation (Fig. 5.19*a*) the methyl group (with yellow hydrogens in the space-filling model) occupies an *axial* position, and in conformation **II** the methyl group occupies an *equatorial* position.

- The most stable conformation for a monosubstituted cyclohexane ring (a cyclohexane ring where one carbon atom bears a group other than hydrogen) is the conformation where the substituent is equatorial.

Studies indicate that conformation **II** with the equatorial methyl group is more stable than conformation **I** with the axial methyl group by about 7.6 kJ mol^{-1}. Thus, in the equilibrium mixture, the conformation with the methyl group in the equatorial position is the predominant one, constituting about 95% of the equilibrium mixture.

The greater stability of methylcyclohexane with an equatorial methyl group can be understood through an inspection of the two forms as they are shown in Figs. 5.19*a–c*.

- Studies done with models of the two conformations show that when the methyl group is axial, it is so close to the two axial hydrogens on the same side of the ring (attached to the C3 and C5 atoms) that **the dispersion forces between them are repulsive**.
- This type of steric strain, because it arises from an interaction between an axial group on carbon atom 1 and an axial hydrogen on carbon atom 3 (or 5), is called a **1,3-diaxial interaction**.
- Studies with other substituents show that **there is generally less repulsion when any group larger than hydrogen is equatorial rather than axial**.

The strain caused by a 1,3-diaxial interaction in methylcyclohexane is the same as the strain caused by the close proximity of the hydrogen atoms of methyl groups in the gauche form of butane (Section 5.9). Recall that the interaction in *gauche*-butane (called, for convenience, a *gauche interaction*) causes *gauche*-butane to be less stable than *anti*-butane by 3.8 kJ mol^{-1}. The following Newman projections will help you to see that the two steric interactions are the same. In the second projection we view axial methylcyclohexane along the C1—C2 bond and see that what we

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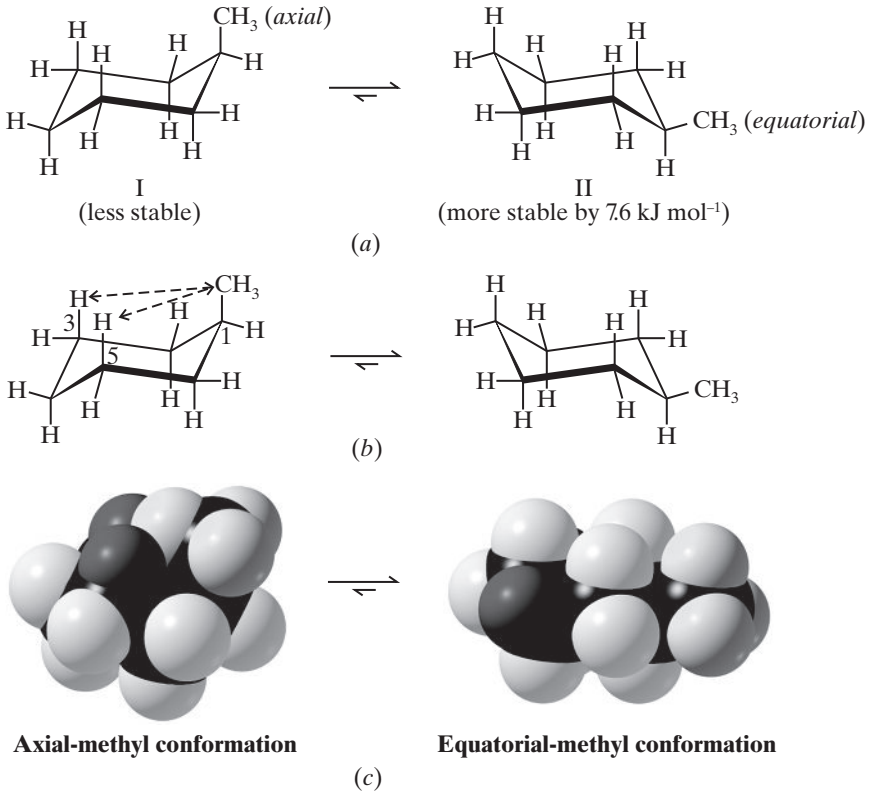
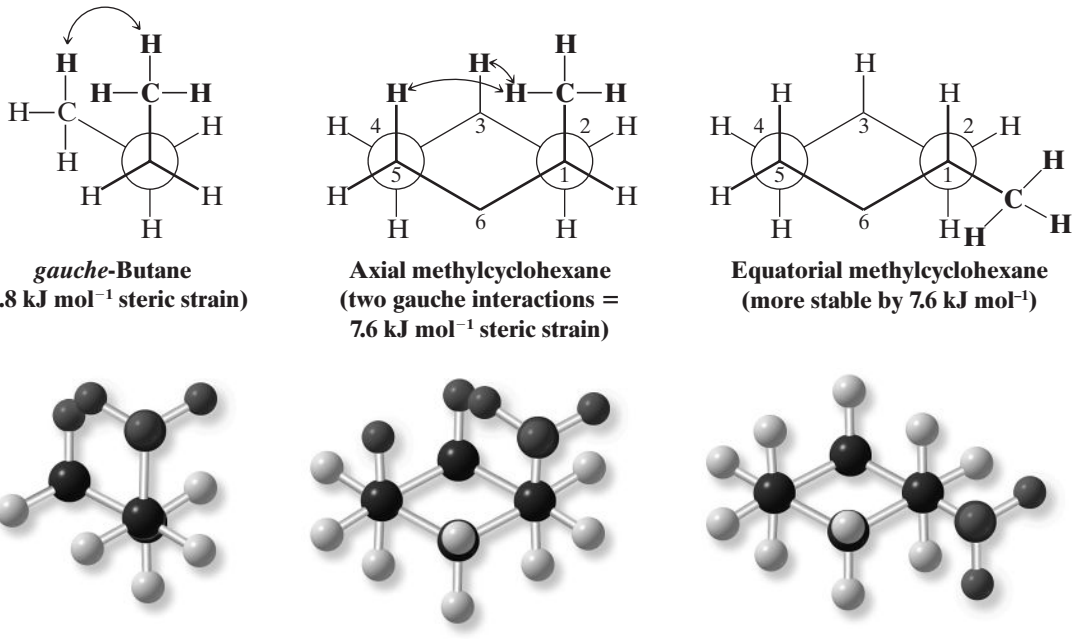


Figure 5.19 (*a*) The conformations of methylcyclohexane with the methyl group axial **(I)** and equatorial **(II)**. (*b*) 1,3-Diaxial interactions between the two axial hydrogen atoms and the axial methyl group in the axial conformation of methylcyclohexane are shown with dashed arrows. Less crowding occurs in the equatorial conformation. (*c*) Space-filling molecular models for the axial–methyl and equatorial–methyl conformers of methylcyclohexane. In the axial–methyl conformer the methyl group (shown with yellow hydrogen atoms) is crowded by the 1,3-diaxial hydrogen atoms (red), as compared to the equatorial–methyl conformer, which has no 1,3-diaxial interactions with the methyl group.

call a 1,3-diaxial interaction is simply a gauche interaction between the hydrogen atoms of the methyl group and the hydrogen atom at C3:



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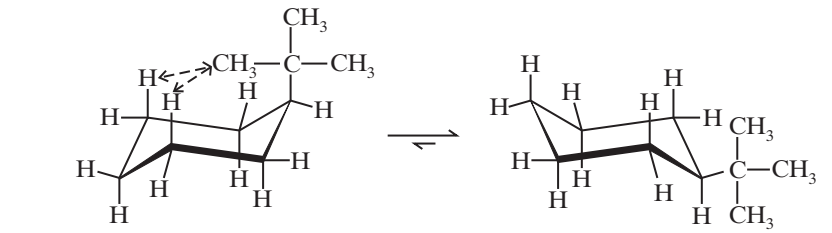
Viewing methylcyclohexane along the C1—C6 bond (do this with a model) shows that it has a second identical gauche interaction between the hydrogen atoms of the methyl group and the hydrogen atom at C5. The methyl group of axial methylcyclohexane, therefore, has two gauche interactions and, consequently, it has 7.6 kJ mol^{-1} of strain. The methyl group of equatorial methylcyclohexane does not have a gauche interaction because it is anti to C3 and C5.

Practice Problem 5.14

Show by a calculation (using the formula $\Delta G° = -RT \ln K_{eq}$) that a free-energy difference of 7.6 kJ mol^{-1} between the axial and equatorial forms of methylcyclohexane at 25 °C (with the equatorial form being more stable) does correlate with an equilibrium mixture in which the concentration of the equatorial form is approximately 95%.

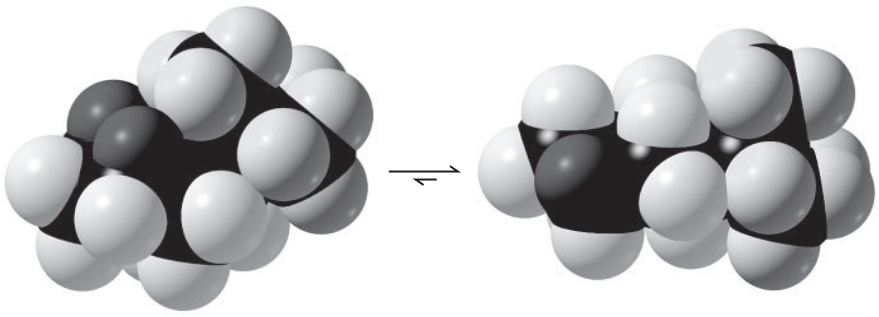
5.12C 1,3-Diaxial Interactions of a *tert*-Butyl Group

In cyclohexane derivatives with larger alkyl substituents, the strain caused by 1,3-diaxial interactions is even more pronounced. The conformation of *tert*-butylcyclohexane with the *tert*-butyl group equatorial is estimated to be approximately 21 kJ mol^{-1} more stable than the axial form (Fig. 5.20). This large energy difference between the two conformations means that, at room temperature, 99.99% of the molecules of *tert*-butylcyclohexane have the *tert*-butyl group in the equatorial position. (The molecule is not conformationally "locked," however; it still flips from one chair conformation to the other.)



Axial *tert*-butylcyclohexane **Equatorial *tert*-butylcyclohexane**

(*a*)



(ax) **(eq)**

(*b*)

Figure 5.20 (*a*) Diaxial interactions with the large *tert*-butyl group axial cause the conformation with the *tert*-butyl group equatorial to be the predominant one to the extent of 99.99%. (*b*) Space-filling molecular models of *tert*-butylcyclohexane in the axial (ax) and equatorial (eq) conformations, highlighting the position of the 1,3-hydrogens (red) and the *tert*-butyl group (shown with yellow hydrogen atoms).

5.13 | DISUBSTITUTED CYCLOALKANES: *CIS–TRANS* ISOMERISM

The presence of two substituents on different carbons of a cycloalkane allows for the possibility of ***cis–trans* isomerism** similar to the kind we saw for alkenes in Section 1.14B. These *cis–trans* isomers are also **stereoisomers** because they differ from each other only in the arrangement of their atoms in space. Consider 1,2-dimethylcyclopropane (Fig. 5.21) as an example.

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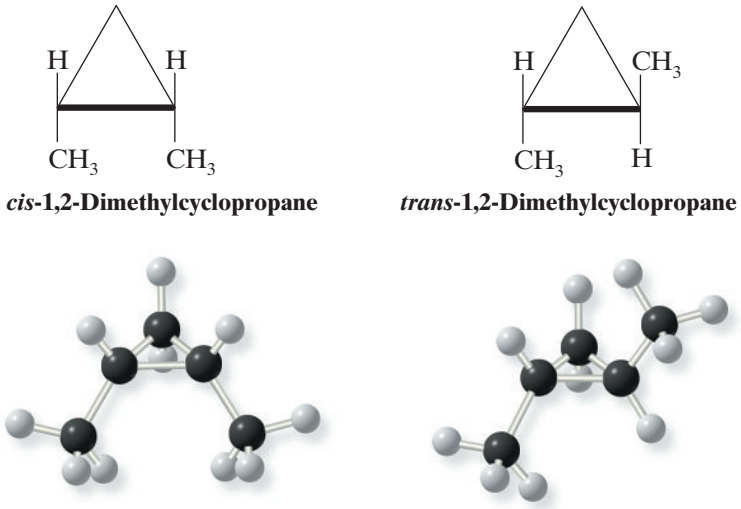

Figure 5.21 The *cis*- and *trans*-1,2-dimethylcyclopropane isomers.

The planarity of the cyclopropane ring makes the *cis–trans* isomerism obvious. In the first structure the methyl groups are on the same side of the ring; therefore, they are *cis*. In the second structure, they are on opposite sides of the ring; they are *trans*.

Cis and *trans* isomers such as these cannot be interconverted without breaking carbon–carbon bonds. They will have different physical properties (boiling points, melting points, and so on). As a result, they can be separated, placed in separate bottles, and kept indefinitely.

Practice Problem 5.15

Write structures for the *cis* and *trans* isomers of **(a)** 1,2-dichlorocyclopentane and **(b)** 1,3-dibromocyclobutane. **(c)** Are *cis–trans* isomers possible for 1,1-dibromocyclobutane?

5.13A *Cis–Trans* Isomerism and Conformational Structures of Cyclohexanes

Trans 1,4-Disubstituted Cyclohexanes

If we consider dimethylcyclohexanes, the structures are somewhat more complex because the cyclohexane ring is not planar. Beginning with *trans*-1,4-dimethylcyclohexane, because it is easiest to visualize, we find there are two possible chair conformations (Fig. 5.22). In one conformation both methyl groups are axial; in the other both are equatorial. The diequatorial conformation is, as we would expect it to be, the more stable conformation, and it represents the structure of at least 99% of the molecules at equilibrium.

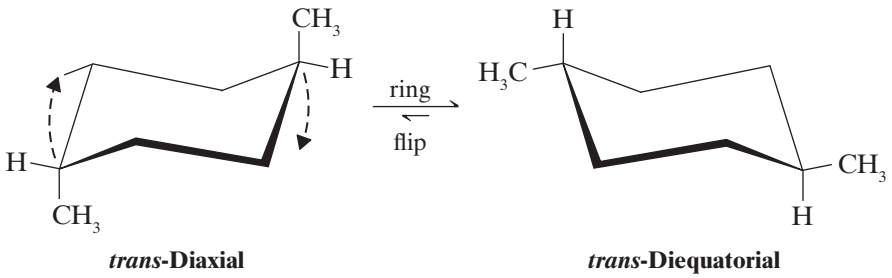

Figure 5.22 The two chair conformations of trans-1,4-dimethylcyclohexane: trans–diequatorial and trans–diaxial. The trans–diequatorial form is more stable by 15.2 kJ mol^{-1}.

That the diaxial form of *trans*-1,4-dimethylcyclohexane is a *trans* isomer is easy to see; the two methyl groups are clearly on opposite sides of the ring. The *trans* relationship of the methyl groups in the diequatorial form is not as obvious, however.

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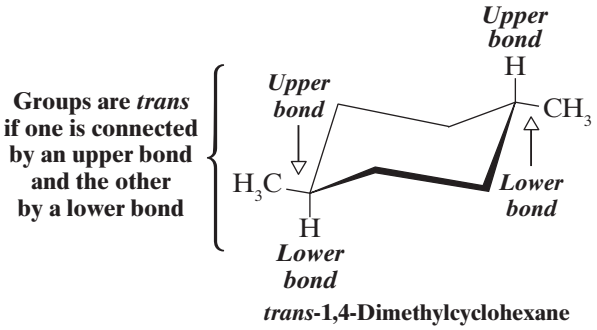
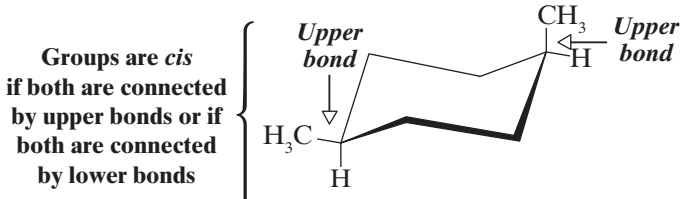
How do we know two groups are *cis* or *trans*? A general way to recognize a *trans*-disubstituted cyclohexane is to notice that one group is attached by the *upper* bond (of the two to its carbon) and one by the *lower* bond:



***trans*-1,4-Dimethylcyclohexane**

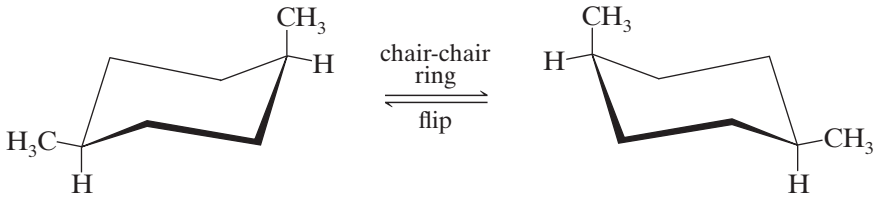
In a *cis* 1,4-disubstituted cyclohexane both groups are attached by an upper bond or both by a lower bond. For example,



***cis*-1,4-Dimethylcyclohexane**

Cis 1,4-Disubstituted Cyclohexanes

cis-1,4-Dimethylcyclohexane exists in two *equivalent* chair conformations (Fig. 5.23). In a *cis* 1,4-disubstituted cyclohexane, one group is axial and the other is equatorial in both of the possible chair conformations.

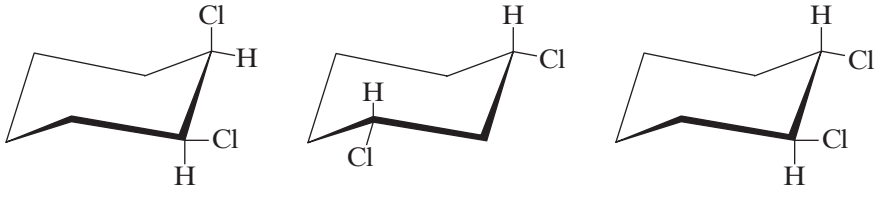


Equatorial–axial **Axial–equatorial**

Figure 5.23 Equivalent conformations of *cis*-1,4-dimethylcyclohexane.

Solved Problem 5.5

Consider each of the following conformational structures and tell whether each is *cis* or *trans*:



(a) **(b)** **(c)**

Answer

(a) Each chlorine is attached by the upper bond at its carbon; therefore, both chlorine atoms are on the same side of the molecule and this is a *cis* isomer. This is a *cis*-1,2-dichlorocyclohexane. **(b)** Here both chlorine atoms are attached by a lower bond; therefore, in this example, too, both chlorine atoms are on the same side of the molecule and this, too, is a *cis* isomer. It is *cis*-1,3-dichlorocyclohexane. **(c)** Here one chlorine atom is attached by a lower bond and one by an upper

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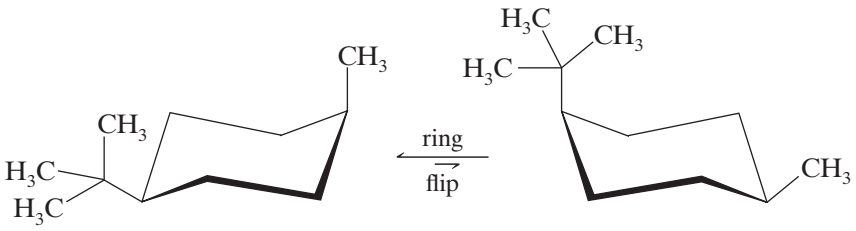
bond. The two chlorine atoms, therefore, are on opposite sides of the molecule, and this is a *trans* isomer. It is *trans*-1,2-dichlorocyclohexane. Verify these facts by building models.

The two conformations of *cis* 1,4-disubstituted cyclohexanes *are not equivalent* if one group is larger than the other. Consider *cis*-1-*tert*-butyl-4-methylcyclohexane:



(More stable because large group is equatorial) **(Less stable because large group is axial)**

***cis*-1-*tert*-Butyl-4-methylcyclohexane**

Here the more stable conformation is the one with the larger group equatorial. This is a general principle:

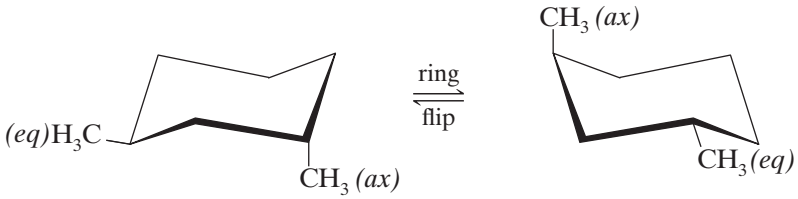
- When one ring substituent group is larger than the other and they cannot both be equatorial, the conformation with the larger group equatorial will be more stable.

Practice Problem 5.16

(a) Write structural formulas for the two chair conformations of *cis*-1-isopropyl-4-methylcyclohexane. **(b)** Are these two conformations equivalent? **(c)** If not, which would be more stable? **(d)** Which would be the preferred conformation at equilibrium?

Trans 1,3-Disubstituted Cyclohexanes

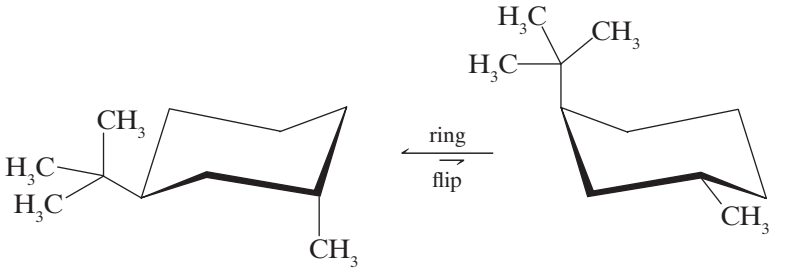
trans-1,3-Dimethylcyclohexane is like the *cis* 1,4 compound in that each conformation has one methyl group in an axial position and one methyl group in an equatorial position. The following two conformations are of equal energy and are equally populated at equilibrium:



***trans*-1,3-Dimethylcyclohexane**

Equal energy and equally populated conformations

The situation is different for *trans*-1-*tert*-butyl-3-methylcyclohexane (shown below) because the two ring substituents are not the same. Again, we find that the lower energy conformation is that with the largest group equatorial.



(More stable because large group is equatorial) **(Less stable because large group is axial)**

***trans*-1-*tert*-Butyl-3-methylcyclohexane**

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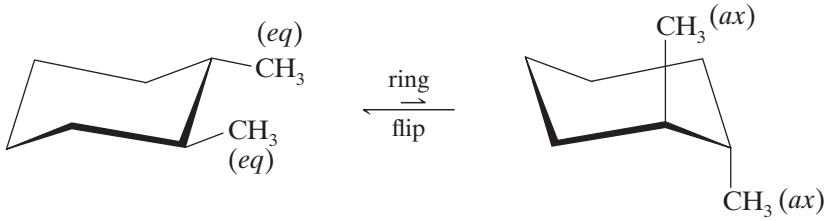
Cis 1,3-Disubstituted Cyclohexanes

cis-1,3-Dimethylcyclohexane has a conformation in which both methyl groups are equatorial and one in which both methyl groups are axial. **As we would expect, the conformation with both methyl groups equatorial is the more stable one**.

Trans 1,2-Disubstituted Cyclohexanes

trans-1,2-Dimethylcyclohexane has a conformation in which both methyl groups are equatorial and one in which both methyl groups are axial. **As we would expect, the conformation with both methyl groups equatorial is the more stable one**.

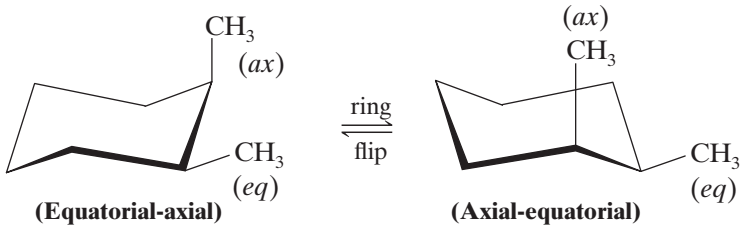


(Diequatorial is much more stable) **(Diaxial is much less stable)**

***trans*-1,2-Dimethylcyclohexane**

Cis 1,2-Disubstituted Cyclohexanes

cis-1,2-Dimethylcyclohexane has one methyl group that is axial and one methyl group that is equatorial in each of its chair conformations, thus its two conformations are of equal stability.



(Equatorial-axial) **(Axial-equatorial)**

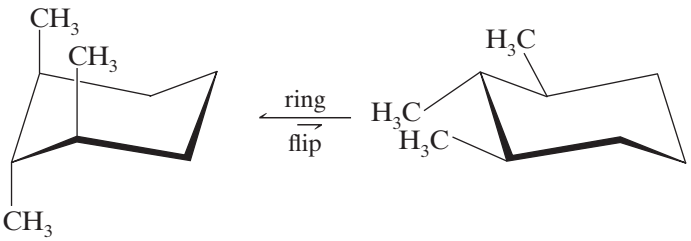
***cis*-1,2-Dimethylcyclohexane**
Equal energy and equally populated conformations

Solved Problem 5.6

Write a conformational structure for 1,2,3-trimethylcyclohexane in which all the methyl groups are axial and then show its more stable conformation.

Answer

A ring flip gives a conformation in which all the groups are equatorial and, therefore, much more stable.



All groups axial. Much less stable conformation. **All groups are equatorial. Much more stable conformation.**

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Practice Problem 5.17

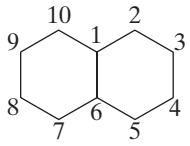
Write a conformational structure for 1-bromo-3-chloro-5-fluorocyclohexane in which all the substituents are equatorial. Then write its structure after a ring flip.

Practice Problem 5.18

(a) Write the two conformations of *cis*-1-*tert*-butyl-2-methylcyclohexane. **(b)** Which conformer has the lower potential energy?

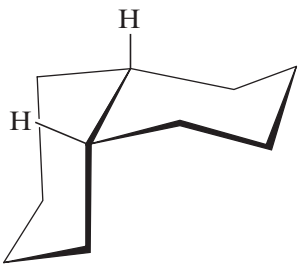
5.14 | BICYCLIC AND POLYCYCLIC ALKANES

Many of the molecules that we encounter in our study of organic chemistry contain more than one ring (Section 5.4B). One of the most important bicyclic systems is bicyclo [4.4.0]decane, a compound that is usually called by its common name, *decalin*:

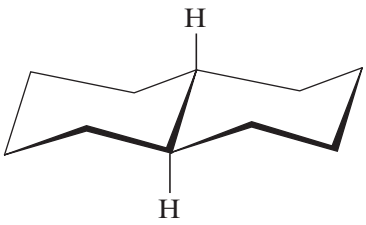


Decalin (bicyclo[4.4.0]decane)
(carbon atoms 1 and 6 are bridgehead carbon atoms)

Decalin shows *cis*–*trans* isomerism:



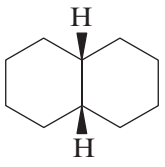
***cis*-Decalin**



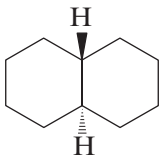
***trans*-Decalin**

Helpful Hint: Chemical Abstracts Service (CAS) determines the number of rings by the formula $S - A + 1 = N$, where S is the number of single bonds in the ring system, A is the number of atoms in the ring system, and N is the calculated number of rings (see Review Problem 5.26).

In *cis*-decalin the two hydrogen atoms attached to the bridgehead atoms lie on the same side of the ring; in *trans*-decalin they are on opposite sides. We often indicate this by writing their structures in the following way:



***cis*-Decalin**



***trans*-Decalin**

Simple rotations of groups about carbon–carbon bonds do not interconvert *cis*- and *trans*-decalins. They are stereoisomers and they have different physical properties.

Adamantane is a tricyclic system that contains a three-dimensional array of cyclohexane rings, all of which are in the chair form.

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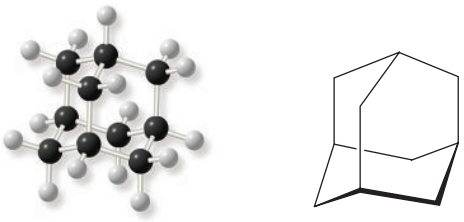


Adamantane

In the chapter closer we shall see several examples of other unusual and highly strained, cyclic hydrocarbons.

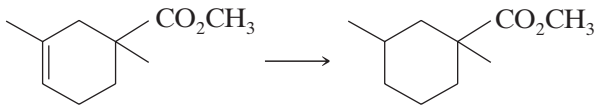
5.15 | CHEMICAL REACTIONS OF ALKANES

Alkanes, as a class, are characterized by a general inertness to many chemical reagents. Carbon–carbon and carbon–hydrogen bonds are quite strong; they do not break unless alkanes are heated to very high temperatures. Because carbon and hydrogen atoms have nearly the same electronegativity, the carbon–hydrogen bonds of alkanes are only slightly polarized. As a consequence, they are generally unaffected by most bases. Molecules of alkanes have no unshared electrons to offer as sites for attack by acids. This low reactivity of alkanes toward many reagents accounts for the fact that alkanes were originally called **paraffins** (*parum affinis*, Latin: little affinity).

The term paraffin, however, was probably not an appropriate one. We all know that alkanes react vigorously with oxygen when an appropriate mixture is ignited. This combustion occurs, for example, in the cylinders of automobiles, in furnaces, and, more gently, with paraffin candles. When heated, alkanes also react with chlorine and bromine, and they react explosively with fluorine. We shall study these reactions in Chapter 9.

5.16 | SYNTHESIS OF ALKANES AND CYCLOALKANES

A chemical synthesis may require, at some point, the conversion of a carbon–carbon double or triple bond to a single bond. Synthesis of the following compound, used as an ingredient in some perfumes, is an example.



(used in some perfumes)

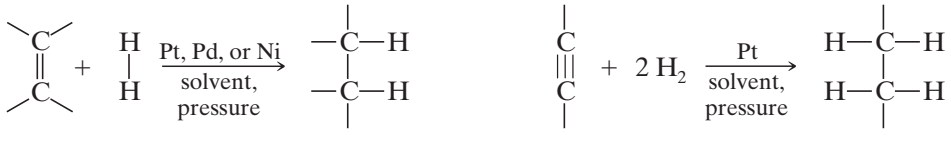
This conversion is easily accomplished by a reaction called **hydrogenation**. There are several reaction conditions that can be used to carry out hydrogenation, but among the common ways is use of hydrogen gas and a solid metal catalyst such as platinum, palladium, or nickel. Equations in the following section represent general examples for the hydrogenation of alkenes and alkynes.

5.16A Hydrogenation of Alkenes and Alkynes

- Alkenes and alkynes react with hydrogen in the presence of metal catalysts such as nickel, palladium, and platinum to produce **alkanes**.

The general reaction is one in which the atoms of the hydrogen molecule add to each atom of the carbon–carbon double or triple bond of the alkene or alkyne. This converts the alkene or alkyne to an alkane:

General Reaction



Alkene **Alkane** **Alkyne** **Alkane**

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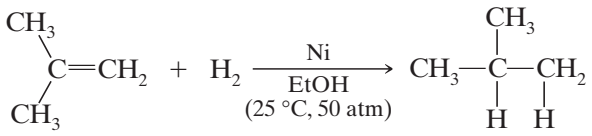
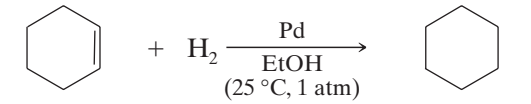
The reaction is usually carried out by dissolving the alkene or alkyne in a solvent such as ethyl alcohol (C_2H_5OH), adding the metal catalyst, and then exposing the mixture to hydrogen gas under pressure in a special apparatus. One molar equivalent of hydrogen is required to reduce an alkene to an alkane. Two molar equivalents are required to reduce an alkyne. (We shall discuss the mechanism of this reaction in Chapter 7.)

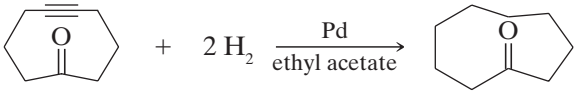
Specific Examples



2-Methylpropene **Isobutane**



Cyclohexene **Cyclohexane**

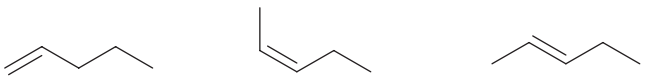


Cyclononyn-6-one **Cyclononanone**

Solved Problem 5.7

Write the structures of three pentenes that would all yield pentane on hydrogenation.

Answer



1-Pentene ***cis*-2-Pentene** ***trans*-2-Pentene**

Practice Problem 5.19

Show the reactions involved for hydrogenation of all the alkenes and alkynes that would yield 2-methylbutane.

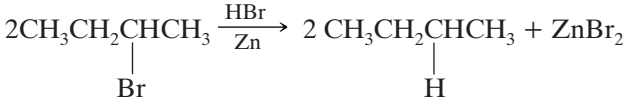
5.16B Reduction of Alkyl Halides

Most alkyl halides react with zinc and aqueous acid to produce an alkane. The general reaction is as follows:

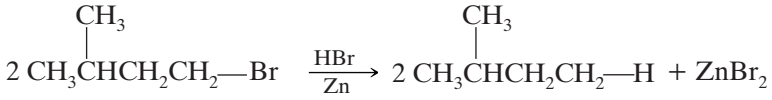
General Reaction

$$R{-}X + Zn + Hx \longrightarrow R{-}H + ZnX_2$$

Specific Examples



sec-Butyl bromide (2-bromobutane) Butane



Isopentyl bromide (1-bromo-3-methylbutane) Isopentane (2-methylbutane)

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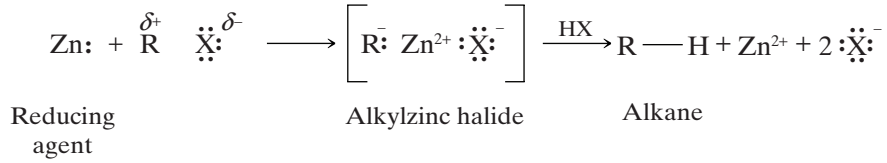
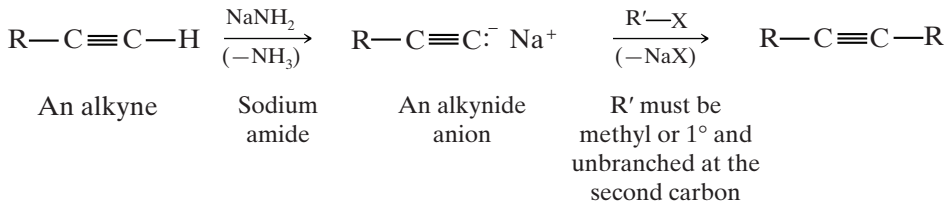
In these reactions zinc atoms *trans*fer electrons to the carbon atom of the alkyl halide. Therefore, the reaction is a **reduction of the alkyl halide.** Zinc is a good reducing agent because it has two electrons in an orbital far from the nucleus which are readily donated to an electron acceptor. The mechanism for the reaction is complex because the reaction takes place in a separate phase at or near the surface of the zinc metal. It is possible that an alkylzinc halide forms first and then reacts with the acid to produce the alkane:

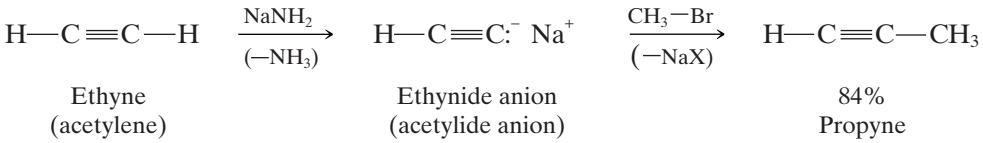


5.16C Alkylation of Terminal Alkynes

We can replace a hydrogen attached to a triply bonded carbon of a terminal alkyne (called an acetylenic hydrogen) by an alkyl group. This type of reaction, called an alkylation, is of considerable use in synthesis. The acetylenic hydrogen is weakly acidic, as described in Section 3.14, and can be removed with a strong base such as sodium amide. Once the terminal hydrogen is removed, the alkyne carbon is an anion (called an alkynide anion), and it can be treated with an appropriate alkyl halide. The following provides an overview of the sequence:

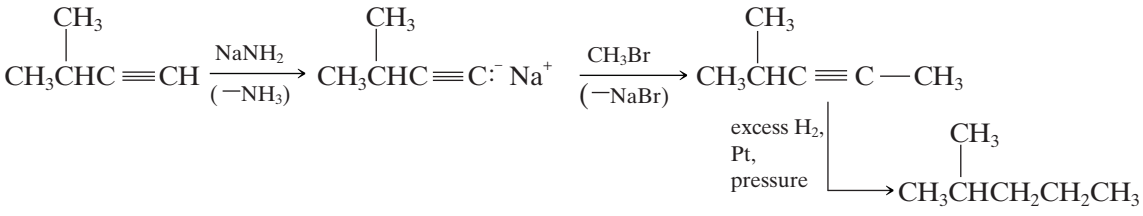


A specific example is the synthesis of propyne from acetylene (ethyne) and bromomethane:



An important point to note is that the alkyl halide used with the alkynide anion must be methyl or primary and also unbranched at its second (beta) carbon. Alkyl halides that are secondary or tertiary or are primary with branching at the beta carbon react to give other products, predominantly by a mechanism called elimination (which we discuss in detail in Chapter 7). Formation of a new carbon–carbon bond by alkylation of an alkynide anion is in itself an important *trans*formation, but the alkyne triple bond also can be used for further reactions. For example, hydrogenation of a newly synthesized alkyne constitutes the formal synthesis of an alkane. A possible synthesis of 2-methylpentane from 3-methyl-1-butyne and bromomethane would be the following:

Note that it would not work to use propyne and 2-bromopropane for the alkylation step of this synthesis because the alkyl halide would have been secondary and elimination would predominate.



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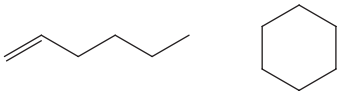
5.17 | HOW TO GAIN STRUCTURAL INFORMATION FROM MOLECULAR FORMULAS AND THE INDEX OF HYDROGEN DEFICIENCY

A chemist working with an unknown compound can obtain considerable information about its structure from the compound's molecular formula and its **index of hydrogen deficiency (IHD)**.

- The **index of hydrogen deficiency** (IHD)* is defined as the difference in the *number of pairs* of hydrogen atoms between the compound under study and an acyclic alkane having the same number of carbons.

Saturated acyclic hydrocarbons have the general molecular formula C_nH_{2n+2}. Each double bond or ring reduces the number of hydrogen atoms by two as compared with the formula for a saturated compound. Thus each ring or double bond provides one unit of hydrogen deficiency. For example, 1-hexene and cyclohexane have the same molecular formula (C_6H_{12}) and they are constitutional isomers.



1-Hexene (C_6H_{12}) **Cyclohexane (C_6H_{12})**

Both 1-hexene and cyclohexane (C_6H_{12}) have an index of hydrogen deficiency equal to 1 (meaning one pair of hydrogen atoms), because the corresponding acyclic alkane is hexane (C_6H_{14}).

C_6H_{14} = formula of corresponding alkane (hexane)
C_6H_{12} = formula of compound (1-hexene or cyclohexane)
H_2 = difference = 1 pair of hydrogen atoms
Index of hydrogen deficiency = 1

Alkynes and alkadienes (alkenes with two double bonds) have the general formula C_nH_{2n-2}. Alkenynes (hydrocarbons with one double bond and one triple bond) and alkatrienes (alkenes with three double bonds) have the general formula C_nH_{2n-4}, and so forth.

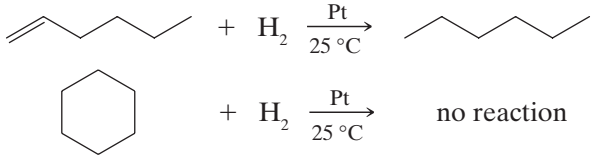


1,3-Butadiene IHD = 2 **But-1-en-3-yne IHD = 3** **1,3,5-Hexatriene IHD = 3**

The index of hydrogen deficiency is easily determined by comparing the molecular formula of a given compound with the formula for its hydrogenation product.

- Each double bond consumes one molar equivalent of hydrogen and counts for one unit of hydrogen deficiency.
- Each triple bond consumes two molar equivalents of hydrogen and counts for two units of hydrogen deficiency.
- Rings are not affected by hydrogenation, but each ring still counts for one unit of hydrogen deficiency.

Hydrogenation, therefore, allows us to distinguish between rings and double or triple bonds. Consider again two compounds with the molecular formula C_6H_{12}: 1-hexene and cyclohexane. 1-Hexene reacts with one molar equivalent of hydrogen to yield hexane; under the same conditions cyclohexane does not react:



*Some organic chemists refer to the index of hydrogen deficiency as the "degree of unsaturation" or "the number of double-bond equivalencies."

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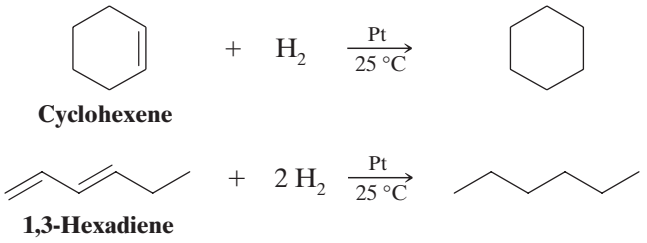
Or consider another example. Cyclohexene and 1,3-hexadiene have the same molecular formula (C_6H_{10}). Both compounds react with hydrogen in the presence of a catalyst, but cyclohexene, because it has a ring and only one double bond, reacts with only one molar equivalent. 1,3-Hexadiene adds two molar equivalents:

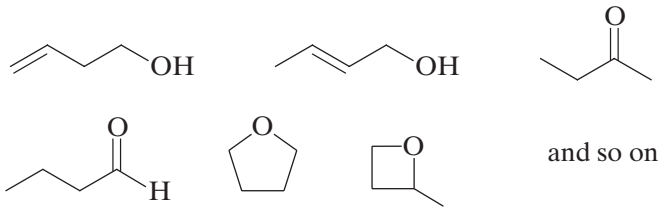


5.17A Compounds Containing Halogens, Oxygen, or Nitrogen

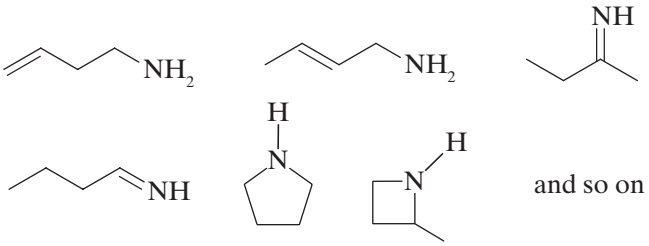
Calculating the index of hydrogen deficiency (IHD) for compounds other than hydrocarbons is relatively easy.

For compounds containing halogen atoms, we simply count the halogen atoms as though they were hydrogen atoms. Consider a compound with the formula $C_4H_6Cl_2$. To calculate the IHD, we change the two chlorine atoms to hydrogen atoms, considering the formula as though it were C_4H_8. This formula has two hydrogen atoms fewer than the formula for a saturated alkane (C_4H_{10}), and this tells us that the compound has IHD = 1. It could, therefore, have either one ring or one double bond. [We can tell which it has from a hydrogenation experiment: If the compound adds one molar equivalent of hydrogen (H_2) on catalytic hydrogenation at room temperature, then it must have a double bond; if it does not add hydrogen, then it must have a ring.]

For compounds containing oxygen, we simply ignore the oxygen atoms and calculate the IHD from the remainder of the formula. Consider as an example a compound with the formula C_4H_8O. For the purposes of our calculation we consider the compound to be simply C_4H_8 and we calculate IHD = 1. Again, this means that the compound contains either a ring or a double bond. Some structural possibilities for this compound are shown next. Notice that the double bond may be present as a carbon–oxygen double bond:



For compounds containing nitrogen atoms we subtract one hydrogen for each nitrogen atom, and then we ignore the nitrogen atoms. For example, we treat a compound with the formula C_4H_9N as though it were C_4H_8, and again we get IHD = 1. Some structural possibilities are the following:



5.18 | APPLICATIONS OF BASIC PRINCIPLES

In this chapter we have seen repeated applications of one basic principle in particular:

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Nature Prefers States of Lower Potential Energy

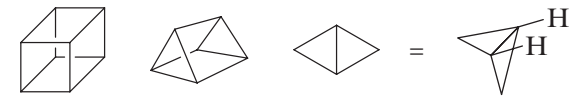
This principle underlies our explanations of conformational analysis in Sections 5.8–5.13. The staggered conformation of ethane (Section 5.8) is preferred (more populated) in a sample of ethane because its potential energy is lowest. In the same way, the anti conformation of butane (Section 5.9) and the chair conformation of cyclohexane (Section 5.11) are the preferred conformations of these molecules because these conformations are of lowest potential energy. Methylcyclohexane (Section 5.12) exists mainly in the chair conformation with its methyl group equatorial for the same reason. Disubstituted cycloalkanes (Section 5.13) prefer a conformation with both substituents equatorial if this is possible, and, if not, they prefer a conformation with the larger group equatorial. The preferred conformation in each instance is the one of lowest potential energy.

Another effect that we encounter in this chapter, and one we shall see again and again, is how **steric factors** (spatial factors) can affect the stability and reactivity of molecules. Unfavorable spatial interactions between groups are central to explaining why certain conformations are higher in energy than others. But fundamentally this effect is derived itself from another familiar principle: **like charges repel.** Repulsive interactions between the electrons of groups that are in close proximity cause certain conformations to have higher potential energy than others. We call this kind of effect *steric hindrance*.

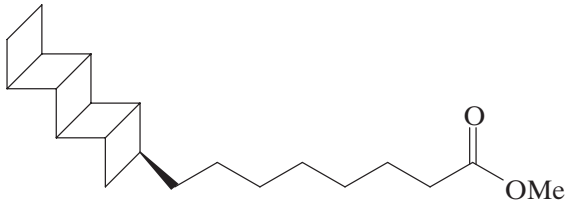
WHY Do These Topics Matter?

PUSHING THE BOUNDARIES OF BONDING, ALL WITHIN THE RULES

In this chapter we have learned many of the rules of bond formation and of conformation. Although there are only a few kinds of bonds in organic molecules, they can be combined in an infinite number of ways, sometimes leading to molecules whose existence defies our expectations. For example, using just C—C and C—H bonds, chemists have been able to synthesize structures such as cubane, prismane, and bicyclo[1.1.0]butane, materials that have incredible strain built into their structures. Strained compounds are also found in nature, with one recent discovery being pentacycloanammoxic acid, a material isolated from a particular bacterial strain. This compound is also known as a ladderane because it has a connected set of five 4-membered rings that exist in three-dimensional space like a ladder, or staircase.



Cubane **Prismane** **Bicyclo[1.1.0]butane**



Pentacycloanammoxic acid methyl ester (a ladderane)

An important thing to note is that these different bond combinations and resultant three-dimensional shapes lead to completely distinct physical properties that can be harnessed for unique practical applications. Perhaps one of the best illustrations of this concept is found in materials comprised only of carbon, materials also known as allotropes since they are formed solely from a single, pure element. For example, when carbon is bonded with itself through single bonds with sp^3 hybridization, the result is diamond, the hardest of all materials found in nature and a popular component of jewelry. When carbon is bonded with itself with sp^2 hybridization through a series of interconnecting C—C and C═C bonds, it forms flat, interconnected sheets of benzene-like rings. These sheets can stack with one another, forming graphite. This material is much softer than diamond and is the material that constitutes the "lead" of pencils. Graphene, which is just one of these sheets, can be wrapped through new bonds into tubes (also called nanotubes) that have impressive properties as thermal and electrical conductors.

(Continued)

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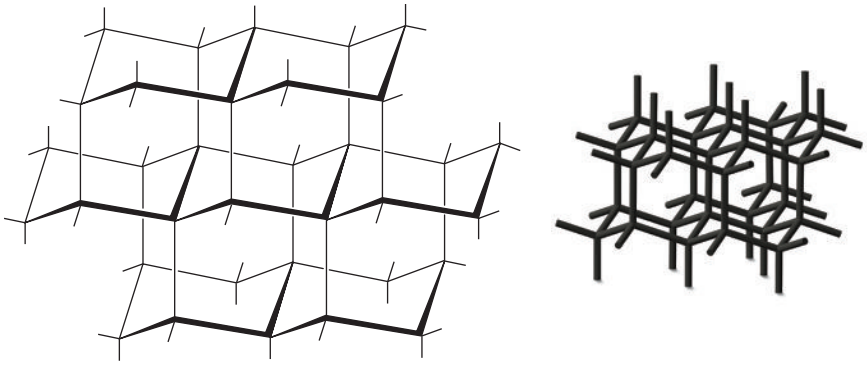
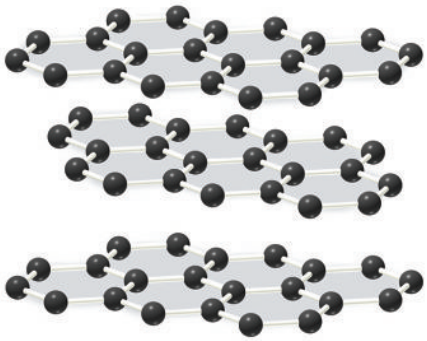


A portion of the diamond structure



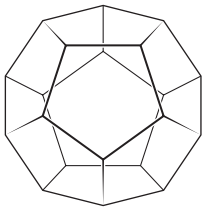
Charles D. Winters/Photo Researchers, Inc.

Carbon is shown here in its diamond and graphite forms

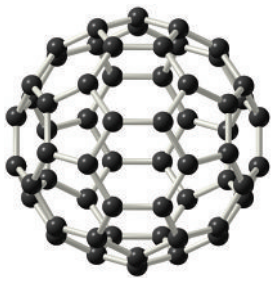


A portion of the structure of graphite

If the rings of graphite and graphene are combined together into discrete balls possessing a finite number of carbon atoms, then materials such as buckminsterfullerene (also known as buckyballs) result. The name of this material derives from its resemblance to the geodesic dome first designed by architect Buckminster Fuller. This particular compound, which is comprised of 60 carbon atoms, has bonds that look exactly like the seams of a soccer ball through its possession of 32 interlocking rings of which 20 are hexagons and 12 are pentagons. The center is large enough, in fact, to hold an atom of argon (such a compound has been made). Another variant of this type of structure is dodecahedrane, a compound composed of 20 carbon atoms and first synthesized in 1982 by scientists at the Ohio State University. Materials of this type collectively are believed to have potential in applications as diverse as armor, drug delivery, and superconductivity.



Dodecahedrane



Buckminsterfullerene

The key point is that the molecular variations are nearly endless, increasing exponentially as more and more atoms are added. This fact is one of the most beautiful elements of organic chemistry, because it means that we are largely limited in terms of possible structures by just two factors: our ability to imagine a molecule and having the tools necessary to forge it in the form of appropriate chemical reactions. This outcome is because the rules, the language, of organic chemistry are consistent.

To learn more about these topics, see:
Hopf, H. *Classics in Hydrocarbon Chemistry*. Wiley-VCH: Weinheim, **2000**, p. 560.

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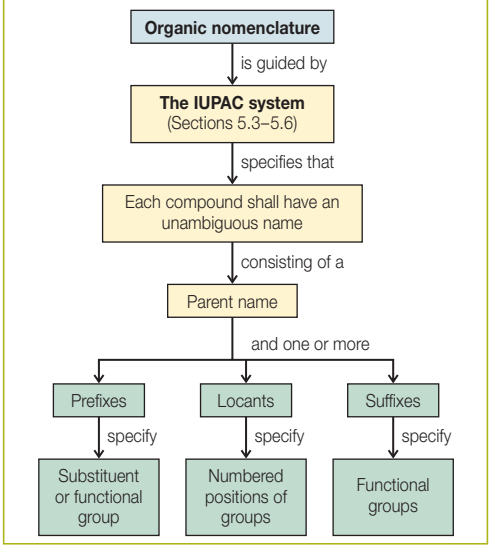
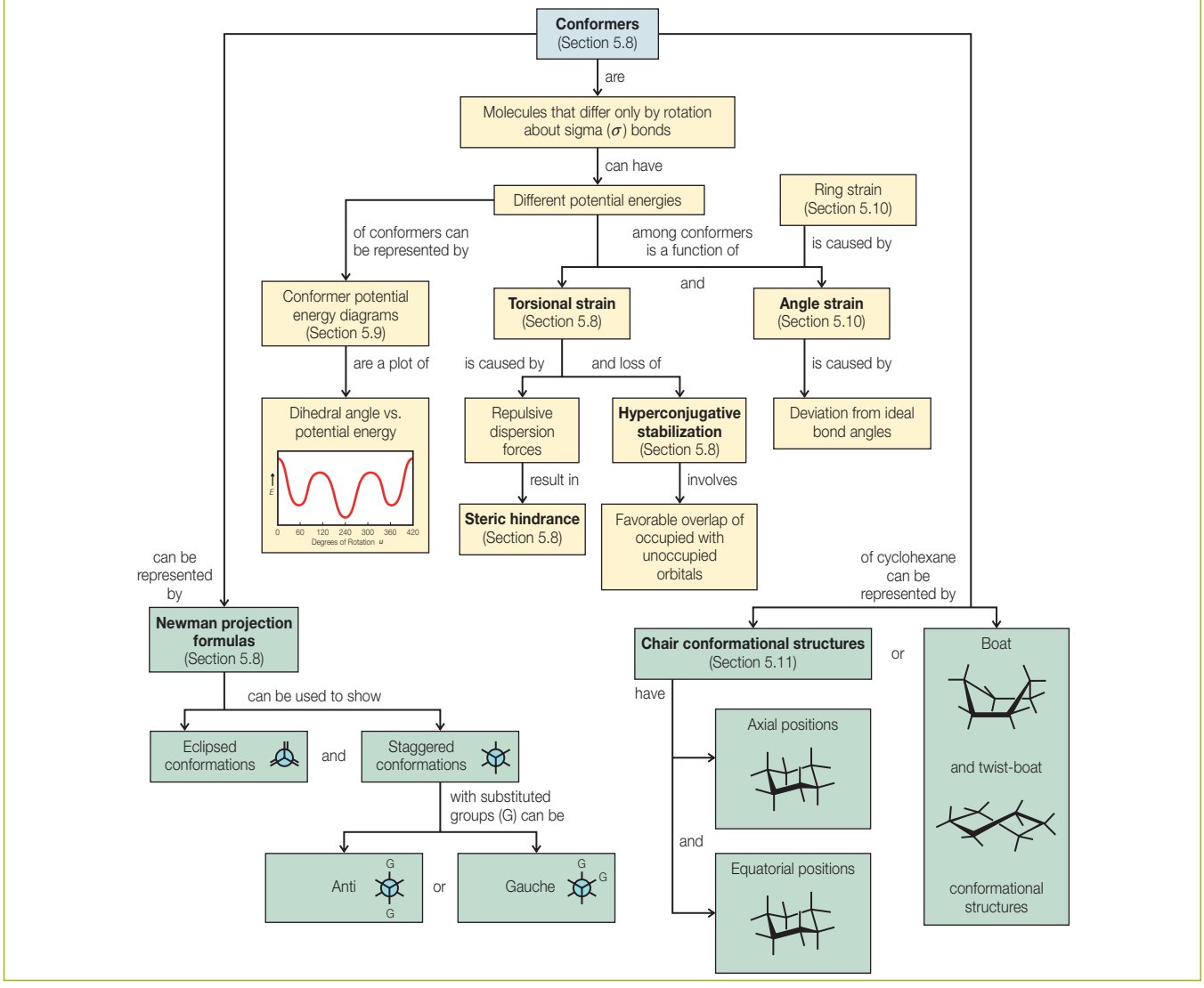
CONCEPT MAP



CONCEPT MAP



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REVIEW PROBLEMS

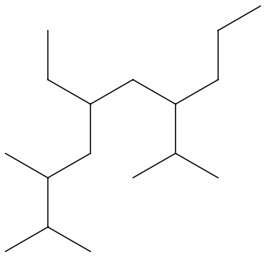
Nomenclature and Isomerism

5.20 Write a bond-line formula for each of the following compounds:

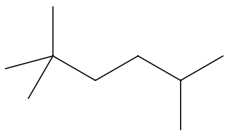
(a) 1,4-Dichloropentane
(b) *sec*-Butyl bromide
(c) 4-Isopropylheptane
(d) 2,2,3-Trimethylpentane
(e) 3-Ethyl-2-methylhexane
(f) 1,1-Dichlorocyclopentane
(g) *cis*-1,2-Dimethylcyclopropane
(h) *trans*-1,2-Dimethylcyclopropane
(i) 4-Methyl-2-pentanol
(j) *trans*-4-Isobutylcyclohexanol
(k) 1,4-Dicyclopropylhexane
(l) Neopentyl alcohol
(m) Bicyclo[2.2.2]octane
(n) Bicyclo[3.1.1]heptane
(o) Cyclopentylcyclopentane

5.21 Give systematic IUPAC names for each of the following:

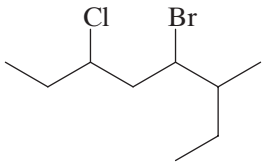
(a)



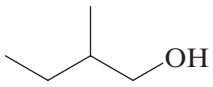
(b)



(c)



(d)



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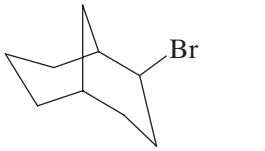

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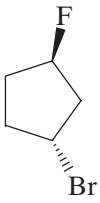

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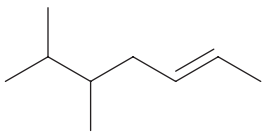
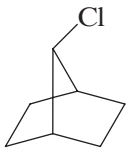


(h)



5.22 The name *sec*-butyl alcohol defines a specific structure but the name *sec*-pentyl alcohol is ambiguous. Explain.

5.23 Write the structure and give the IUPAC systematic name of an alkane or cycloalkane with the formulas **(a)** C_8H_{18} that has only primary hydrogen atoms, **(b)** C_6H_{12} that has only secondary hydrogen atoms, **(c)** C_6H_{12} that has only primary and secondary hydrogen atoms, and **(d)** C_8H_{14} that has 12 secondary and 2 tertiary hydrogen atoms.

5.24 Write the structure(*s*) of the simplest alkane(*s*), i.e., one(*s*) with the fewest number of carbon atoms, wherein each possesses primary, secondary, tertiary, and quaternary carbon atoms. (A quaternary carbon is one that is bonded to four other carbon atoms.) Assign an IUPAC name to each structure.

5.25 Ignoring compounds with double bonds, write structural formulas and give names for all of the isomers with the formula C_5H_{10}.

5.26 Use the $S - A + 1 = N$ method (Helpful Hint, Section 5.14) to determine the number of rings in cubane (Section 5.14).

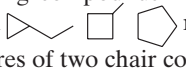
5.27 Tell what is meant by a homologous series and illustrate your answer by writing structures for a homologous series of alkyl halides.

Hydrogenation

5.28 Four different cycloalkenes will all yield methylcyclopentane when subjected to catalytic hydrogenation. What are their structures? Show the reactions.

5.29 An alkane with the formula C_6H_{14} can be prepared by hydrogenation of either of only two precursor alkenes having the formula C_6H_{12}. Write the structure of this alkane, give its IUPAC name, and show the reactions.

Conformations and Stability

5.30 Rank the following compounds in order of increasing stability based on  relative ring strain.

5.31 Write the structures of two chair conformations of 1-*tert*-butyl-1-methylcyclohexane. Which conformation is more stable? Explain your answer.

5.32 Sketch curves similar to the one given in Fig. 5.8 showing the energy changes that arise from rotation about the C2—C3 bond of **(a)** 2,3-dimethylbutane and **(b)** 2,2,3,3-tetramethylbutane. You need not concern yourself with actual numerical values of the energy changes, but you should label all maxima and minima with the appropriate conformations.

5.33 Without referring to tables, decide which member of each of the following pairs would have the higher boiling point. Explain your answers.

(a) Pentane or 2-methylbutane
(b) Heptane or pentane
(c) Propane or 2-chloropropane
(d) Butane or 1-propanol
(e) Butane or CH_3COCH_3

5.34 Which compound would you expect to be the more stable: *cis*-1,2-dimethylcyclopropane or *trans*-1,2-dimethylcyclopropane? Explain your answer.

5.35 Consider that cyclobutane exhibits a puckered geometry. Judge the relative stabilities of the 1,2-disubstituted cyclobutanes and of the 1,3-disubstituted cyclobutanes.

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(You may find it helpful to build handheld molecular models of representative compounds.)

5.36 Write the two chair conformations of each of the following and in each part designate which conformation would be the more stable:

(a) *cis*-1-*tert*-butyl-3-methylcyclohexane,

(b) *trans*-1-*tert*-butyl-3-methylcyclohexane,

(c) *trans*-1-*tert*-butyl-4-methylcyclohexane,

(d) *cis*-1-*tert*-butyl-4-methylcyclohexane.

5.37 *trans*-1,3-Dibromocyclobutane has a measurable dipole moment. Explain how this proves that the cyclobutane ring is not planar.

ADDITIONAL OBJECTIVE QUESTIONS

Single Correct Choice Type

1. Identify the correct IUPAC name.

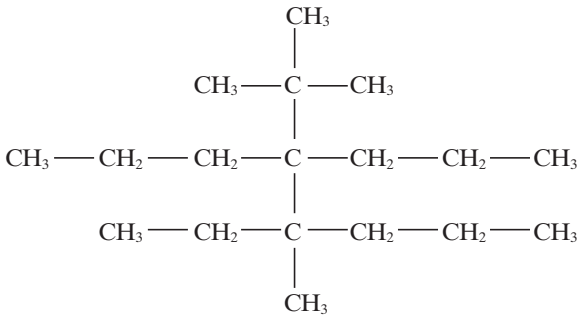
(a) 2,2-Dimethyl-4-ethyl heptane.

(b) 5-Ethyl-2-methyl hexane.

(c) 1,3-Dimethyl butane.

(d) 3-Ethyl-1,1-dimethyl cyclohexane.

2. Total number of carbon atoms present in parent chain is:



(a) 5 **(b)** 6 **(c)** 7 **(d)** None of these

3. Give the name of the compound: $(CH_3)_3CCH_2CH_2Cl$

(a) 2,2–Dimethyl–4–chloro butane

(b) 1–Chloro–3,3–dimethyl butane

(c) 4–Chloro–2,2–dimethyl butane

(d) None of these

4. The compound which has one isopropyl group is

(a) 2,2,3,3-tetramethyl pentane.

(b) 3,3-dimethyl pentane.

(c) 2,2,3-trimethyl pentane.

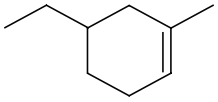
(d) 2-methyl pentane.

5. Among the butane conformers, which occur at energy minima on a graph of potential energy versus dihedral angle?

(a) Gauche only **(c)** Gauche and anti

(b) Eclipsed and totally eclipsed **(d)** Eclipsed only

6. Give the correct IUPAC name for the following compound.



(a) 1-Methyl-3-ethylcyclohexene

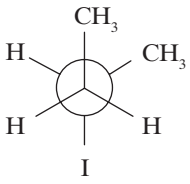
(b) 5-Ethyl-1-methylcyclohexene

(c) 2-Ethyl-4-methylcyclohexene

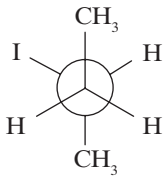
(d) 3-Ethyl-1-methylcyclohexene

7. Which of the Newman projections shown below represents the most stable conformation about the C1–C2 bond of 1-iodo-2-methyl propane?

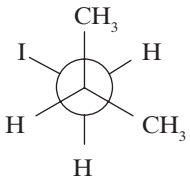
(a)



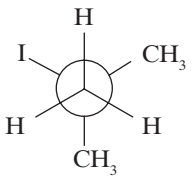
(b)



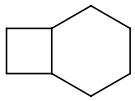
(c)



(d)



8. What is the name of this compound?

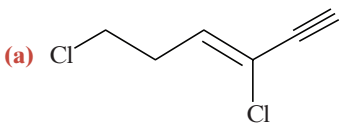


(a) Bicyclo[2.2.2]octane **(b)** Bicyclo[3.2.1]octane

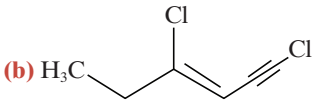
(c) Bicyclo[4.1.1]octane **(d)** Bicyclo[4.2.0]octane

9. Which structure represents 1, 4-dichlorohex-3-en-1-yne?

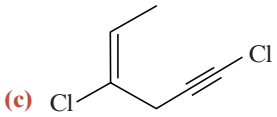
(a)



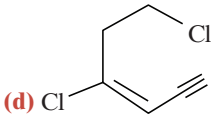
(b)



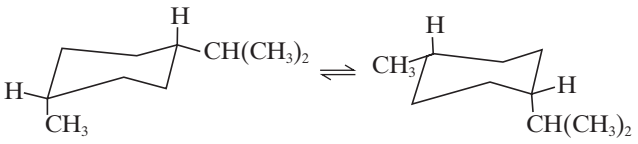
(c)



(d)



10. What can be said about the magnitude of the equilibrium constant K for the following process?



(a) $K = 1$ **(b)** $K > 1$

(c) $K < 1$ **(d)** No estimate of K can be made

11. How many carbons in triaheptacontane?

(a) 73 **(b)** 37

(c) 703 **(d)** 370

12. Which of the following best explains the reason for the relative stabilities of the conformers shown?

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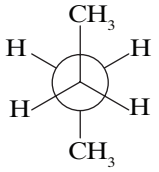
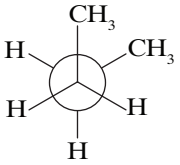
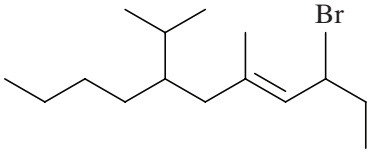
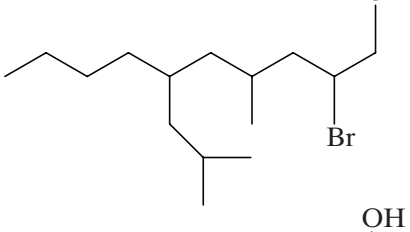
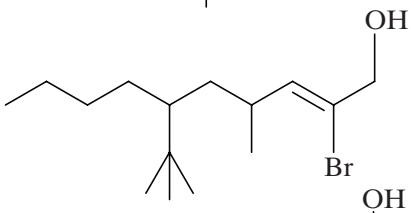
(I)  (II) 

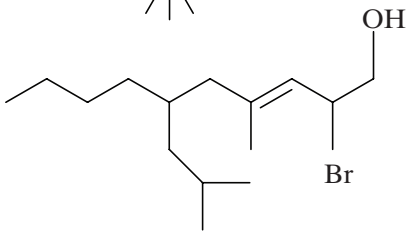
(a) I has more torsional strain.
(b) I has more steric strain.
(c) II has more torsional strain.
(d) II has more steric strain.

13. Which of the following structures represents 2-bromo-6-isobutyl-4-methyldec-3-en-1-ol?

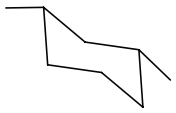
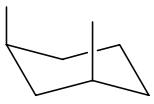
(a) 

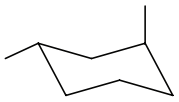
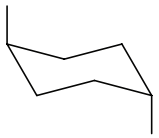
(b) 

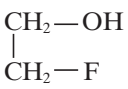
(c) 

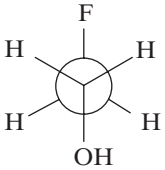
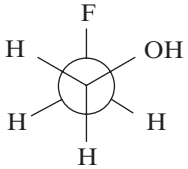
(d) 

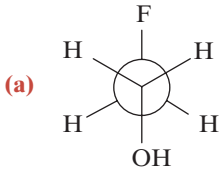
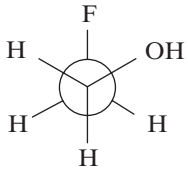
14. Which represents the chair structure of the following with both groups axial?

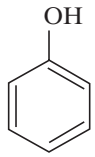
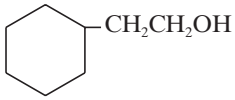
(a)  **(b)** 

(c)  **(d)** 

15. Most stable conformer of compound  is

(a)  **(b)** 

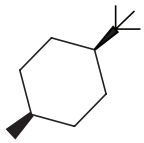
(a)  **(b)** 

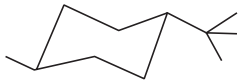
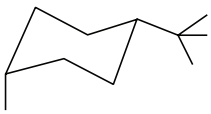
16.  (i) and (ii) 

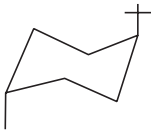
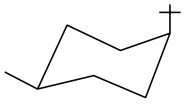
True statement for the above compounds is

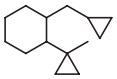
(a) (i) is phenol while (ii) is alcohol.
(b) Both (i) and (ii) are primary alcohols.
(c) (i) is primary and (ii) is secondary alcohol.
(d) (i) is secondary and (ii) is primary alcohol.

17. Most stable conformer of the following compound is



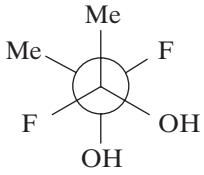
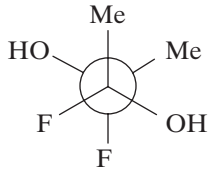
(a)  **(b)** 

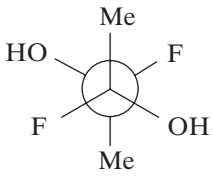
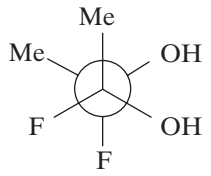
(c)  **(d)** 

18. The IUPAC name of 

(a) 1-[1-cyclopropylmethyl]-2-[1-methylcyclopropyl]-cyclohexane.
(b) 1-[1-methylcyclopropyl]-2-[1-cyclopropylmethyl]-cyclohexane.
(c) 1-[1-methylcyclopyl]-2-[1-methylcyclopropyl]-cyclohexane.
(d) 1-[1-cyclopropyl methyl]-2-[1-cyclopropylmethyl]-cyclohexane.

19. Most stable form of meso-2,3-difluoro-2,3-butandiol (across C2—C3 bond) is

(a)  **(b)** 

(c)  **(d)** 

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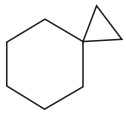
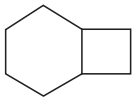
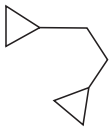
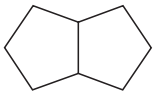
20. Which of the following isomers of the formula C_8H_{14} would you expect to give the highest heat of combustion?

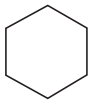
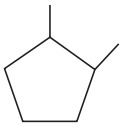
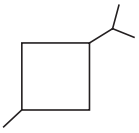
(a)  **(b)** 

(c)  **(d)** 

21. The IUPAC name of *neo*-pentane is

(a) 2-methylbutane. **(b)** 2,2-dimethylpropane.
(c) 2-methylpropane. **(d)** 2,2-dimethylbutane.

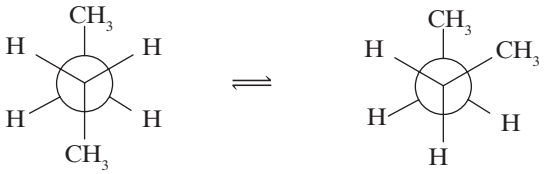
22. Give decreasing order of heat of combustion (HOC):

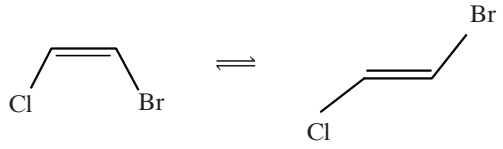
(i)  (ii)  (iii) 

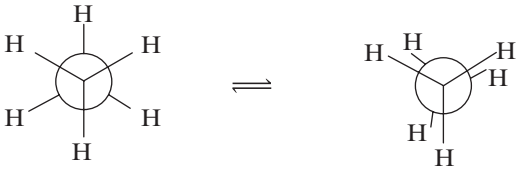
(a) ii > i > iii **(b)** i > ii > iii **(c)** iii > ii > i **(d)** iii > i > ii

23. Which of following equilibrium is not rapid at room temperature?

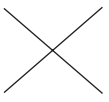
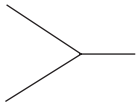
(a) 

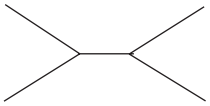
(b) 

(c) 

(d) 

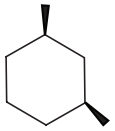
24. Find out the order of heat of combustion:

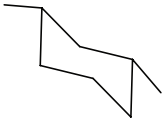
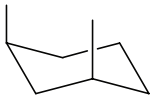
(i)  (ii) 

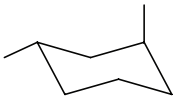
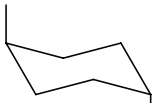
(iii) 

(a) i > ii > iii **(b)** ii > i > iii
(c) iii > i > ii **(d)** ii > iii > i

25. Which represents the chair structure of the following with both groups axial?



(a)  **(b)** 

(c)  **(d)** 

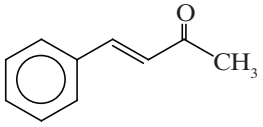
Multiple Correct Choice Type

1. Which of following common names and IUPAC names is/are correctly matched?

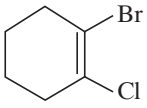
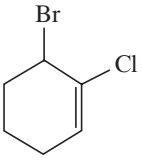
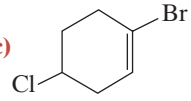
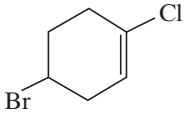
(a) *t*-Butyl alcohol and 2-methyl-2-propanol
(b) *s*-Butyl alcohol and 1-methyl-1-propanol
(c) *iso*-Butyl alcohol and 2-methyl-1-propanol
(d) *neo*-Pentyl alcohol and 2,2-dimethyl-1-propanol

Integer Type

1. How many carbon atoms are present in the parent chain in the following compound?



Matrix Match Type

1. Column I Compound	Column II IUPAC Name
(a) 	**(p)** 1-Bromo-4-chlorocyclohexene
(b) 	**(q)** 4-Bromo-1-chlorocyclohexene
(c) 	**(r)** 1-Bromo-2-chlorocyclohexene
(d) 	**(s)** 6-bromo-1-chlorocyclohexene

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2. Column I (Number of carbon atoms)	Column II (Alkane)
(a) 62	**(p)** pentatetracontane
(b) 45	**(q)** triaheptacontane
(c) 34	**(r)** tetratriacontane
(d) 73	**(s)** dohexacontane

ANSWER KEY

Single Correct Choice Type

1. (d)	**2.** (d)	**3.** (c)	**4.** (d)	**5.** (c)
6. (b)	**7.** (c)	**8.** (d)	**9.** (b)	**10.** (c)
11. (a)	**12.** (d)	**13.** (d)	**14.** (b)	**15.** (b)
16. (a)	**17.** (b)	**18.** (a)	**19.** (c)	**20.** (c)
21. (d)	**22.** (c)	**23.** (c)	**24.** (c)	**25.** (b)

Multiple Correct Choice Type

1. (a), (c)

Integer Type

1. (4)

Matrix Match Type

1. a → (r); b → (s); c → (p); d → (q)

2. a → (s); b → (p); c → (q); d → (r)

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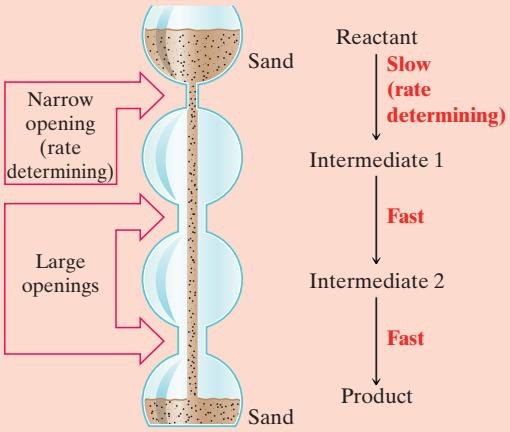
6

Ionic Reactions

Nucleophilic Substitution and Elimination Reactions of Alkyl Halides



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6.2 | Nucleophilic Substitution Reactions
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6.4 | Leaving Groups
6.5 | Kinetics of a Nucleophilic Substitution Reaction: An S_N2 Reaction
6.6 | A Mechanism for the S_N2 Reaction
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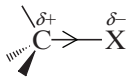
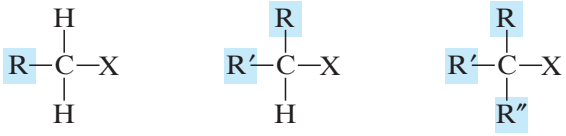
6.1 | ALKYL HALIDES

- An **alkyl halide** has a halogen atom bonded to an sp^3-hybridized (tetrahedral) carbon atom.
- The carbon–halogen bond in an alkyl halide is polarized because the halogen is more electronegative than carbon. Therefore, the carbon atom has a partial positive charge ($\delta+$) and the halogen has a partial negative charge ($\delta-$).



- Alkyl halides are classified as primary (1°), secondary (2°), or tertiary (3°) according to the number of carbon groups (R) directly bonded to the carbon bearing the halogen atom (Section 2.4).



Primary (1°) **Secondary (2°)** **Tertiary (3°)**

Halogen atom size increases as we go down the periodic table: fluorine atoms are the smallest and iodine atoms the largest. Consequently, the carbon–halogen *bond length increases* and carbon–halogen *bond strength decreases* as we go down the periodic table (Table 6.1). Maps of electrostatic potential (see Table 6.1) at the van der Waals surface for the four methyl halides, with ball-and-stick models inside, illustrate the trend in polarity, C—X bond length, and halogen atom size as one progresses from fluorine to iodine substitution. Fluoromethane is highly polar and has the shortest C—X bond length and the strongest C—X bond. Iodomethane is much less polar and has the longest C—X bond length and the weakest C—X bond.

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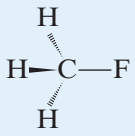
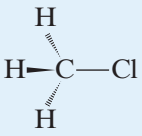
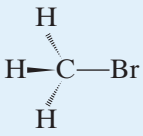
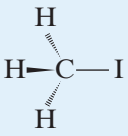
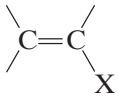
Table 6.1 Carbon–Halogen Bond Lengths and Bond Strengths

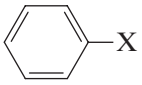
				
C—X Bond length (Å)	1.39	1.78	1.93	2.14
C—X Bond strength (kJ mol^{-1})	472	350	293	239

In the laboratory and in industry, alkyl halides are used as solvents for relatively nonpolar compounds, and they are used as the starting materials for the synthesis of many compounds. As we shall learn in this chapter, the halogen atom of an alkyl halide can be easily replaced by other groups, and the presence of a halogen atom on a carbon chain also affords us the possibility of introducing a multiple bond.

Compounds in which a halogen atom is bonded to an alkene carbon are called **alkenyl halides**. In older nomenclature these were called vinylic halides. Compounds having a halogen bonded to an aromatic ring are called **aryl halides**. When the aromatic ring is specifically a benzene ring these compounds are called **phenyl halides**. The reactivity of compounds in which a halogen is bonded to an sp^2 carbon, as in alkenyl, aryl, and phenyl halides, is markedly different than when a halogen is bonded to an sp^3 carbon, as in an alkyl halide. The reactions that we discuss in this chapter will pertain to alkyl halides, not alkenyl, aryl, or phenyl halides.



An alkenyl halide



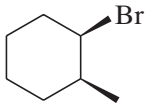
A phenyl halide or aryl halide

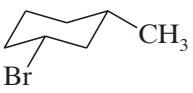
6.1A Physical Properties of Alkyl Halides

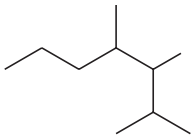
Most alkyl halides have very low solubilities in water, but as we might expect, they are miscible with each other and with other relatively nonpolar solvents. Dichloromethane (CH_2Cl_2, also called *methylene chloride*), trichloromethane ($CHCl_3$, also called *chloroform*), and tetrachloromethane (CCl_4, also called *carbon tetrachloride*) are sometimes used as solvents for nonpolar and moderately polar compounds. Many chloroalkanes, including CH_2Cl_2, $CHCl_3$, and CCl_4, have cumulative toxicity and are carcinogenic, however, and should therefore be used only in fume hoods and with great care.

Practice Problem 6.1

Give IUPAC names for each of the following.

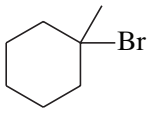
(a) 

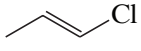
(b) 

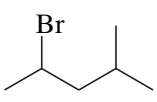
(c) 

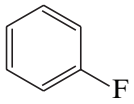
Practice Problem 6.2

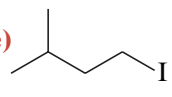
Classify each of the following organic halides as primary, secondary, tertiary, alkenyl, or aryl.

(a) 

(b) 

(c) 

(d) 

(e) 

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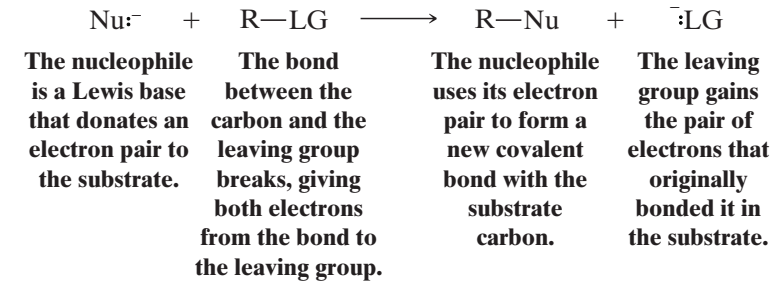
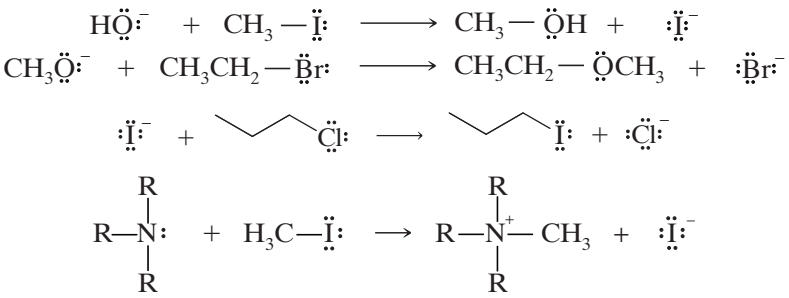
6.2 | NUCLEOPHILIC SUBSTITUTION REACTIONS

Nucleophilic substitution reactions are among the most fundamental types of organic reactions. In a **nucleophilic substitution reaction** a nucleophile (Nu:) displaces a leaving group (LG) in the molecule that undergoes the substitution (the substrate).

- The **nucleophile** is always a Lewis base, and it may be negatively charged or neutral.
- The **leaving group** is always a species that takes a pair of electrons with it when it departs.

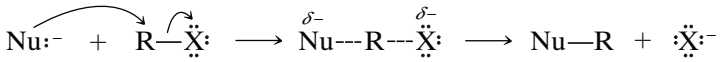
Often the **substrate** is an alkyl halide (R—$\ddot{X}$:) and the leaving group is a halide anion (:$\ddot{X}$:$^-$). The following equations include a generic nucleophilic substitution reaction and some specific examples.



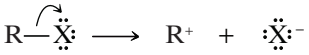


In nucleophilic substitution reactions the bond between the substrate carbon and the leaving group undergoes *heterolytic* bond cleavage. The unshared electron pair of the nucleophile forms the new bond to the carbon atom.

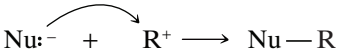
A key question we shall want to address later in this chapter is this: when does the bond between the leaving group and the carbon break? Does it break at the same time that the new bond between the nucleophile and carbon forms, as shown below?



Or, does the bond to the leaving group break first?



Followed by



We shall find in Sections 6.9 and 6.14A that the answer depends greatly on the structure of the substrate.

Solved Problem 6.1

(a) A solution containing methoxide ions, CH_3O^- ions (as $NaOCH_3$), in methanol can be prepared by adding sodium hydride (NaH) to methanol (CH_3OH). A flammable gas is the other product. Write the acid–base reaction that takes place. **(b)** Write the nucleophilic substitution that takes place when CH_3I is added and the resulting solution is heated.

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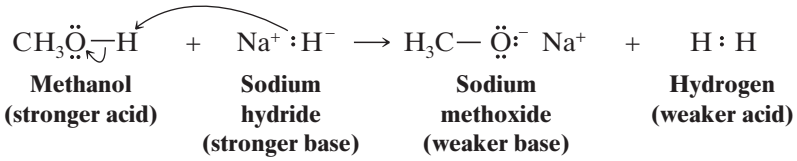
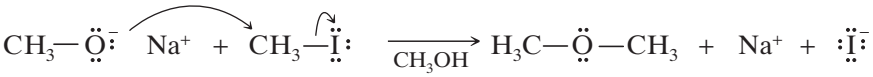
Answer

(a) We recall from Section 3.15 that sodium hydride consists of Na^+ ions and hydride ions ($H:^-$ ions), and that the hydride ion is a very strong base. [It is the conjugate base of H_2, a very weak acid ($pK_a = 35$, see Table 3.1).] The acid–base reaction that takes place is



(b) The methoxide ion reacts with the alkyl halide (CH_3I) in a nucleophilic substitution:

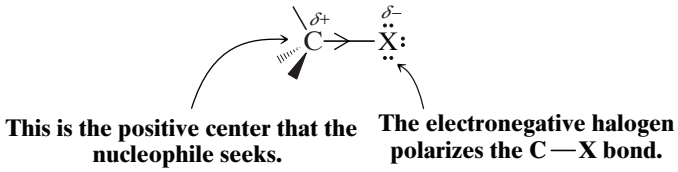


6.3 | NUCLEOPHILES

A nucleophile is a reagent that seeks a positive center.

- Any negative ion or uncharged molecule with an unshared electron pair is a potential nucleophile.

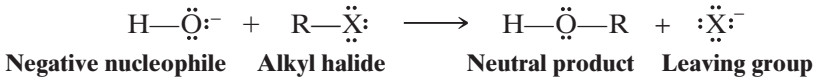
When a nucleophile reacts with an alkyl halide, the carbon atom bearing the halogen atom is the positive center that attracts the nucleophile. This carbon carries a partial positive charge because the electronegative halogen pulls the electrons of the carbon–halogen bond in its direction.



Let us look at two examples, one in which the nucleophile is a negatively charged Lewis base, and one in which the nucleophile is a neutral Lewis base.

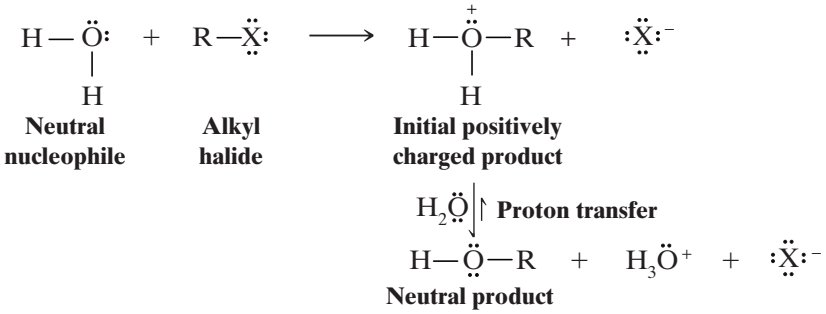
1. Use of a **negatively charged nucleophile** (hydroxide in this case) **results in a neutral product** (an alcohol in this case). Formation of the covalent bond between the negative nucleophile and the substrate neutralizes the formal charge of the nucleophile.

Nucleophilic Substitution by a Negatively Charged Nucleophile Results Directly in a Neutral Product



2. Use of a **neutral nucleophile** (water in this case) **results initially in a positively charged product**. The neutral nucleophile gains a positive formal charge through formation of the covalent bond with the substrate. A neutral product results only after a proton is removed from the atom with the formal positive charge in the initial product.

Nucleophilic Substitution by a Neutral Nucleophile Results Initially in a Positively Charged Product



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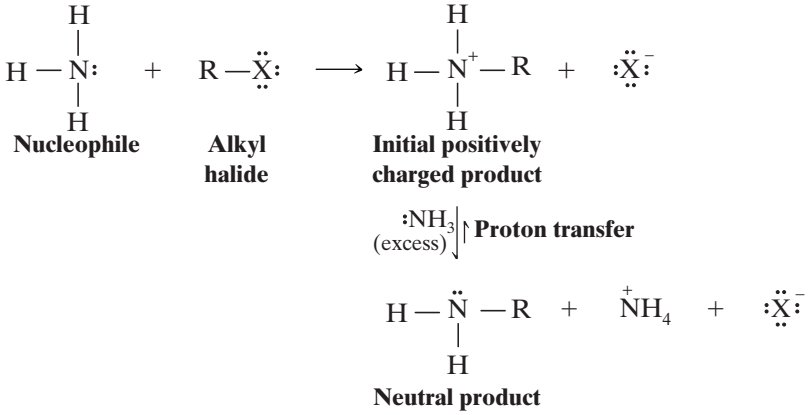
Helpful Hint: A deprotonation step is always required to complete the reaction when the nucleophile was a neutral atom that bore a proton.

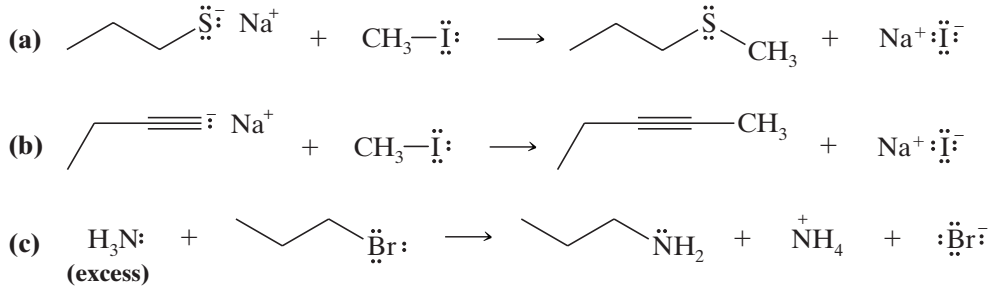
In a reaction like this the nucleophile is a solvent molecule (as is often the case when neutral nucleophiles are involved). Since solvent molecules are present in great excess, the equilibrium favors transfer of a proton from the alkyloxonium ion to a water molecule. This type of reaction is an example of solvolysis, which we shall discuss further in Section 6.12B.

The reaction of ammonia (NH_3) with an alkyl halide, as shown below, provides another example where the nucleophile is uncharged. An excess of ammonia favors equilibrium removal of a proton from the alkylaminium ion to form the neutral amine.



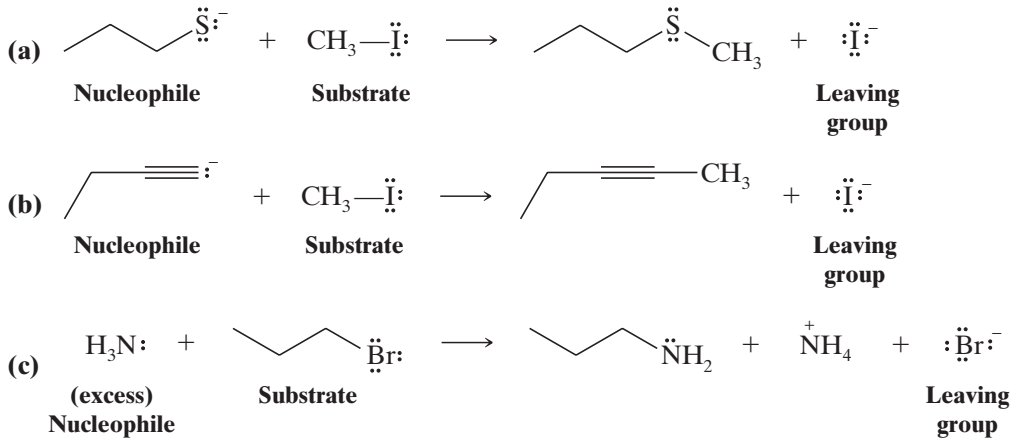
Solved Problem 6.2

Write the following as net ionic equations and designate the nucleophile, substrate, and leaving group in each case.



Answer

The net ionic equations are as follows for **(a)** and **(b)**, and there is no abbreviated equation possible for **(c)**. Nucleophiles, substrates, and leaving groups are labeled accordingly.



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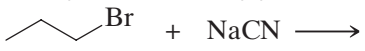
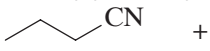
Practice Problem 6.3

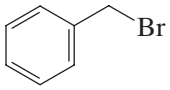
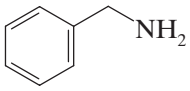
Write the following as net ionic equations and designate the nucleophile, substrate, and leaving group in each reaction:

(a) $CH_3I + CH_3CH_2ONa \longrightarrow CH_3OCH_2CH_3 + NaI$

(b) $NaI + CH_3CH_2Br \longrightarrow CH_3CH_2I + NaBr$

(c) $2\,CH_3OH + (CH_3)_3CCl \longrightarrow (CH_3)_3COCH_3 + CH_3\overset{+}{O}H_2 + Cl^-$

(d)  $+ NaCN \longrightarrow$  $+ NaBr$

(e)  $+ 2\,NH_3 \longrightarrow$  $+ NH_4Br$

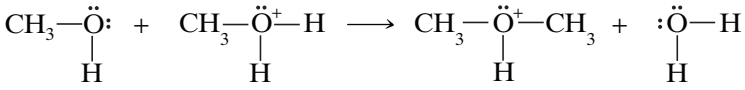
6.4 | LEAVING GROUPS

To act as the substrate in a nucleophilic substitution reaction, a molecule must have a good leaving group.

- A good **leaving group** is a substituent that can leave as a relatively stable, weakly basic molecule or ion.

In the examples shown above (Sections 6.2 and 6.3) the leaving group has been a halogen. Halide anions are weak bases (they are the conjugate bases of strong acids, HX), and therefore halogens are good leaving groups.

Some leaving groups depart as neutral molecules, such as a molecule of water or an alcohol. For this to be possible, the leaving group must have a formal positive charge while it is bonded to the substrate. When this group departs with a pair of electrons the leaving group's formal charge goes to zero. The following is an example where the leaving group departs as a water molecule.



As we shall see later, the positive charge on a leaving group (like that above) usually results from protonation of the substrate by an acid. However, use of an acid to protonate the substrate and make a positively charged leaving group is feasible only when the nucleophile itself is not strongly basic, and when the nucleophile is present in abundance (such as in solvolysis).

Let us now begin to consider the mechanisms of nucleophilic substitution reactions. How does the nucleophile replace the leaving group? Does the reaction take place in one step or is more than one step involved? If more than one step is involved, what kinds of intermediates are formed? Which steps are fast and which are slow? In order to answer these questions, we need to know something about the rates of chemical reactions.

6.5 | KINETICS OF A NUCLEOPHILIC SUBSTITUTION REACTION: AN S_N2 REACTION

To understand how the rate of a reaction (**kinetics**) might be measured, let us consider an actual example: the reaction that takes place between chloromethane and hydroxide ion in aqueous solution:

$$CH_3{-}Cl + {}^-OH \xrightarrow[H_2O]{60^\circ C} CH_3{-}OH + Cl^-$$

Although chloromethane is not highly soluble in water, it is soluble enough to carry out our kinetic study in an aqueous solution of sodium hydroxide. Because reaction rates are known to be temperature dependent (Section 6.7), we carry out the reaction at a constant temperature.

6.5A How Do We Measure the Rate of This Reaction?

The rate of the reaction can be determined experimentally by measuring the rate at which chloromethane or hydroxide ion *disappears* from the solution or the rate at which methanol or chloride ion *appears* in the solution. We can make any of these measurements by withdrawing a small sample from the reaction mixture soon after the reaction

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begins and analyzing it for the concentrations of CH_3Cl or HO^- and CH_3OH or Cl^-. We are interested in what are called *initial rates*, because as time passes the concentrations of the reactants change. Since we also know the initial concentrations of reactants (because we measured them when we made up the solution), it will be easy to calculate the rate at which the reactants are disappearing from the solution or the products are appearing in the solution.

We perform several such experiments keeping the temperature the same but varying the initial concentrations of the reactants. The results that we might get are shown in Table 6.2.

Table 6.2 Rate Study of Reaction of CH_3Cl with HO^- at 60°C

Experiment Number	Initial $[CH_3Cl]$	Initial $[HO^-]$	Initial Rate (mol L^{-1} s^{-1})
1	0.0010	1.0	4.9×10^{-7}
2	0.0020	1.0	9.8×10^{-7}
3	0.0010	2.0	9.8×10^{-7}
4	0.0020	2.0	19.6×10^{-7}

Notice that the experiments show that the rate depends on the concentration of chloromethane *and* on the concentration of hydroxide ion. When we doubled the concentration of chloromethane in experiment 2, the rate *doubled*. When we doubled the concentration of hydroxide ion in experiment 3, the rate *doubled*. When we doubled both concentrations in experiment 4, the rate increased by a factor of *four*.

We can express these results as a proportionality,

$$\text{Rate} \propto [CH_3Cl][HO^-]$$

and this proportionality can be expressed as an equation through the introduction of a proportionality constant (k) called the rate constant:

$$\text{Rate} = k\,[CH_3Cl][HO^-]$$

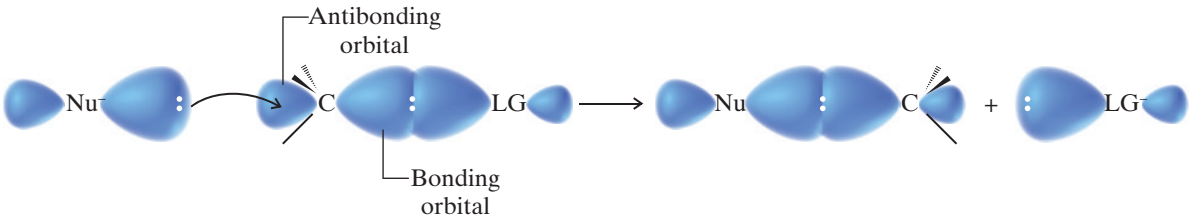
For this reaction at this temperature we find that $k = 4.9 \times 10^{-4}$ L mol^{-1} s^{-1}. (Verify this for yourself by doing the calculation.)

6.5B What Is the Order of This Reaction?

This reaction is said to be **second order overall**.* It is reasonable to conclude, therefore, that *for the reaction to take place a hydroxide ion and a chloromethane molecule must collide*. We also say that the reaction is **bimolecular**. (By *bimolecular* we mean that two species are involved in the step whose rate is being measured. In general the number of species involved in a reaction step is called the **molecularity** of the reaction.) We call this kind of reaction an **S_N2 reaction**, meaning **substitution, nucleophilic, bimolecular**.

6.6 | A MECHANISM FOR THE S_N2 REACTION

A schematic representation of orbitals involved in an S_N2 reaction—based on ideas proposed by Edward D. Hughes and Sir Christopher Ingold in 1937—is outlined below.



*In general, the overall order of a reaction is equal to the sum of the exponents a and b in the rate equation Rate = $k[A]^a\,[B]^b$. If in some other reaction, for example, we found that Rate = $k[A]^2\,[B]$, then we would say that the reaction is second order with respect to [A], first order with respect to [B], and third order overall.

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According to this mechanism:

- The nucleophile approaches the carbon bearing the leaving group from the **back side**, that is, from the side directly opposite the leaving group.

The orbital that contains the electron pair of the nucleophile (its highest occupied molecular orbital, or HOMO) begins to overlap with an empty orbital (the lowest unoccupied molecular orbital, or LUMO) of the carbon atom bearing the leaving group. As the reaction progresses, the bond between the nucleophile and the carbon atom strengthens, and the bond between the carbon atom and the leaving group weakens.

- As the nucleophile forms a bond and the leaving group departs, the substrate carbon atom undergoes **inversion*** — its tetrahedral bonding configuration is turned inside out.

The formation of the bond between the nucleophile and the carbon atom provides most of the energy necessary to break the bond between the carbon atom and the leaving group. We can represent this mechanism with chloromethane and hydroxide ion as shown in the "Mechanism for the S_N2 Reaction" box below.

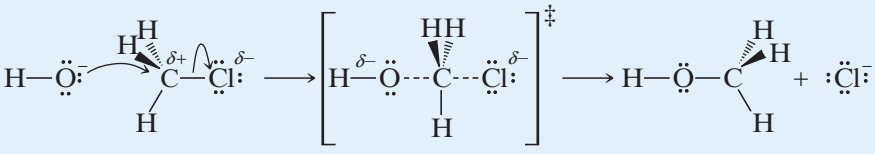
- The S_N2 reaction proceeds in a single step (without any intermediates) through an unstable arrangement of atoms called the **transition state**.

A MECHANISM FOR THE REACTION — Mechanism for the S_N2 Reaction

Reaction

$$HO^- + CH_3Cl \longrightarrow CH_3OH + Cl^-$$

Mechanism



Transition state

The negative hydroxide ion brings a pair of electrons to the partially positive carbon from the back side with respect to the leaving group. The chlorine begins to move away with the pair of electrons that bonded it to the carbon.

In the transition state, a bond between oxygen and carbon is partially formed and the bond between carbon and chlorine is partially broken. The configuration of the carbon atom begins to invert.

Now the bond between the oxygen and carbon has formed and the chloride ion has departed. The configuration of the carbon has inverted.

The transition state is a fleeting arrangement of the atoms in which the nucleophile and the leaving group are both partially bonded to the carbon atom undergoing substitution. Because the transition state involves both the nucleophile (e.g., a hydroxide ion) and the substrate (e.g., a molecule of chloromethane), this mechanism accounts for the second-order reaction kinetics that we observe.

- The S_N2 reaction is said to be a **concerted reaction**, because bond forming and bond breaking occur in concert (*simultaneously*) through a single transition state.

*Considerable evidence had appeared in the years prior to Hughes and Ingold's 1937 publication indicating that in reactions like this an inversion of configuration of the carbon bearing the leaving group takes place. The first observation of such an inversion was made by the Latvian chemist Paul Walden in 1896, and such inversions are called **Walden inversions** in his honor. We shall study this aspect of the S_N2 reaction further in Section 6.8.

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The transition state has an extremely brief existence. It lasts only as long as the time required for one molecular vibration, about 10^{-12} s. The structure and energy of the transition state are highly important aspects of any chemical reaction. We shall, therefore, examine this subject further in Section 6.7.

6.7 | TRANSITION STATE THEORY: FREE-ENERGY DIAGRAMS

- A reaction that proceeds with a negative free-energy change (releases energy to its surroundings) is said to be **exergonic**; one that proceeds with a positive free-energy change (absorbs energy from its surroundings) is said to be **endergonic**.

The reaction between chloromethane and hydroxide ion in aqueous solution is highly exergonic; at 60 °C (333 K), $\Delta G^\circ = -100$ kJ mol^{-1}. (The reaction is also exothermic, $\Delta H^\circ = -75$ kJ mol^{-1}.)

$$CH_3{-}Cl + {}^-OH \longrightarrow CH_3{-}OH + Cl^- \quad \Delta G^\circ = -100 \text{ kJ mol}^{-1}$$

The equilibrium constant for the reaction is extremely large, as we show by the following calculation:

$$\Delta G^\circ = -RT \ln K_{eq}$$

$$\ln K_{eq} = \frac{-\Delta G^\circ}{RT}$$

$$\ln K_{eq} = \frac{-(-100 \text{ kJ mol}^{-1})}{0.00831 \text{ kJ K}^{-1}\text{ mol}^{-1} \times 333 \text{ K}}$$

$$\ln K_{eq} = 36.1$$

$$K_{eq} = 5.0 \times 10^{15}$$

An equilibrium constant as large as this means that the reaction goes to completion.

Because the free-energy change is negative, we can say that in energy terms the reaction goes **downhill**. The products of the reaction are at a lower level of free energy than the reactants. However, if covalent bonds are broken in a reaction, the reactants must go up an energy hill first, before they can go downhill. This will be true even if the reaction is exergonic.

We can represent the energy changes in a reaction using a graph called a **free-energy diagram**, where we plot the free energy of the reacting particles (y-axis) against the reaction coordinate (x-axis). Figure 6.1 is an example for a generalized S_N2 reaction.

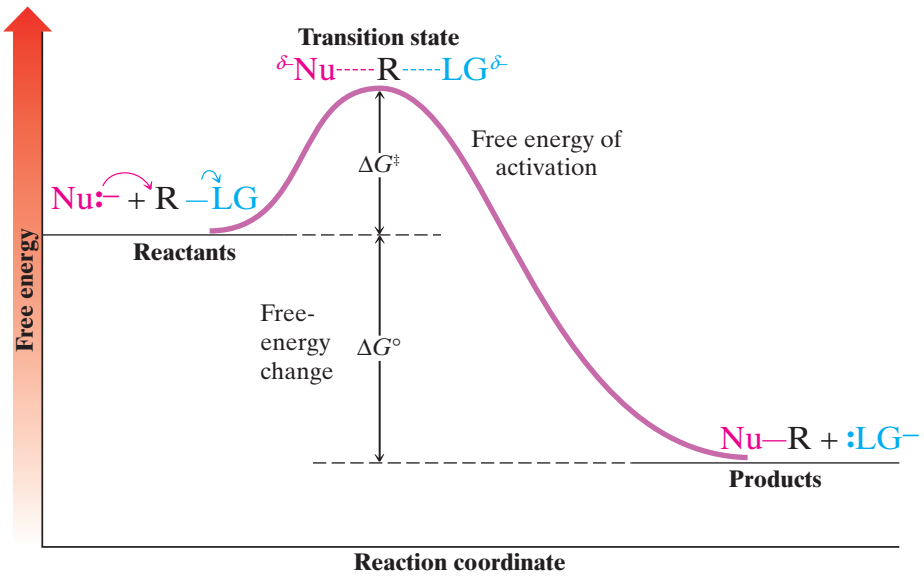

Figure 6.1 A free-energy diagram for a hypothetical exergonic S_N2 reaction (i.e., that takes place with a negative ΔG°, releasing energy to the surroundings).

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- The **reaction coordinate** indicates the progress of the reaction, in terms of the conversion of reactants to products.
- The top of the energy curve corresponds to the **transition state** for the reaction.
- The **free energy of activation** ($\Delta G^{\ddagger}$) for the reaction is the difference in energy between the reactants and the transition state.
- The **free energy change for the reaction** (ΔG°) is the difference in energy between the reactants and the products.

The top of the energy hill corresponds to the transition state. *The difference in free energy between the reactants and the transition state is the free energy of activation,* $\Delta G^{\ddagger}$. *The difference in free energy between the reactants and products is the free-energy change for the reaction,* ΔG°. For our example in Fig. 6.1, the free-energy level of the products is lower than that of the reactants. In terms of our analogy, we can say that the reactants in one energy valley must surmount an energy hill (the transition state) in order to reach the lower energy valley of the products.

If a reaction in which covalent bonds are broken proceeds with a positive free-energy change (Fig. 6.2), there will still be a free energy of activation. That is, if the products have greater free energy than reactants, the free energy of activation will be even higher. ($\Delta G^{\ddagger}$ will be larger than ΔG°.) In other words, in the **uphill** (endergonic) reaction an even larger energy hill lies between the reactants in one valley and the products in a higher one.

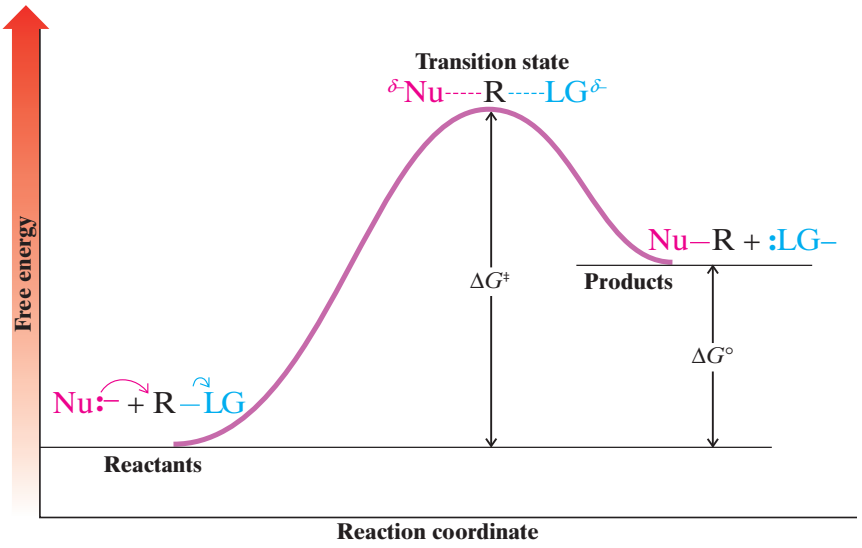

Figure 6.2 A free-energy diagram for a hypothetical endergonic S_N2 reaction (i.e., that takes place with a positive ΔG°, absorbing energy from the surroundings).

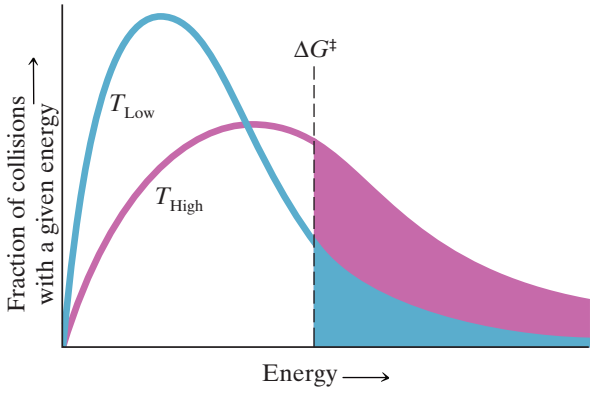

Figure 6.3 The distribution of energies at two different temperatures, T_{Low} and T_{High}. The number of collisions with energies greater than the free energy of activation is indicated by the corresponding shaded area under each curve.

6.7A Temperature and Reaction Rate

Most chemical reactions occur much more rapidly at higher temperatures. The increase in reaction rate for S_N2 reactions relates to the fact that at higher temperatures the number of collisions between reactants with sufficient energy to surmount the activation energy ($\Delta G^{\ddagger}$) increases significantly (see Fig. 6.3).

- A 10°C increase in temperature will cause the reaction rate to double for many reactions taking place near room temperature.

This dramatic increase in reaction rate results from a large increase in the number of collisions between reactants that together have sufficient energy to surmount the barrier at the higher temperature. The kinetic energies of molecules at a given temperature are not all the same. Figure 6.3 shows the distribution of energies brought to collisions at two temperatures (that do not differ greatly), labeled T_{Low} and T_{High}. Because of

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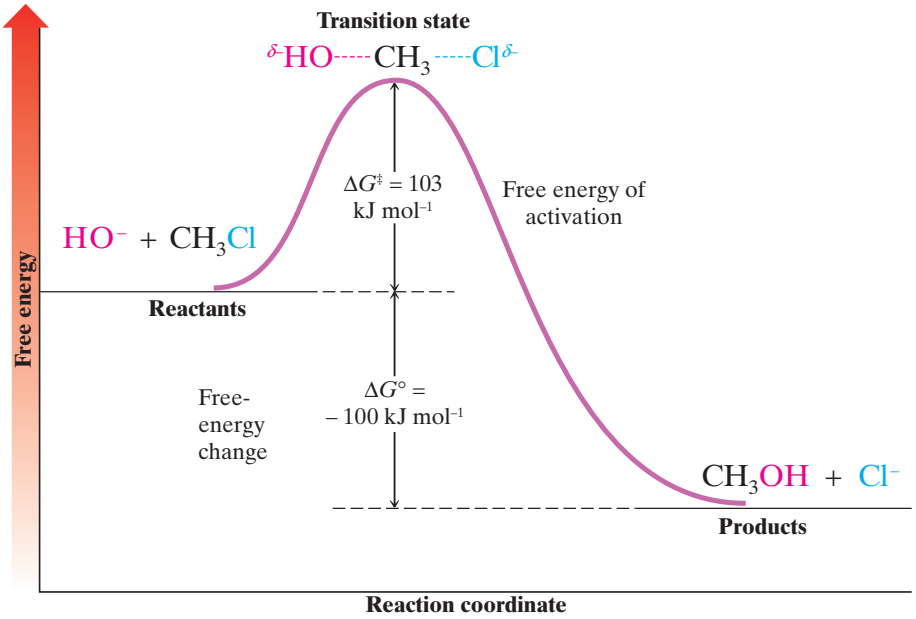


Figure 6.4 A free-energy diagram for the reaction of chloromethane with hydroxide ion at 60 °C.

the way energies are distributed at different temperatures (as indicated by the shapes of the curves), increasing the temperature by only a small amount causes a large increase in the number of collisions with larger energies. In Fig. 6.3 we have designated an arbitrary minimum free energy of activation as being required to bring about a reaction between colliding molecules.

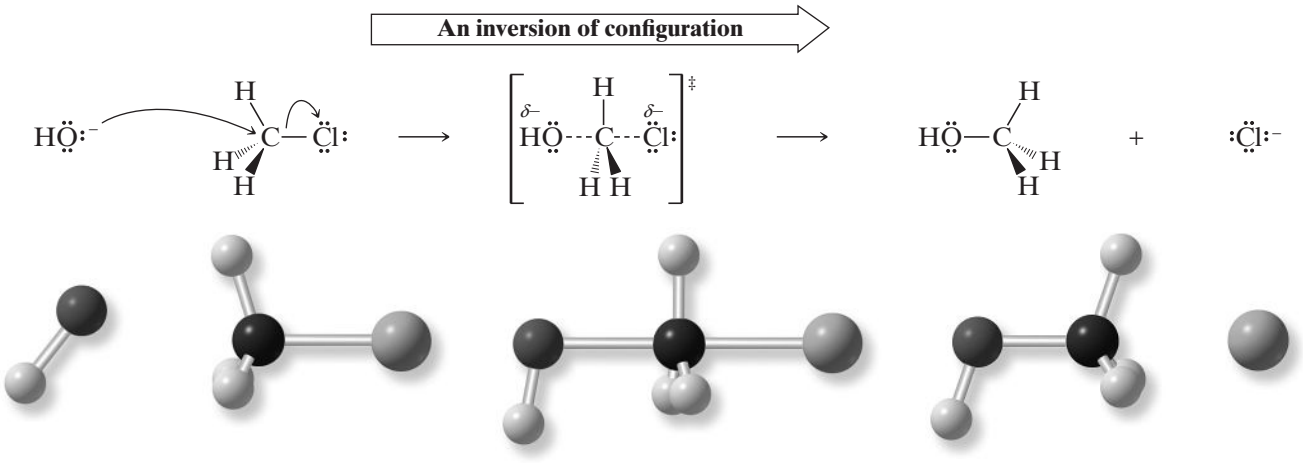
A free-energy diagram for the reaction of chloromethane with hydroxide ion is shown in Fig. 6.4. At 60 °C, $\Delta G^{\ddagger}$ = 103 kJ mol^{-1}, which means that at this temperature the reaction reaches completion in a matter of a few hours.

6.8 | THE STEREOCHEMISTRY OF S_N2 REACTIONS

The **stereochemistry** of S_N2 reactions is directly related to key features of the mechanism that we learned earlier:

- **The nucleophile approaches the substrate carbon from the back side with respect to the leaving group**. In other words, the bond to the nucleophile that is forming is opposite (at 180°) to the bond to the leaving group that is breaking.
- Nucleophilic displacement of the leaving group in an S_N2 reaction causes **inversion of configuration** at the substrate carbon.

We depict the inversion process as follows. It is much like the way an umbrella is inverted in a strong wind.



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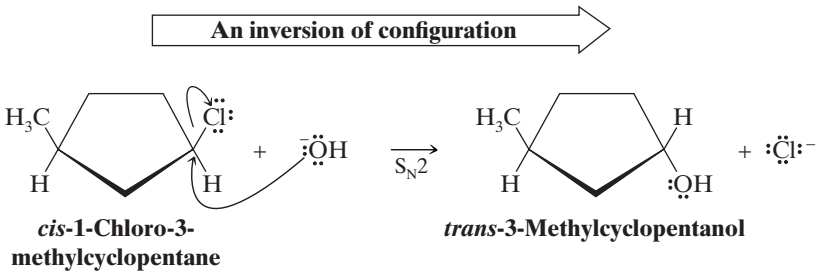
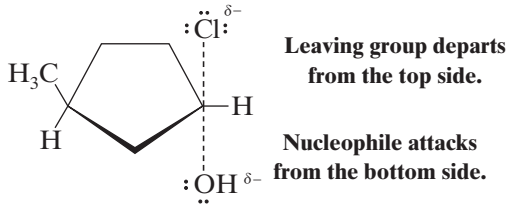
With a molecule such as chloromethane, however, there is no way to prove that attack by the nucleophile has involved inversion of configuration of the carbon atom because one form of methyl chloride is identical to its inverted form. With a molecule containing chirality centers such as *cis*-1-chloro-3-methylcyclopentane, however, we can observe the results of an inversion of configuration by the change in stereochemistry that occurs. When *cis*-1-chloro-3-methylcyclopentane reacts with hydroxide ion in an S_N2 reaction, the product is *trans*-3-methylcyclopentanol. *The hydroxyl group ends up bonded on the opposite side of the ring from the chlorine it replaces*:



***cis*-1-Chloro-3-methylcyclopentane** ***trans*-3-Methylcyclopentanol**

Presumably, the transition state for this reaction is like that shown here.

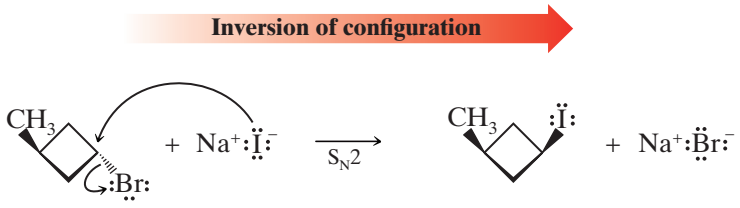


Solved Problem 6.3

Give the structure of the product that would be formed when *trans*-1-bromo-3-methylcyclobutane undergoes an S_N2 reaction with NaI.

Answer

First, write the formulas for the reactants and identify the nucleophile, the substrate, and the leaving group. Then, recognizing that the nucleophile will attack the back side of the substrate carbon atom that bears the leaving group, causing an inversion of configuration at that carbon, write the structure of the product.



Leaving group **Nucleophile**

***trans*-1-Bromo-3-methylcyclobutane (substrate)** ***cis*-1-Iodo-3-methylcyclobutane (product)**

Practice Problem 6.4

Using chair conformational structures (Section 5.11), show the nucleophilic substitution reaction that would take place when *trans*-1-bromo-4-*tert*-butylcyclohexane reacts with iodide ion. (Show the most stable conformation of the reactant and the product.)

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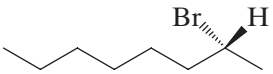
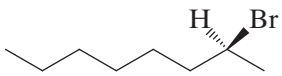
- **S_N2 reactions always occur with inversion of configuration.**

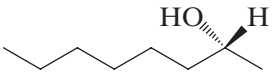
We can also observe inversion of configuration when an S_N2 reaction occurs at a chirality center in an acyclic molecule. The reaction of (*R*)-(−)-2-bromooctane with sodium hydroxide provides an example. We can determine whether or not inversion of configuration occurs in this reaction because the configurations and optical rotations for both enantiomers of 2-bromooctane and the expected product, 2-octanol, are known.



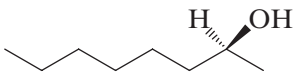
(*R*)-(−)-2-Bromooctane
$[\alpha]_D^{25} = -34.25$



(*S*)-(+)-2-Bromooctane
$[\alpha]_D^{25} = +34.25$



(*R*)-(−)-2-Octanol
$[\alpha]_D^{25} = -9.90$

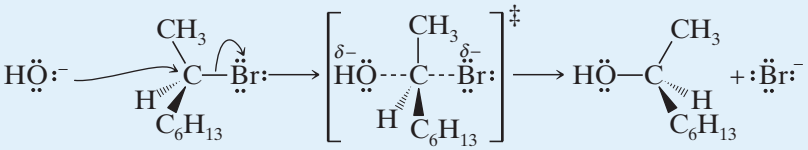


(*S*)-(+)-2-Octanol
$[\alpha]_D^{25} = +9.90$

When the reaction is carried out, we find that enantiomerically pure (*R*)-(−)-2-bromooctane ($[\alpha]_D^{25} = -34.25$) has been converted to enantiomerically pure (*S*)-(+)-2-octanol ($[\alpha]_D^{25} = +9.90$).

A MECHANISM FOR THE REACTION — The Stereochemistry of an S_N2 Reaction

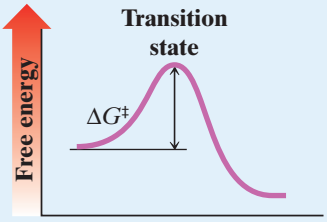
The reaction of (*R*)-(−)-2-bromooctane with hydroxide is an S_N2 reaction and takes place with *inversion of configuration:*



An inversion of configuration

(*R*)-(−)-2-Bromooctane
$[\alpha]_D^{25} = -34.25°$
Enantiomeric purity = 100%

(*S*)-(1)-2-Octanol
$[\alpha]_D^{25} = +9.90°$
Enantiomeric purity = 100%



An S_N2 reaction has one transition state.

Practice Problem 6.5

S_N2 reactions that involve breaking a bond to a chirality center can be used to relate configurations of molecules because the *stereochemistry* of the reaction is known.

(a) Illustrate how this is true by assigning *R*,*S* configurations to the 2-chlorobutane enantiomers based on the following data. [The configuration of (−)-2-butanol is given in Section 4.8C.]

(+)-2-Chlorobutane $\xrightarrow[S_N2]{HO^-}$ (−)-2-Butanol

$[\alpha]_D^{25} = +36.00$
Enantiomerically pure

$[\alpha]_D^{25} = -13.52$
Enantiomerically pure

(b) When optically pure (+)-2-chlorobutane is allowed to react with potassium iodide in acetone in an S_N2 reaction, the 2-iodobutane that is produced has a minus rotation. What is the configuration of (−)-2-iodobutane? Of (+)-2-iodobutane?

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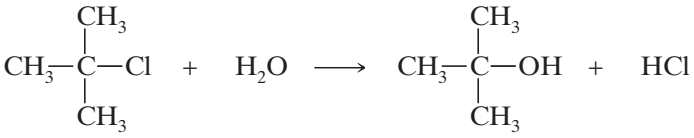
6.9 | THE REACTION OF *TERT*-BUTYL CHLORIDE WITH WATER: AN S_N1 REACTION

Let us now consider another mechanism for nucleophilic substitution: the S_N1 reaction. When Hughes (Section 6.6) and co-workers studied the reaction of *tert*-butyl chloride with water they found the kinetics leading to formation of *tert*-butyl alcohol to be quite different than for other substitution reactions that they had studied.



***tert*-Butyl chloride** ***tert*-Butyl alcohol**

Hughes found that the rate of *tert*-butyl chloride substitution was the same whether the reaction was run at pH 7, where the hydroxide ion concentration is 10^{-7} M and the predominant nucleophile is water, or in 0.05 M hydroxide, where the more powerful hydroxide nucleophile is present in roughly 500,000 times higher concentration. These results suggest that neither water nor hydroxide ions are involved in the rate-determining step of the reaction. Instead, the rate of substitution is dependent only on the concentration of *tert*-butyl chloride. The reaction is thus first order in *tert*-butyl chloride, and first order overall.

$$\text{Rate} = k[(CH_3)_3CCl]$$

The reaction rate is first order in *tert*-butyl chloride and first order overall.

Furthermore, these results indicate that the transition state governing the rate of reaction involves only molecules of *tert*-butyl chloride, and not water or hydroxide ions. The reaction is said to be **unimolecular** (first-order) in the rate-determining step, and we call it an **S_N1 reaction (substitution, nucleophilic, unimolecular)**. In Section 6.15 we shall see that elimination reactions can compete with S_N1 reactions, leading to the formation of alkenes, but in the case of the conditions used above for the experiments with *tert*-butyl chloride (moderate temperature and dilute base), S_N1 is the dominant process.

How can we explain an S_N1 reaction in terms of a mechanism? To do so, we shall need to consider the possibility that the mechanism involves more than one step. But what kind of kinetic results should we expect from a multistep reaction? Let us consider this point further.

6.9A Multistep Reactions and the Rate-Determining Step

- If a reaction takes place in a series of steps, and if one step is intrinsically slower than all the others, then the rate of the overall reaction will be essentially the same as the rate of this slow step. This slow step, consequently, is called the **rate-limiting step** or the **rate-determining step**.

Consider a multistep reaction such as the following:

$$\text{Reactant} \xrightarrow[\text{(slow)}]{k_1} \text{intermediate 1} \xrightarrow[\text{(fast)}]{k_2} \text{intermediate 2} \xrightarrow[\text{(fast)}]{k_3} \text{product}$$

Step 1 ***Step 2*** ***Step 3***

When we say that the first step in this example is intrinsically slow, we mean that the rate constant for step 1 is very much smaller than the rate constant for step 2 or for step 3. That is, $k_1 \ll k_2$ or k_3. When we say that steps 2 and 3 are *fast*, we mean that because their rate constants are larger, they could (in theory) take place rapidly if the concentrations of the two intermediates ever became high. In actuality, the concentrations of the intermediates are always very small because of the slowness of step 1.

As an analogy, imagine an hourglass modified in the way shown in Fig. 6.5. The opening between the top chamber and the one just below is considerably smaller than the other two. The overall rate at which sand falls from the top to the bottom of the hourglass is limited by the rate at which sand passes through the small orifice. This step, in the passage of sand, is analogous to the rate-determining step of the multistep reaction.

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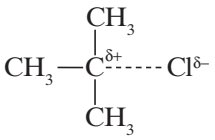
6.10 | A MECHANISM FOR THE S_N1 REACTION

The mechanism for the reaction of *tert*-butyl chloride with water (Section 6.9) can be described in three steps. See the box "Mechanism for the S_N1 Reaction" below, with a schematic free-energy diagram highlighted for each step. Two distinct **intermediates** are formed. The first step is the slow step—it is the rate-determining step. In it a molecule of *tert*-butyl chloride ionizes and becomes a *tert*-butyl cation and a chloride ion. In the transition state for this step the carbon–chlorine bond of *tert*-butyl chloride is largely broken and ions are beginning to develop:



The solvent (water) stabilizes these developing ions by solvation. Carbocation formation, in general, takes place slowly because it is usually a highly endothermic process and is uphill in terms of free energy.

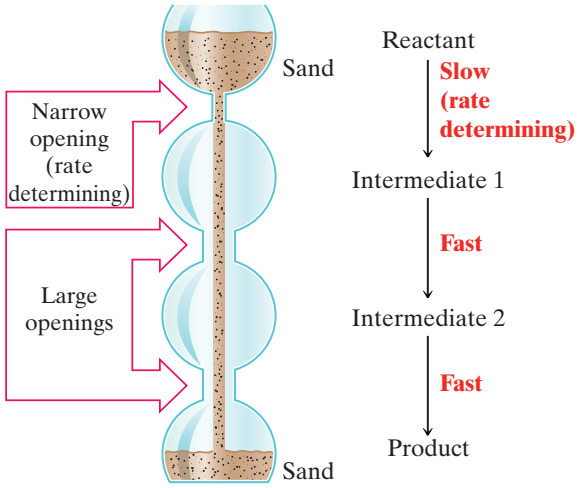


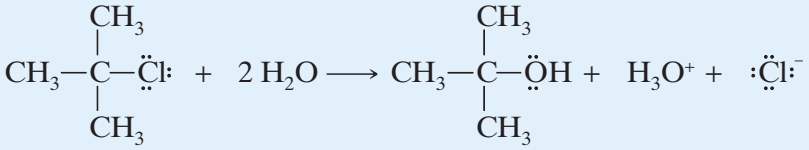
Figure 6.5 A modified hourglass that serves as an analogy for a multistep reaction. The overall rate is limited by the rate of the slow step.

The first step requires heterolytic cleavage of the carbon–chlorine bond. Because no other bonds are formed in this step, it should be highly endothermic and it should have a high free energy of activation, as we see in the free-energy diagram. **That departure of the halide takes place at all is largely because of the ionizing ability of the solvent, water**. Experiments indicate that in the gas phase (i.e., in the absence of a solvent), the free energy of activation is about 630 kJ mol^{-1}! In aqueous solution, however, the free energy of activation is much lower—about 84 kJ mol^{-1}. **Water molecules surround and stabilize the cation and anion that are produced** (cf. Section 2.12D).

In the second step the intermediate *tert*-butyl cation reacts rapidly with water to produce a *tert*-butyloxonium ion, $(CH_3)_3COH_2^+$, which in the third step, rapidly transfers a proton to a molecule of water producing *tert*-butyl alcohol.

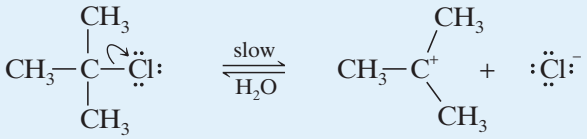
A MECHANISM FOR THE REACTION — Mechanism for the S_N1 Reaction

Reaction



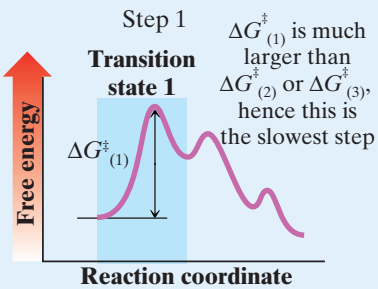
Mechanism

Step 1



Aided by the polar solvent, a chlorine departs with the electron pair that bonded it to the carbon.

This slow step produces the 3° carbocation intermediate and a chloride ion. Although not shown here, the ions are solvated (and stabilized) by water molecules.



(Mechanism continues on the next page)

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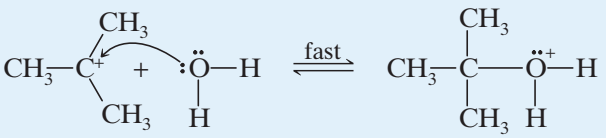
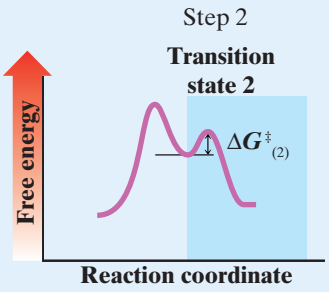
Step 2

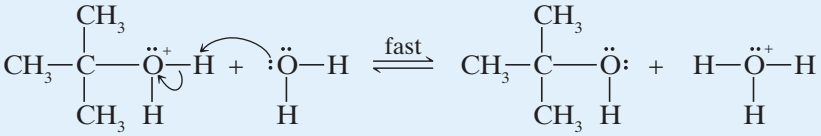


A water molecule acting as a Lewis base donates an electron pair to the carbocation (a Lewis acid). This gives the cationic carbon eight electrons.

The product is a *tert*-butyloxonium ion (or protonated *tert*-butyl alcohol).

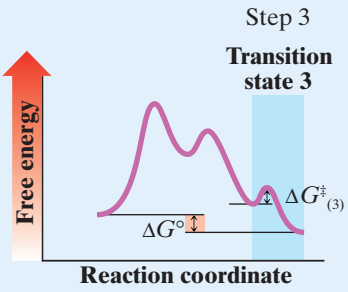


Step 3



A water molecule acting as a Brønsted base accepts a proton from the *tert*-butyloxonium ion.

The products are *tert*-butyl alcohol and a hydronium ion.



6.11 | CARBOCATIONS

Beginning in the 1920s much evidence began to accumulate implicating simple alkyl cations as intermediates in a variety of ionic reactions. However, because alkyl cations are highly unstable and highly reactive, they were, in all instances studied before 1962, very short-lived, transient species that could not be observed directly.* However, in 1962 George A. Olah (University of Southern California) and co-workers published the first of a series of papers describing experiments in which alkyl cations were prepared in an environment in which they were reasonably stable and in which they could be observed by a number of spectroscopic techniques.

6.11A The Structure of Carbocations

- Carbocations are trigonal planar.

Just as the trigonal planar structure of BF_3 (Section 1.16D) can be accounted for on the basis of sp^2 hybridization, so, too (Fig. 6.6), can the trigonal planar structure of carbocations.

- The central carbon atom in a carbocation is electron deficient; it has only six electrons in its valence shell.

In our model (Fig. 6.6) these six electrons are used to form three sigma (σ) covalent bonds to hydrogen atoms or alkyl groups.

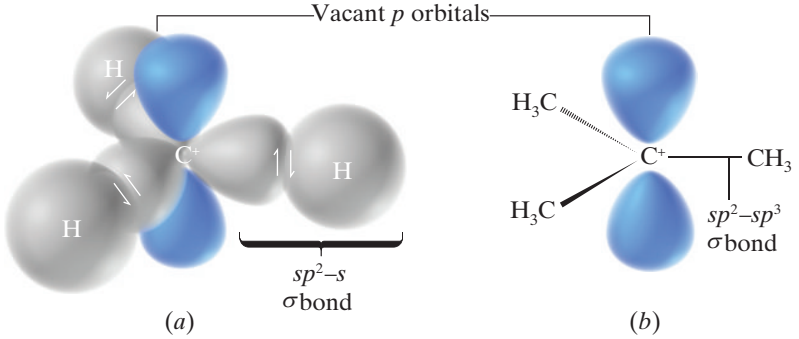


Figure 6.6 *(a)* A stylized orbital structure of the methyl cation. The bonds are sigma (σ) bonds formed by overlap of the carbon atom's three sp^2 orbitals with the 1*s* orbitals of the hydrogen atoms. The *p* orbital is vacant. *(b)* A dashed line–wedge representation of the *tert*-butyl cation. The bonds between carbon atoms are formed by overlap of sp^3 orbitals of the methyl groups with sp^2 orbitals of the central carbon atom.

*As we shall learn later, carbocations bearing aromatic groups can be much more stable; one of these had been studied as early as 1901.

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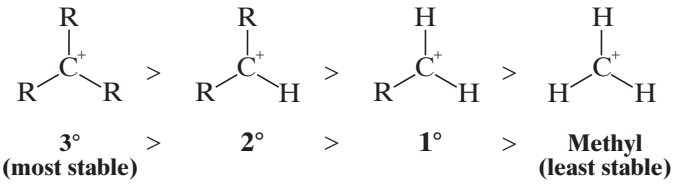
- The *p* orbital of a carbocation contains no electrons, but it can accept an electron pair when the carbocation undergoes further reaction.

Not all types of carbocations have the same relative stability, as we shall learn in the next section.

6.11B The Relative Stabilities of Carbocations

The relative stabilities of carbocations are related to the number of alkyl groups attached to the positively charged trivalent carbon.

- Tertiary carbocations are the most stable, and the methyl carbocation is the least stable.
- The overall order of stability is as follows:



This order of carbocation stability can be explained on the basis of hyperconjugation.

- **Hyperconjugation** involves electron delocalization (via partial orbital overlap) from a filled bonding orbital to an adjacent unfilled orbital (Section 5.8).

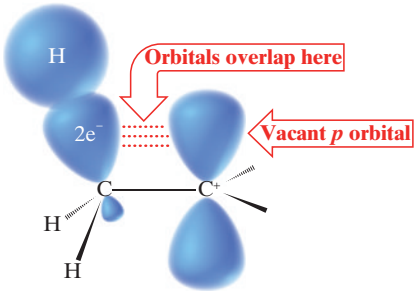


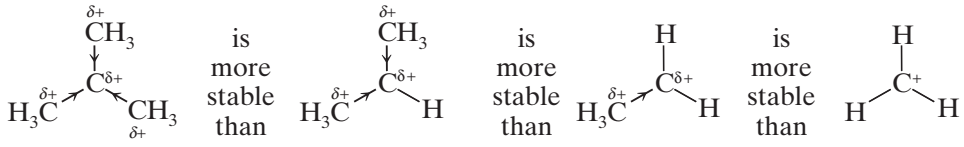
Figure 6.7 How an adjacent sigma bond helps stabilize the positive charge of a carbocation. Electron density from one of the carbon–hydrogen sigma bonds of the methyl group flows into the vacant *p* orbital of the carbocation because the orbitals can partly overlap. Shifting electron density in this way makes the sp^2-hybridized carbon of the carbocation somewhat less positive, and the hydrogens of the methyl group assume some of the positive charge. Delocalization (dispersal) of the charge in this way leads to greater stability. This interaction of a bond orbital with a *p* orbital is called hyperconjugation.

In the case of a carbocation, the unfilled orbital is the vacant *p* orbital of the carbocation, and the filled orbitals are C—H or C—C sigma bonds at the carbons *adjacent* to the *p* orbital of the carbocation. Sharing of electron density from adjacent C—H or C—C sigma bonds with the carbocation *p* orbital delocalizes the positive charge.

- Any time a charge can be dispersed or delocalized by hyperconjugation, inductive effects, or resonance, a system will be stabilized.

Figure 6.7 shows a stylized representation of hyperconjugation between a sigma bonding orbital and an adjacent carbocation *p* orbital.

Tertiary carbocations have three carbons with C—H bonds (or, depending on the specific example, C—C bonds instead of C—H) adjacent to the carbocation that can overlap partially with the vacant *p* orbital. Secondary carbocations have only two adjacent carbons with C—H or C—C bonds to overlap with the carbocation; hence, the possibility for hyperconjugation is less and the secondary carbocation is less stable. Primary carbocations have only one adjacent carbon from which to derive hyperconjugative stabilization, and so they are even less stable. A methyl carbocation has no possibility for hyperconjugation, and it is the least stable of all in this series. The following are specific examples:



***tert*-Butyl cation (3°) (most stable)** — **Isopropyl cation (2°)** — **Ethyl cation (1°)** — **Methyl cation (least stable)**

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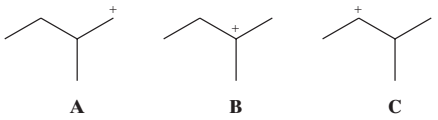
In summary:

- **The relative stability of carbocations is 3° > 2° > 1° > methyl.**

Solved Problem 6.4

Rank the following carbocations in order of increasing stability:

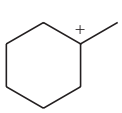
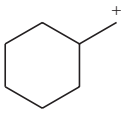
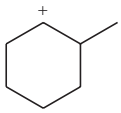


Answer

Structure **A** is a primary carbocation, **B** is tertiary, and **C** is secondary. Therefore, in order of increasing stability, **A < C < B**.

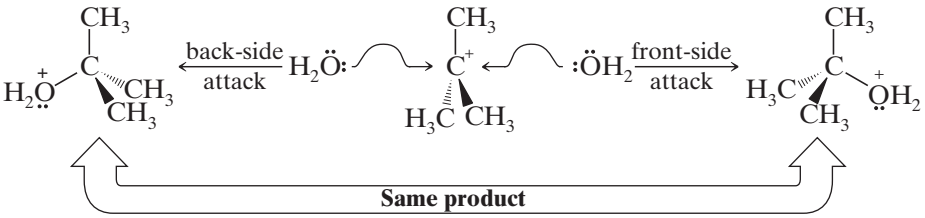
Practice Problem 6.6

Rank the following carbocations in order of increasing stability:

(a) 
(b) 
(c) 

6.12 | THE STEREOCHEMISTRY OF S_N1 REACTIONS

Because the carbocation formed in the first step of an S_N1 reaction has a trigonal planar structure (Section 6.11A), when it reacts with a nucleophile, it may do so from either the front side or the back side (see below). With the *tert*-butyl cation this makes no difference; since the *tert*-butyl group is not a chirality center, the same product is formed by either mode of attack. (Convince yourself of this result by examining models.)



With some cations, however, stereoisomeric products arise from the two reaction possibilities. We shall study this point next.

6.12A Reactions That Involve Racemization

A reaction that transforms an optically active compound into a racemic form is said to proceed with **racemization**. If the original compound loses all of its optical activity in the course of the reaction, chemists describe the reaction as having taken place with *complete* racemization. If the original compound loses only part of its optical activity, as would be the case if an enantiomer were only partially converted to a racemic form, then chemists describe this as proceeding with *partial* racemization.

- Racemization takes place whenever the reaction causes chiral molecules to be converted to an achiral intermediate.

Examples of this type of reaction are S_N1 reactions in which the leaving group departs from a chirality center. These reactions almost always result in extensive and sometimes complete racemization. For example, heating optically

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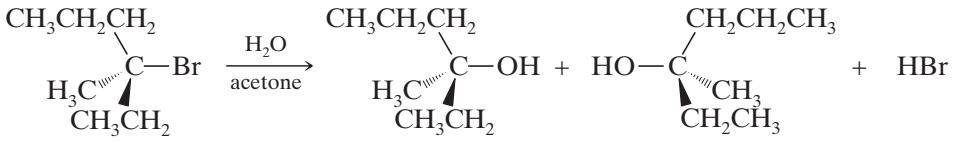
active (*S*)-3-bromo-3-methylhexane with aqueous acetone results in the formation of 3-methyl-3-hexanol as a mixture of 50% (*R*) and 50% (*S*).



(*S*)-3-Bromo-3-methylhexane (optically active)

50% (*S*)-3-Methyl-3-hexanol

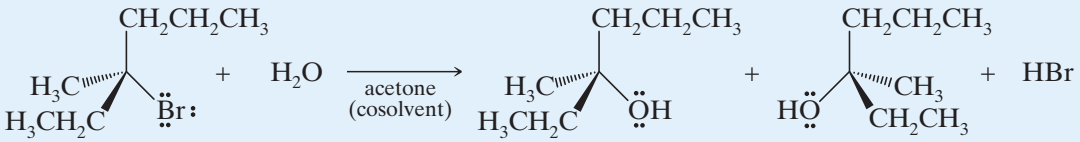
50% (*R*)-3-Methyl-3-hexanol

(optically inactive, a racemic form)

The reason: the S_N1 reaction proceeds through the formation of an intermediate carbocation and the carbocation, because of its trigonal planar configuration, *is achiral*. It reacts with water at equal rates from either side to form the enantiomers of 3-methyl-3-hexanol in equal amounts.

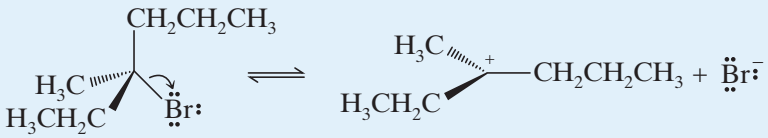
A MECHANISM FOR THE REACTION — The Stereochemistry of an S_N1 Reaction

Reaction



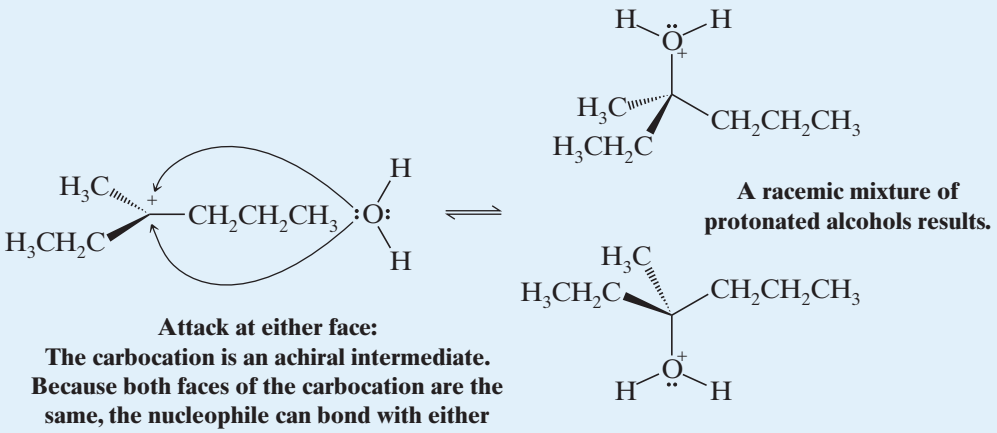
Mechanism

Step 1



Departure of the leaving group (assisted by hydrogen bonding with water) leads to the carbocation.

Step 2



A racemic mixture of protonated alcohols results.

Attack at either face: The carbocation is an achiral intermediate. Because both faces of the carbocation are the same, the nucleophile can bond with either face to form a mixture of stereoisomers.

(Mechanism continues on the next page)

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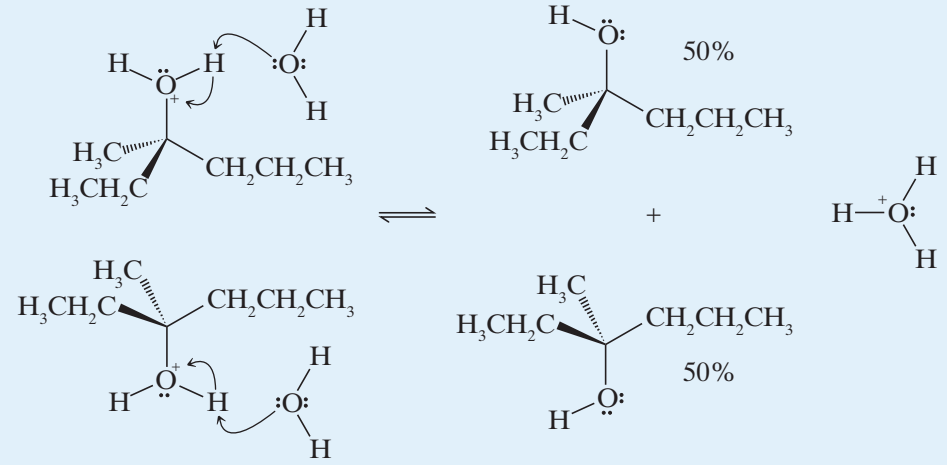


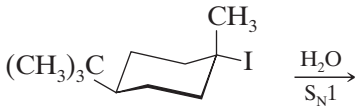
Additional solvent molecules (water) deprotonate the alkyloxonium ion.

The product is a racemic mixture.

The S_N1 reaction of (*S*)-3-bromo-3-methylhexane proceeds with racemization because the intermediate carbocation is achiral and attack by the nucleophile can occur from either side.

Practice Problem 6.7

Keeping in mind that carbocations have a trigonal planar structure, (a) write a structure for the carbocation intermediate and (b) write structures for the alcohol (or alcohols) that you would expect from reaction of iodocyclohexane in water:



6.12B Solvolysis

- A **solvolysis reaction** is a nucleophilic substitution in which *the nucleophile is a molecule of the solvent* (*solvent* + *lysis*: cleavage by the solvent). The S_N1 reaction of an alkyl halide with water is an example of **solvolysis**.

When the solvent is water, we could also call the reaction a **hydrolysis**. If the reaction had taken place in methanol, we would call it a **methanolysis**.

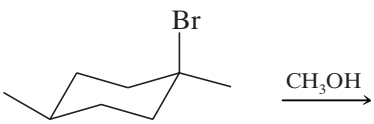
Examples of Solvolysis

$$(CH_3)_3C{-}Br + H_2O \longrightarrow (CH_3)_3C{-}OH + HBr$$

$$(CH_3)_3C{-}Cl + CH_3OH \longrightarrow (CH_3)_3C{-}OCH_3 + HCl$$

Solved Problem 6.5

What product(s) would you expect from the following solvolysis?



Answer

We observe that this cyclohexyl bromide is tertiary, and therefore in methanol it should lose a bromide ion to form a tertiary carbocation. Because the carbocation is trigonal planar at the positive carbon, it can react with a solvent molecule (methanol) to form two products.

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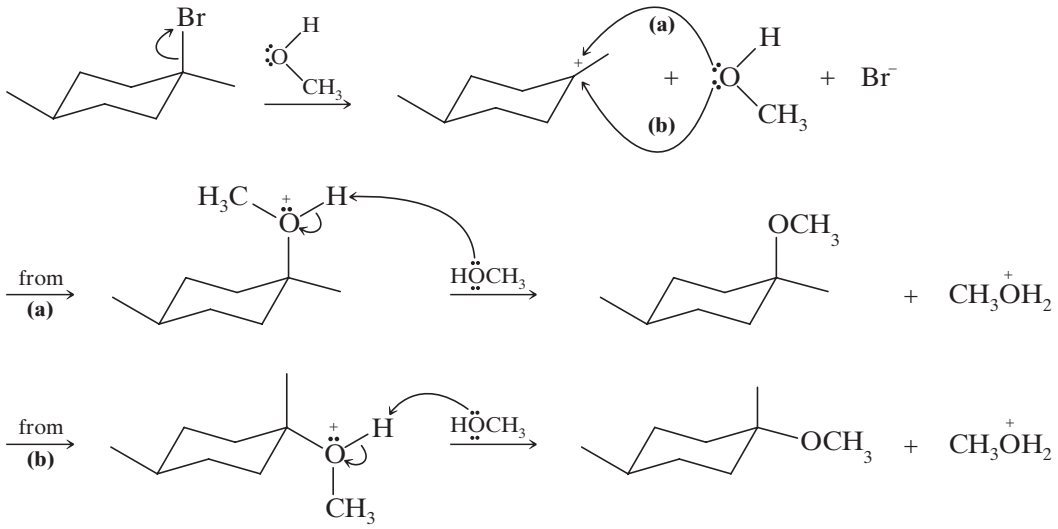

Practice Problem 6.8

What product(s) would you expect from the methanolysis of the iodocyclohexane derivative given as the reactant in Practice Problem 6.7?

6.13 | FACTORS AFFECTING THE RATES OF S_N1 AND S_N2 REACTIONS

Now that we have an understanding of the mechanisms of S_N2 and S_N1 reactions, our next task is to explain why chloromethane reacts by an S_N2 mechanism and *tert*-butyl chloride by an S_N1 mechanism. We would also like to be able to predict which pathway—S_N1 or S_N2—would be followed by the reaction of any alkyl halide with any nucleophile under varying conditions.

The answer to this kind of question is to be found in the *relative rates of the reactions that occur*. If a given alkyl halide and nucleophile react *rapidly* by an S_N2 mechanism but *slowly* by an S_N1 mechanism under a given set of conditions, then an S_N2 pathway will be followed by most of the molecules. On the other hand, another alkyl halide and another nucleophile may react very slowly (or not at all) by an S_N2 pathway. If they react rapidly by an S_N1 mechanism, then the reactants will follow an S_N1 pathway.

- A number of factors affect the relative rates of S_N1 and S_N2 reactions. The most important factors are:

1. the structure of the substrate,
2. the concentration and reactivity of the nucleophile (for S_N2 reactions only),
3. the effect of the solvent, and
4. the nature of the leaving group.

6.13A The Effect of the Structure of the Substrate

S_N2 Reactions Simple alkyl halides show the following general order of reactivity in S_N2 reactions:

Methyl > primary > secondary ≫ (tertiary—unreactive)

Methyl halides react most rapidly, and tertiary halides react so slowly as to be unreactive by the S_N2 mechanism. Table 6.3 gives the relative rates of typical S_N2 reactions.

Neopentyl halides, even though they are primary halides, are very unreactive:

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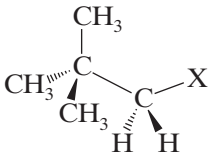
Table 6.3 Relative Rates of Reactions of Alkyl Halides in S_N2 Reactions

Substituent	Compound	Approximate Relative Rate
Methyl	CH_3X	30
1°	CH_3CH_2X	1
2°	$(CH_3)_2CHX$	0.03
Neopentyl	$(CH_3)_3CCH_2X$	0.00001
3°	$(CH_3)_3CX$	~0



A neopentyl halide

The important factor behind this order of reactivity is a steric effect, and in this case, steric hindrance.

- A **steric effect** is an effect on the relative rates caused by the space-filling properties of those parts of a molecule attached at or near the reacting site.
- **Steric hindrance** is when the spatial arrangement of atoms or groups at or near a reacting site of a molecule hinders or retards a reaction.

For particles (molecules and ions) to react, their reactive centers must be able to come within bonding distance of each other. Although most molecules are reasonably flexible, very large and bulky groups can often hinder the formation of the required transition state. In some cases they can prevent its formation altogether.

An S_N2 reaction requires an approach by the nucleophile to a distance within the bonding range of the carbon atom bearing the leaving group. Because of this, bulky substituents on *or near* that carbon atom have a dramatic inhibiting effect (Fig. 6.8). Nearby bulky groups cause the free energy of an S_N2 transition state to be higher and, consequently, the free energy of activation for the reaction is larger, and the rate of reaction is slower. Of the simple alkyl halides, methyl halides react most rapidly in S_N2 reactions because only three small hydrogen atoms interfere with the approaching nucleophile. Neopentyl and tertiary halides are the least reactive because bulky groups present a strong hindrance to the approaching nucleophile. (Tertiary substrates, for all practical purposes, do not react by an S_N2 mechanism.)

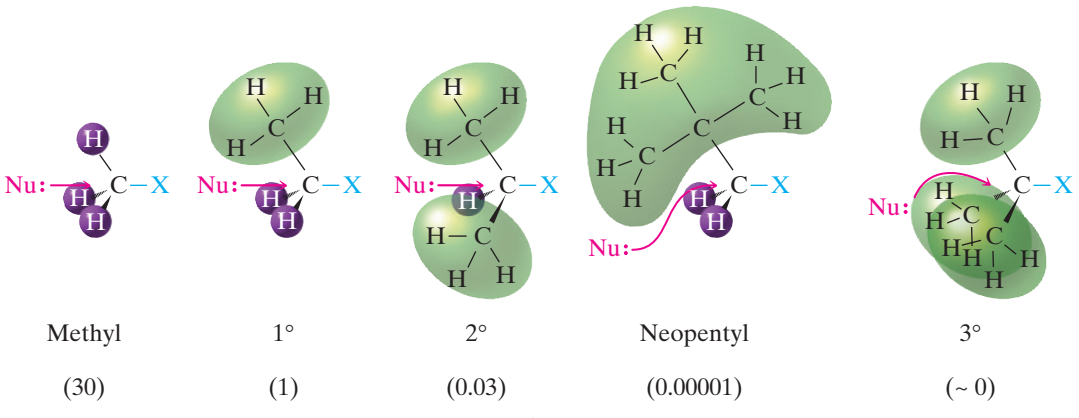


Figure 6.8 Steric effects and relative rates in the S_N2 reaction.

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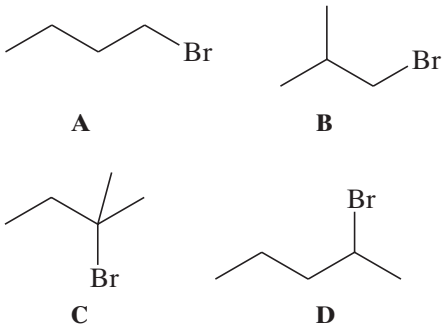
Solved Problem 6.6

Rank the following alkyl bromides in order of decreasing reactivity (from fastest to slowest) as a substrate in an S_N2 reaction.



A **B** **C** **D**

Answer

We examine the carbon bearing the leaving group in each instance to assess the steric hindrance to an S_N2 reaction at that carbon. In **C** it is 3°; therefore, three groups would hinder the approach of a nucleophile, so this alkyl bromide would react most slowly. In **D** the carbon bearing the leaving group is 2° (two groups hinder the approach of the nucleophile), while in both **A** and **B** it is 1° (one group hinders the nucleophile's approach). Therefore, **D** would react faster than **C**, but slower than either **A** or **B**. But, what about **A** and **B**? They are both 1° alkyl bromides, but **B** has a methyl group on the carbon adjacent to the one bearing the bromine, which would provide steric hindrance to the approaching nucleophile that would not be present in **A**. The order of reactivity, therefore, is **A** > **B** > **D** ≫ **C**.

S_N1 Reactions

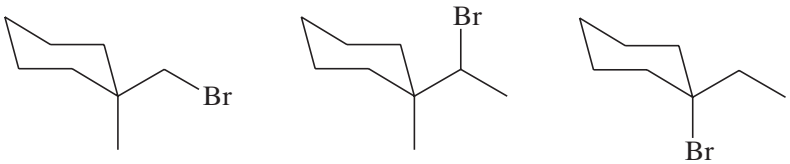
- The primary factor that determines the reactivity of organic substrates in an S_N1 reaction is the relative stability of the carbocation that is formed.

Of the simple alkyl halides that we have studied so far, this means (for all practical purposes) that only tertiary halides react by an S_N1 mechanism. (Later we shall see that certain organic halides, called *allylic halides* and *benzylic halides*, can also react by an S_N1 mechanism because they can form relatively stable carbocations; see Section 14.15.)

Tertiary carbocations are stabilized because sigma bonds at three adjacent carbons contribute electron density to the carbocation *p* orbital by hyperconjugation (Section 6.11B). Secondary and primary carbocations have less stabilization by hyperconjugation. A methyl carbocation has no stabilization. Formation of a relatively stable carbocation is important in an S_N1 reaction because it means that the free energy of activation for the slow step of the reaction (e.g., R—L $\longrightarrow$ $R^+ + L^-$) will be low enough for the reaction to take place at a reasonable rate.

Practice Problem 6.9

Which of the following alkyl halides is most likely to undergo substitution by an S_N1 mechanism?



(a) **(b)** **(c)**

The Hammond–Leffler Postulate If you review the free-energy diagrams that accompany the mechanism for the S_N1 reaction of *tert*-butyl chloride and water (Section 6.10), you will see that step 1, the ionization of the leaving group to form the carbocation, is *uphill in terms of free energy* ($\Delta G°$ for this step is positive). It is also uphill in terms of enthalpy ($\Delta H°$ is also positive), and, therefore, this step is *endothermic*.

- According to the **Hammond–Leffler postulate**, **the transition-state structure for a step that is uphill in energy should show a strong resemblance to the structure of the product of that step**.

Since the product of this step (actually an intermediate in the overall reaction) is a carbocation, any factor that stabilizes the carbocation—such as dispersal of the positive charge by electron-releasing groups—should also stabilize the transition state in which the positive charge is developing.

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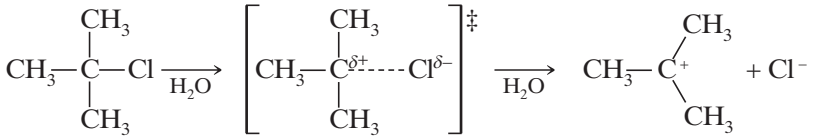
Ionization of the Leaving Group



A methyl, primary, or secondary alkyl halide would have to ionize to form a methyl, primary, or secondary carbocation to react by an S_N1 mechanism. These carbocations, however, are much higher in energy than a tertiary carbocation, and the transition states leading to these carbocations are even higher in energy.

- The activation energy for an S_N1 reaction of a simple methyl, primary, or secondary halide is so large (therefore the reaction is so slow) that, for all practical purposes, an S_N1 reaction with a methyl, primary, or secondary halide does not compete with the corresponding S_N2 reaction.

The Hammond–Leffler postulate is quite general and can be better understood through consideration of Fig. 6.9. One way that the postulate can be stated is to say that *the structure of a transition state resembles the stable species that is nearest it in free energy*. For example, in a highly **endergonic** step (blue curve) the transition state lies close to the products in free energy, and we assume, therefore, that **it resembles the products of that step in structure**. Conversely, in a highly exergonic step (red curve) the transition state lies close to the reactants in free energy, and we assume **it resembles the reactants in structure** as well. The great value of the Hammond–Leffler postulate is that it gives us an intuitive way of visualizing those important, but fleeting, species that we call transition states. We shall make use of it in many future discussions.

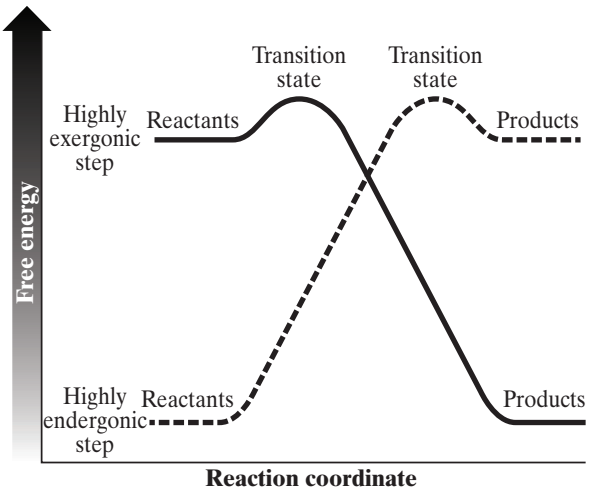


Figure 6.9 The transition state for a highly exergonic step (—— curve) lies close to and resembles the reactants. The transition state for an endergonic step (- - - - curve) lies close to and resembles the products of a reaction. (Reprinted with permission of the McGraw-Hill Companies from Pryor, W., *Free Radicals*, p. 156, copyright 1966.)

Practice Problem 6.10

The relative rates of ethanolysis of four primary alkyl halides are as follows: CH_3CH_2Br, 1.0; $CH_3CH_2CH_2Br$, 0.28; $(CH_3)_2CHCH_2Br$, 0.030; $(CH_3)_3CCH_2Br$, 0.00000042.

(a) Is each of these reactions likely to be S_N1 or S_N2?

(b) Provide an explanation for the relative reactivities that are observed.

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6.13B The Effect of the Concentration and Strength of the Nucleophile

- The rate of an S_N1 reaction is unaffected by either the concentration or the identity of the nucleophile, because the nucleophile does not participate in the rate-determining step of an S_N1 reaction.
- The rate of an S_N2 reaction depends on *both* the concentration *and* the identity of the attacking nucleophile.

We saw in Section 6.5 how increasing the concentration of the nucleophile increases the rate of an S_N2 reaction. We can now examine how the rate of an S_N2 reaction depends on the identity of the nucleophile.

- The relative strength of a nucleophile (its **nucleophilicity**) is measured in terms of the relative rate of its S_N2 reaction with a given substrate.

A good nucleophile is one that reacts rapidly in an S_N2 reaction with a given substrate. A poor nucleophile is one that reacts slowly in an S_N2 reaction with the same substrate under comparable reaction conditions. (As mentioned above, we cannot compare nucleophilicities with regard to S_N1 reactions because the nucleophile does not participate in the rate-determining step of an S_N1 reaction.)

Methoxide anion, for example, is a good nucleophile for a substitution reaction with iodomethane. It reacts rapidly by an S_N2 mechanism to form dimethyl ether:

$$CH_3O^- + CH_3I \xrightarrow{\text{rapid}} CH_3OCH_3 + I^-$$

Methanol, on the other hand, is a poor nucleophile for reaction with iodomethane. Under comparable conditions it reacts very slowly. It is not a sufficiently powerful Lewis base (i.e., nucleophile) to cause displacement of the iodide leaving group at a significant rate:

$$\mathbf{CH_3OH} + CH_3\mathbf{I} \xrightarrow{\text{very slow}} \mathbf{CH_3\overset{+}{O}HCH_3} + \mathbf{I^-}$$

- The relative strengths of nucleophiles can be correlated with three structural features:

1. **A negatively charged nucleophile is always a more reactive nucleophile than its conjugate acid**. Thus HO^- is a better nucleophile than H_2O and RO^- is better than ROH.
2. **In a group of nucleophiles in which the nucleophilic atom is the same, nucleophilicities parallel basicities**. Oxygen compounds, for example, show the following order of reactivity:

$$RO^- > HO^- \gg RCO_2^- > ROH > H_2O$$

This is also their order of basicity. An alkoxide ion (RO^-) is a slightly stronger base than a hydroxide ion (HO^-), a hydroxide ion is a much stronger base than a carboxylate ion (RCO_2^-), and so on.

3. **When the nucleophilic atoms are different, nucleophilicities may not parallel basicities**. For example, in protic solvents HS^-, $N{\equiv}C^-$, and I^- are all weaker bases than HO^-, yet they are **stronger nucleophiles** than HO^-.

$$HS^- > N{\equiv}C^- > I^- > HO^-$$

Nucleophilicity versus Basicity While nucleophilicity and basicity are related, they are not measured in the same way.

- Basicity, as expressed by pK_a, is measured *by the position of an equilibrium* in an acid–base reaction.
- Nucleophilicity is measured *by the relative rates of substitution reactions*.

For example, the hydroxide ion (HO^-) is a stronger base than a cyanide ion ($N{\equiv}C^-$); at equilibrium it has the greater affinity for a proton (the pK_a of H_2O is ~16, while the pK_a of HCN is ~10). Nevertheless, cyanide ion is a stronger nucleophile; it reacts more rapidly with a carbon bearing a leaving group than does hydroxide ion.

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Practice Problem 6.11

Rank the following in terms of *decreasing* nucleophilicity:

$CH_3CO_2^-$ CH_3OH CH_3O^- CH_3CO_2H $N{\equiv}C^-$

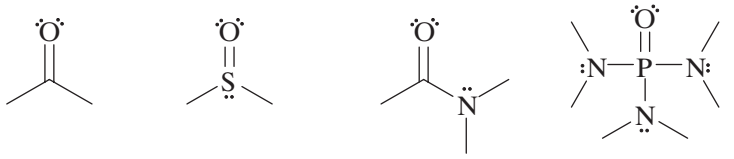
6.13C Solvent Effects in S_N2 and S_N1 Reactions

- S_N2 reactions are favored by **polar aprotic solvents** (e.g., acetone, DMF, DMSO).
- S_N1 reactions are favored by **polar protic solvents** (e.g., EtOH, MeOH, H_2O).

Important reasons for these **solvent effects** have to do with (a) minimizing the solvent's interaction with the nucleophile in S_N2 reactions, and (b) facilitating ionization of the leaving group and stabilizing ionic intermediates by solvents in S_N1 reactions. In the following subsections we will explain these factors in further detail.

Polar Aprotic Solvents Favor S_N2 Reactions

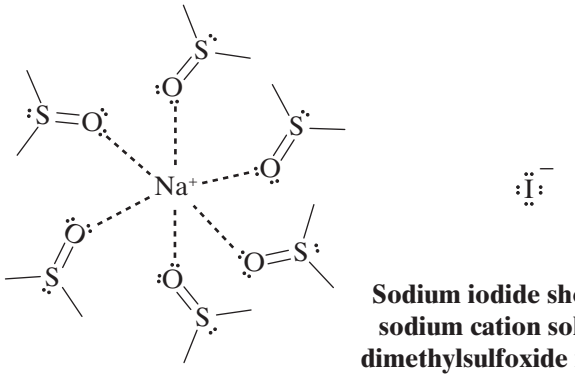
- An aprotic solvent does not have hydrogen atoms that are capable of hydrogen bonding.
- Polar, aprotic solvents such as acetone, DMF, DMSO, and HMPA are often used alone or as co-solvents for S_N2 reactions.



Acetone **DMSO (Dimethylsulfoxide)** **DMF (*N*,*N*-Dimethylformamide)** **HMPA (Hexamethyl phosphoramide)**

- The rates of S_N2 reactions generally are vastly increased when they are carried out in polar aprotic solvents. The increase in rate can be as large as a millionfold.

Polar aprotic solvents solubilize cations well using their unshared electron pairs, but do not interact as strongly with anions because they cannot hydrogen bond with them and because the positive regions of the solvent are shielded by steric effects from the anion. This differential solvation leaves anions more free to act as nucleophiles because they are less encumbered by the cation and solvent, thus enhancing the rate of S_N2 reaction. Sodium ions of sodium iodide, for example, can be solvated by DMSO as shown here, leaving the iodide anion more free to act as a nucleophile.



Sodium iodide showing the sodium cation solvated by dimethylsulfoxide molecules.

"Naked" anions in polar aprotic solvents are also more reactive as bases, as well as in their capacity as nucleophiles. In DMSO, for example, the relative order of halide ion basicity is the same as their relative order of nucleophilicity. Halide basicity is opposite to nucleophilicity in protic solvents, however, as we shall explain shortly.

F^- > Cl^- > Br^- > I^-

Halide nucleophilicity in aprotic solvents

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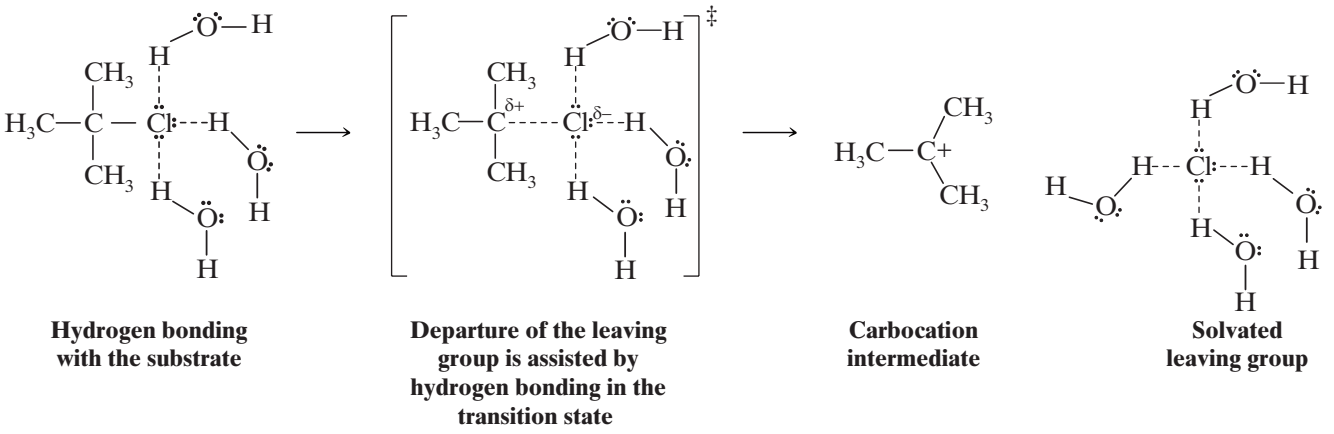
Helpful Hint: Polar aprotic solvents increase S_N2 rates.

Polar Protic Solvents Favor S_N1 Reactions

- A protic solvent has at least one hydrogen atom capable of participating in a hydrogen bond.
- Protic solvents, such as water, EtOH, and MeOH, facilitate formation of a carbocation by forming hydrogen bonds with the leaving group as it departs, thereby lowering the energy of the transition state leading to a carbocation.



A rough indication of a solvent's polarity is a quantity called the **dielectric constant**. The dielectric constant is a measure of the solvent's ability to insulate opposite charges (or separate ions) from each other. Electrostatic attractions and repulsions between ions are smaller in solvents with higher dielectric constants. Table 6.4 gives the dielectric constants of some common solvents.

Table 6.4 Dielectric Constants of Common Solvents

	Solvent	Formula	Dielectric Constant
↑	Water	H_2O	80
	Formic acid	HCO_2H	59
	Dimethyl sulfoxide (DMSO)	CH_3SOCH_3	49
Increasing	*N,N*-Dimethylformamide (DMF)	$HCON(CH_3)_2$	37
solvent	Acetonitrile	$CH_3C{\equiv}N$	36
polarity	Methanol	CH_3OH	33
	Hexamethylphosphoramide (HMPA)	$[(CH_3)_2N]_3P{=}O$	30
	Ethanol	CH_3CH_2OH	24
	Acetone	CH_3COCH_3	21
↓	Acetic acid	CH_3CO_2H	6

Water is the most effective solvent for promoting ionization, but most organic compounds do not dissolve appreciably in water. They usually dissolve, however, in alcohols, and quite often mixed solvents are used. Methanol—water and ethanol—water are common mixed solvents for nucleophilic substitution reactions.

Protic Solvents Hinder the Nucleophile in S_N2 Reactions

A solvated nucleophile must shed some of its solvent molecules to react with the substrate. In a polar aprotic solvent, the nucleophile is less unencumbered by solvent molecules because hydrogen bonding between the solvent and the nucleophile is not possible.

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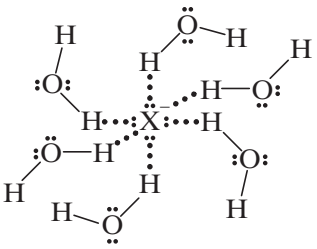
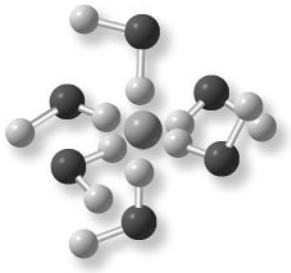
- Hydrogen bonding with a protic solvent such as water, EtOH, or MeOH, encumbers a nucleophile and hinders its reactivity in a nucleophilic substitution reaction.



Molecules of the protic solvent, water, solvate a halide ion by forming hydrogen bonds to it.



- The extent of hydrogen bonding with the nucleophile varies with the identity of the nucleophile. Hydrogen bonding with a small nucleophilic atom is stronger than to a larger nucleophilic atom among elements in the same group (column) of the periodic table.

For example, fluoride anion is more strongly solvated than the other halides because it is the smallest halide anion and its charge is the most concentrated. Hence, in a protic solvent fluoride is not as effective a nucleophile as the other halide anions. Iodide is the largest halide anion and it is the most weakly solvated in a protic solvent; hence, it is the strongest nucleophile among the halide anions.

- In a protic solvent, the general trend in *nucleophilicity* among the halide anions is as follows:

$$I^- > Br^- > Cl^- > F^-$$

Halide nucleophilicity in protic solvents

The same effect holds true when we compare sulfur nucleophiles with oxygen nucleophiles. Sulfur atoms are larger than oxygen atoms and hence they are not solvated as strongly in a protic solvent. Thus, thiols (R—SH) are stronger nucleophiles than alcohols, and RS^- anions are better nucleophiles than RO^- anions.

The greater reactivity of nucleophiles with large nucleophilic atoms is not entirely related to solvation. Larger atoms have greater **polarizability** (their electron clouds are more easily distorted); therefore, a larger nucleophilic atom can donate a greater degree of electron density to the substrate than a smaller nucleophile whose electrons are more tightly held.

The relative nucleophilicities of some common nucleophiles in protic solvents are as follows:

$$HS^- > N{\equiv}C^- > I^- > HO^- > N_3^- > Br^- > CH_3CO_2^- > Cl^- > F^- > H_2O$$

Relative nucleophilicity in protic solvents

Practice Problem 6.12

Rank the following in terms of decreasing nucleophilicity in a protic solvent.

$CH_3CO_2^-$ CH_3O^- CH_3S^- CH_3SH CH_3OH

Practice Problem 6.13

Classify the following solvents as being protic or aprotic: formic acid, HCO_2H; acetone, CH_3COCH_3; acetonitrile, $CH_3C{\equiv}N$; formamide, $HCONH_2$; sulfur dioxide, SO_2; ammonia, NH_3; trimethylamine, $N(CH_3)_3$; ethylene glycol, $HOCH_2CH_2OH$.

Practice Problem 6.14

Would you expect the reaction of propyl bromide with sodium cyanide (NaCN), that is,

$$CH_3CH_2CH_2Br + NaCN \longrightarrow CH_3CH_2CH_2CN + NaBr$$

to occur faster in DMF or in ethanol? Explain your answer.

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Practice Problem 6.15

Which would you expect to be the stronger nucleophile in a polar aprotic solvent?
(a) $CH_3CO_2^-$ or CH_3O^- **(b)** H_2O or H_2S **(c)** $(CH_3)_3P$ or $(CH_3)_3N$

Practice Problem 6.16

When *tert*-butyl bromide undergoes solvolysis in a mixture of methanol and water, the rate of solvolysis (measured by the rate at which bromide ions form in the mixture) *increases* when the percentage of water in the mixture is increased. **(a)** Explain this occurrence. **(b)** Provide an explanation for the observation that the rate of the S_N2 reaction of ethyl chloride with potassium iodide in methanol and water *decreases* when the percentage of water in the mixture is increased.

6.13D The Nature of the Leaving Group

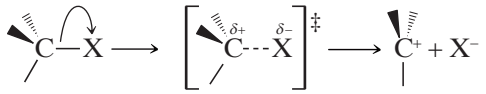
- Leaving groups depart with the electron pair that was used to bond them to the substrate.
- The best leaving groups are those that become either a relatively stable anion or a neutral molecule when they depart.

First, let us consider leaving groups that become anions when they separate from the substrate. Because weak bases stabilize a negative charge effectively, leaving groups that become weak bases are good leaving groups.

Helpful Hint: Good leaving groups are weak bases.

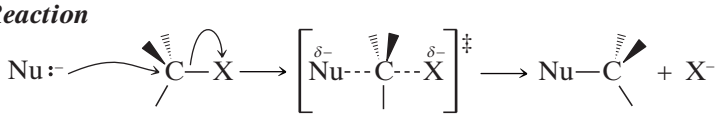
The reason that stabilization of the negative charge is important can be understood by considering the structure of the transition states. In either an S_N1 or S_N2 reaction the leaving group begins to acquire a negative charge as the transition state is reached:

S_N1 Reaction (Rate-Limiting Step)



Transition state

S_N2 Reaction



Transition state

Stabilization of this developing negative charge at the leaving group stabilizes the transition state (lowers its free energy); this lowers the free energy of activation and thereby increases the rate of the reaction.

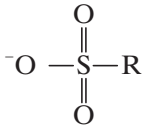
- Among the halogens, an iodide ion is the best leaving group and a fluoride ion is the poorest:

$$I^- > Br^- > Cl^- \gg F^-$$

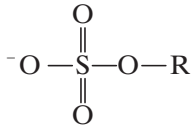
The order is the opposite of the basicity in an aprotic solvent:

$$F^- \gg Cl^- > Br^- > I^-$$

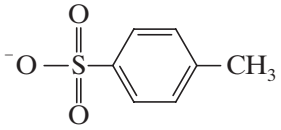
Other weak bases that are good leaving groups, which we shall study later, are alkanesulfonate ions, alkyl sulfate ions, and the *p*-toluenesulfonate ion:



An alkanesulfonate ion



An alkyl sulfate ion



***p*-Toluenesulfonate ion**

These anions are all the conjugate bases of very strong acids.

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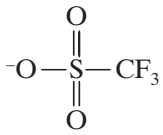
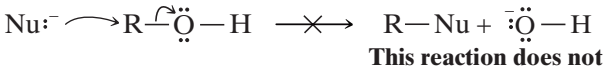
The trifluoromethanesulfonate ion ($CF_3SO_3^-$, commonly called the **triflate ion**) is one of the best leaving groups known to chemists. It is the conjugate base of CF_3SO_3H, an exceedingly strong acid (pK_a ~ –5 to –6):



Triflate ion
(a "super" leaving group)

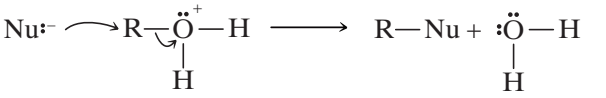
- Strongly basic ions rarely act as leaving groups.

The hydroxide ion, for example, is a strong base and thus reactions like the following do not take place:



This reaction does not take place because the leaving group is a strongly basic hydroxide ion.

However, when an alcohol is dissolved in a strong acid, it can undergo substitution by a nucleophile. Because the acid protonates the —OH group of the alcohol, the leaving group no longer needs to be a hydroxide ion; it is now a molecule of water—a much weaker base than a hydroxide ion and a good leaving group:



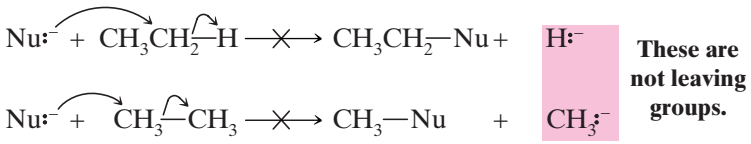
This reaction takes place because the leaving group is a weak base.

Practice Problem 6.17

List the following compounds in order of decreasing reactivity toward CH_3O^- in an S_N2 reaction carried out in CH_3OH: CH_3F, CH_3Cl, CH_3Br, CH_3I, $CH_3OSO_2CF_3$, $^{14}CH_3OH$.

- Very powerful bases such as hydride ions ($H:^-$) and alkanide ions ($R:^-$) virtually never act as leaving groups.

Therefore, **reactions such as the following are not feasible**:

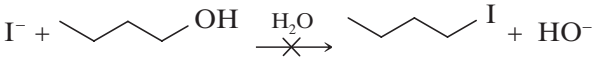


These are not leaving groups.

Remember: The best leaving groups are weak bases after they depart.

Solved Problem 6.7

Explain why the following reaction is not feasible as a synthesis of butyl iodide.



Answer

The strongly basic HO^- ion (hydroxide ion) virtually never acts as a leaving group, something this reaction would require. This reaction would be feasible under acidic conditions, in which case the leaving group would be a water molecule.

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SUMMARY OF S_N1 VERSUS S_N2 REACTIONS

S_N1: The Following Conditions Favor an S_N1 Reaction

1. A substrate that can form a relatively stable carbocation (such as a substrate with a leaving group at a tertiary position).
2. A relatively weak nucleophile.
3. A polar, protic solvent such as EtOH, MeOH, or H_2O.

The S_N1 mechanism is, therefore, important in solvolysis reactions of tertiary alkyl halides, especially when the solvent is highly polar. In a solvolysis reaction the nucleophile is weak because it is a neutral molecule (of the polar protic solvent) rather than an anion.

S_N2: The Following Conditions Favor an S_N2 Reaction

1. A substrate with a relatively unhindered leaving group (such as a methyl, primary, or secondary alkyl halide). The order of reactivity is

$$\underset{\textbf{Methyl}}{CH_3-X} > \underset{\textbf{1°}}{R-CH_2-X} > \underset{\textbf{2°}}{R-\overset{\overset{R}{|}}{CH}-X}$$

   Tertiary halides do not react by an S_N2 mechanism.

2. A strong nucleophile (usually negatively charged).
3. High concentration of the nucleophile.
4. A polar, aprotic solvent.

The trend in reaction rate for a halogen as the leaving group is the same in S_N1 and S_N2 reactions:

$$R{-}I > R{-}Br > R{-}Cl \qquad S_N1 \text{ or } S_N2$$

Because alkyl fluorides react so slowly, they are seldom used in nucleophilic substitution reactions.

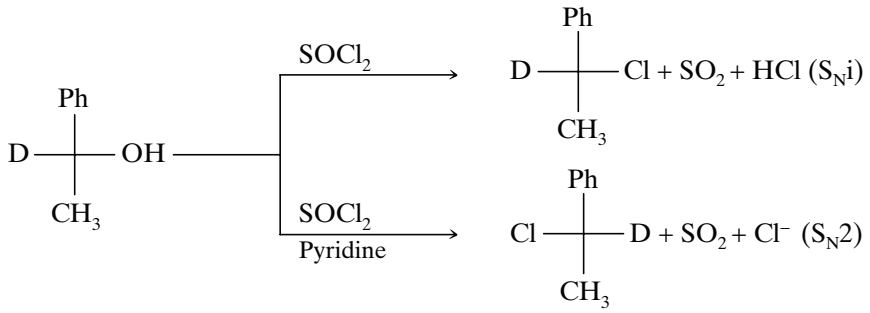
These factors are summarized in Table 6.5.

Table 6.5 Factors Favoring S_N1 versus S_N2 Reactions

Factor	S_N1	S_N2
Substrate	3° (requires formation of a relatively stable carbocation)	Methyl > 1° > 2° (requires unhindered substrate)
Nucleophile	Weak Lewis base, neutral molecule, nucleophile may be the solvent (solvolysis)	Strong Lewis base, rate increased by high concentration of nucleophile
Solvent	Polar protic (e.g., alcohols, water)	Polar aprotic (e.g., DMF, DMSO)
Leaving group	I > Br > Cl > F for both S_N1 and S_N2 (the weaker the base after the group departs, the better the leaving group)	

6.13E S_Ni Mechanism: Retention of Configuration

If an optically active alcohol undergoes reaction with thionyl chloride, the product retains the configuration. However, if the reaction is carried out with thionyl chloride in presence of pyridine, then inversion of configuration takes place.



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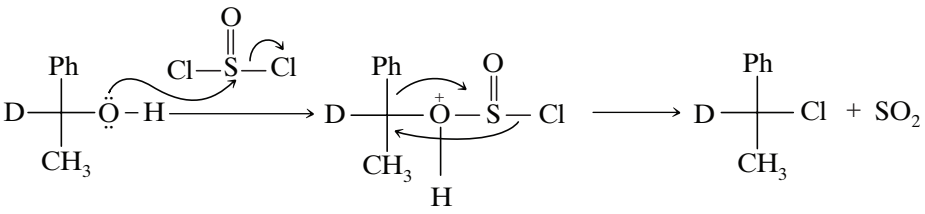
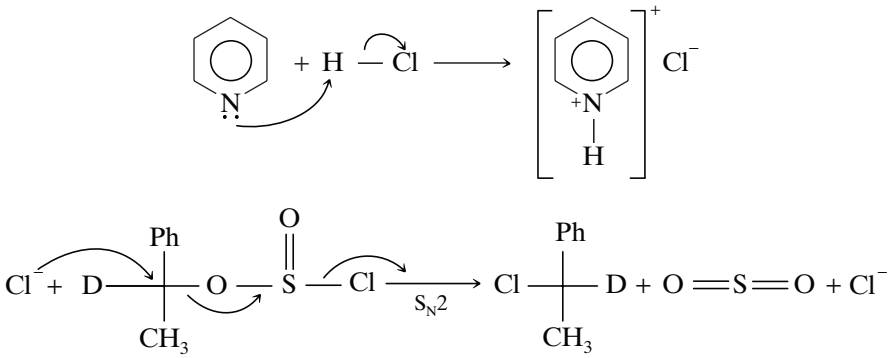
The mechanism of the first reaction can be explained as follows:



The attack of internal nucleophile and removal of the leaving group will be from the same side, therefore, there will be retention of configuration. It is a second order reaction that follows the rate equation

$$\text{Rate} = K\,[\text{alcohol}]\,[SOCl_2]$$

This rate is similar to the rate of S_N2 reaction but there is retention of configuration. However, in the presence of pyridine (a base), a better nuclecophile Cl^- will be generated by an acid–base reaction.



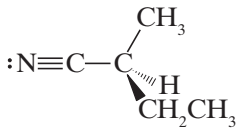
6.14 | ORGANIC SYNTHESIS: FUNCTIONAL GROUP TRANSFORMATIONS USING S_N2 REACTIONS

S_N2 reactions are highly useful in organic synthesis because they enable us to convert one functional group into another—a process that is called a **functional group transformation** or a **functional group interconversion**. With the S_N2 reactions shown in Fig. 6.10, methyl, primary, or secondary alkyl halides can be transformed into alcohols, ethers, thiols, thioethers, nitriles, esters, and so on. (*Note*: The use of the prefix *thio-* in a name means that a sulfur atom has replaced an oxygen atom in the compound.)

Alkyl chlorides and bromides are also easily converted to alkyl iodides by nucleophilic substitution reactions.

$$\left.\begin{matrix}\text{R—Cl}\\ \text{or}\\ \text{R—Br}\end{matrix}\right\} \xrightarrow{I^-} \text{R—I}\ (+Cl^-\ \text{or}\ Br^-)$$

One other aspect of the S_N2 reaction that is of great importance is **stereochemistry** (Section 6.8). S_N2 reactions always occur with **inversion of configuration** at the atom that bears the leaving group. This means that when we use S_N2 reactions in syntheses we can be sure of the configuration of our product if we know the configuration of our reactant. For example, suppose we need a sample of the following nitrile with the (*S*) configuration:



(*S*)-2-Methylbutanenitrile

If we have available (*R*)-2-bromobutane, we can carry out the following synthesis:

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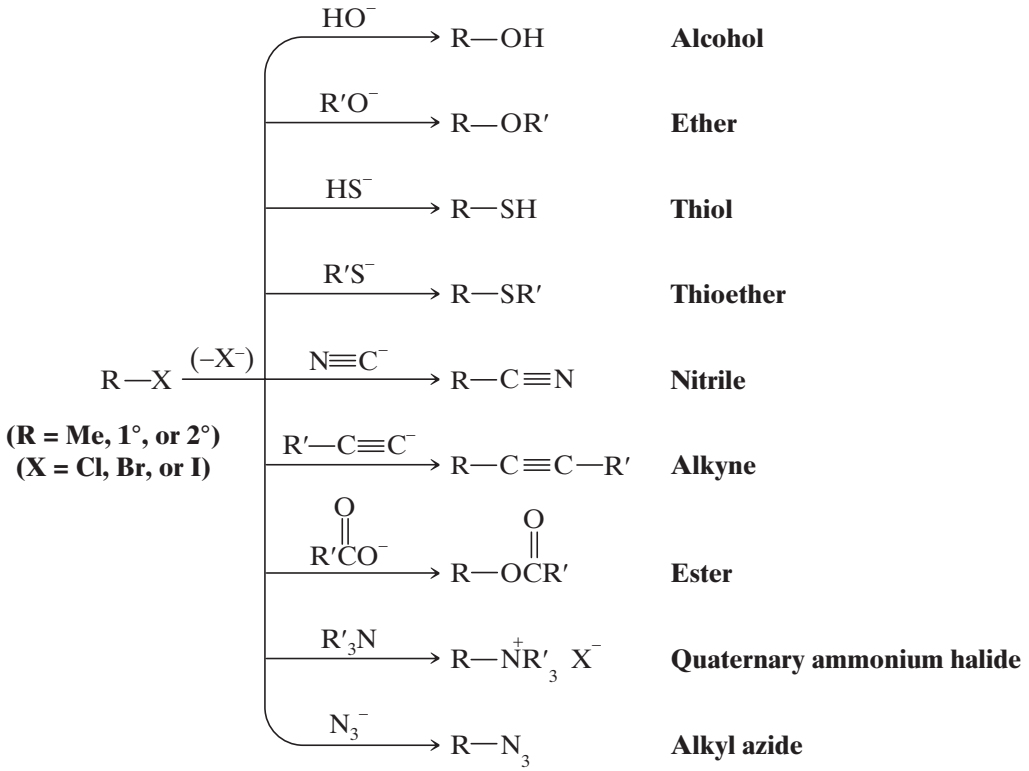
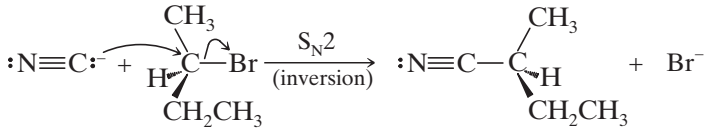


Figure 6.10 Functional group interconversions of methyl, primary, and secondary alkyl halides using S_N2 reactions.



(*R*)-2-Bromobutane (*S*)-2-Methylbutanenitrile

Practice Problem 6.18

Starting with (*S*)-2-bromobutane, outline syntheses of each of the following compounds:

(a) (*R*)-$CH_3CHCH_2CH_3$ (OCH_2CH_3)

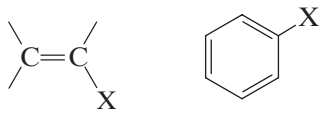
(b) (*R*)-$CH_3CHCH_2CH_3$ ($OCCH_3$, O)

(c) (*R*)-$CH_3CHCH_2CH_3$ (SH)

(d) (*R*)-$CH_3CHCH_2CH_3$ (SCH_3)

6.14A The Unreactivity of Vinylic and Phenyl Halides

As we learned in Section 6.1, compounds that have a halogen atom attached to one carbon atom of a double bond are called **alkenyl** or **vinylic halides**; those that have a halogen atom attached to a benzene ring are called **aryl** or **phenyl halides**:



An alkenyl halide **A phenyl halide**

- Alkenyl and phenyl halides are generally unreactive in S_N1 or S_N2 reactions.

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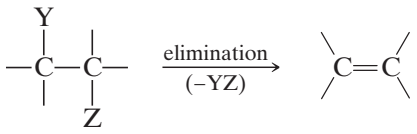
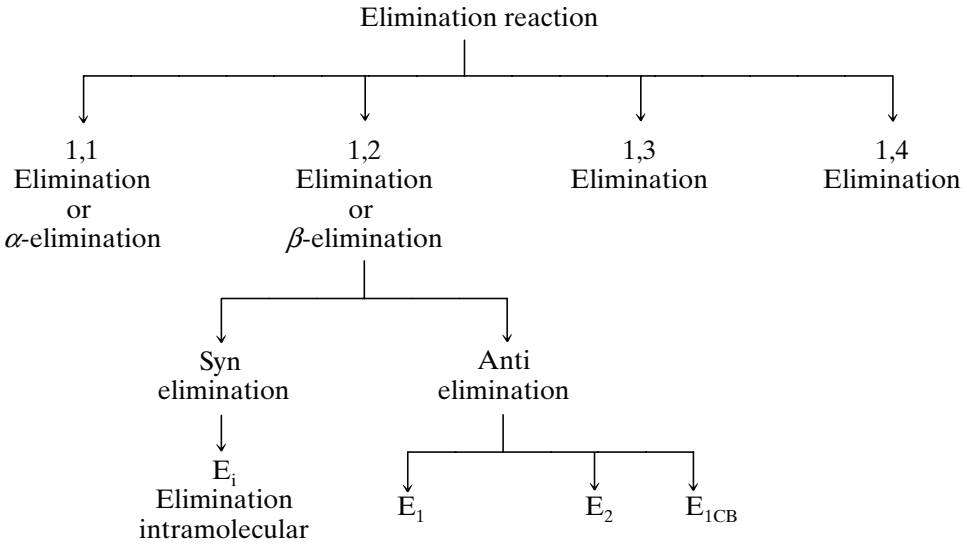
They are unreactive in S_N1 reactions because alkenyl and phenyl cations are relatively unstable and do not form readily. They are unreactive in S_N2 reactions because the carbon–halogen bond of an alkenyl or phenyl halide is stronger than that of an alkyl halide (we shall see why later), and the electrons of the double bond or benzene ring repel the approach of a nucleophile from the back side.

6.15 | ELIMINATION REACTIONS OF ALKYL HALIDES

Elimination reactions of alkyl halides are important reactions that compete with substitution reactions. In an **elimination reaction** the fragments of some molecule (YZ) are removed (eliminated) from adjacent atoms of the reactant. This elimination leads to the creation of a multiple bond:



In other words, the reaction in which two atoms or groups are removed from a compound is referred to as an elimination reaction. The elimination reaction can be classified as shown below:



6.15A 1,1-Elimination or α-Elimination

Removal of two atoms or groups attached to the same atom is known as 1,1-elimination or α-elimination. For example, the formation of carbene in the following reactions:

1. $CHCl_3 \xrightarrow[\Delta]{KOH} K\overset{+}{}\overset{-}{O}CCl_3 \xrightarrow{\Delta} K{-}Cl + Cl{-}\ddot{C}{-}Cl$ (Dichlorocarbene)

2. $Ph{-}CHCl_2 \xrightarrow{t\text{–}Bu{-}\overset{-}{O}\overset{+}{K}} K\overset{+}{}\overset{-}{C}Cl_2Ph \longrightarrow KCl + Ph{-}\ddot{C}{-}Cl$

3. $CH_3{-}CH_2{-}Cl \xrightarrow[Ph-Na]{\delta-\ \ \delta+} CH_3{-}\overset{-}{C}H{-}Cl\ \overset{+}{N}a \longrightarrow CH_3{-}CH{:} + NaCl$

The reagent Ph^-Na^+ is a strong base, is taken in decane solution. The carbene is produced to the extent of 94% in this reaction.

6.15B 1,2-Elimination or β-Elimination

Removal of two atoms or groups from adjacent atoms is known as 1,2-elimination or β-elimination.

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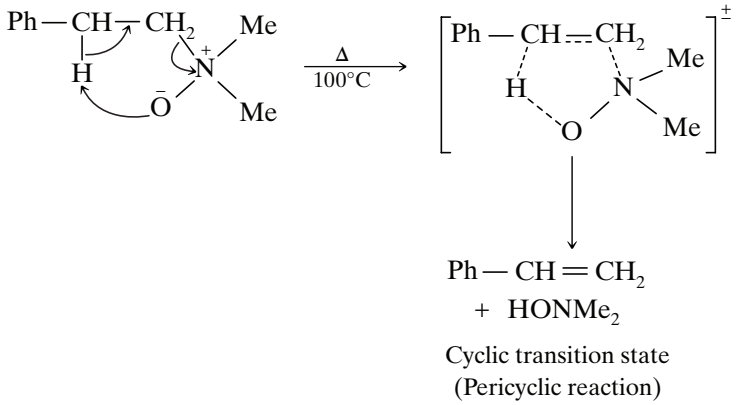
Pyrolytic Syn Elimination Ei (Elimination Intramolecular): A number of organic compounds such as an amine oxide, ester or xanthate undergo pyrolytic elimination of HX (in the absence of any reagent), either in an inert solvent or, in some cases, in the gas phase.

In general these eliminations follow the rate law:

$$\text{Rate} = K\,[\text{substrate}]$$

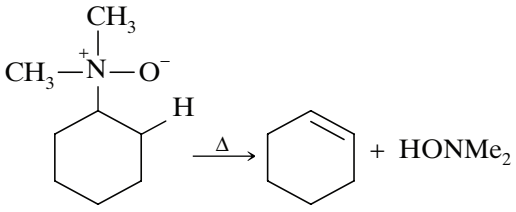
6.15C Cope Reaction

When a tertiary amine oxide is heated at approximately 100°C, elimination reaction takes place as follows:



Elimination of the above type is named as Cope reaction. H and NMe_2O must lie on the same side for elimination as Me_2NOH. The reaction proceeds via a five-membered cyclic transition state. Some examples of Cope reaction are:

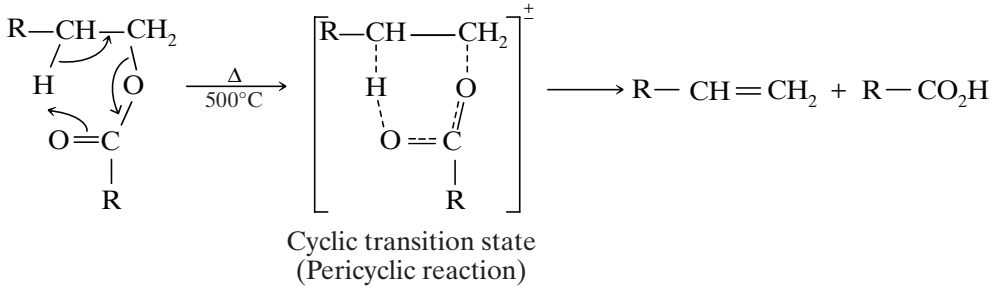
1.



2. $CH_3-CH_2-\overset{\overset{CH_3}{|}}{\underset{\underset{O^-}{|}}{N^+}}-CH_3 \xrightarrow{\Delta} H_2C=CH_2 + HONMe_2$

6.15D Pyrolysis of Esters

Pyrolysis of an ester takes place when it is heated at 500°C.



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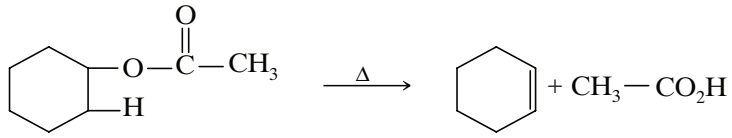
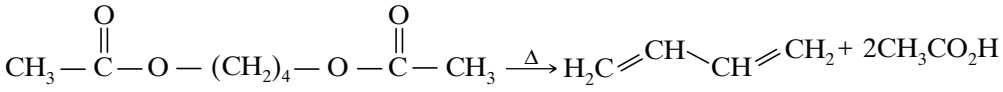
Some examples of pyrolysis of esters are:

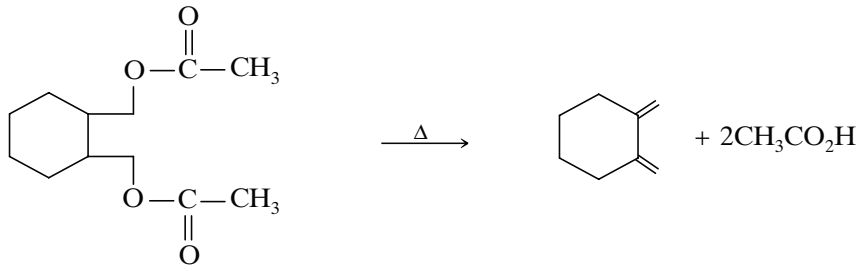
1.



2.

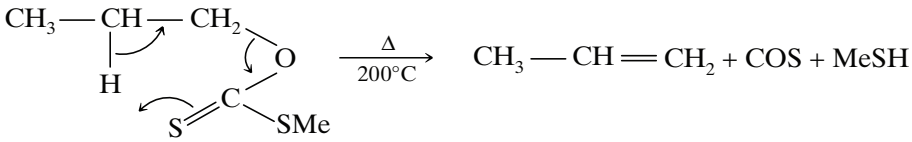


3.

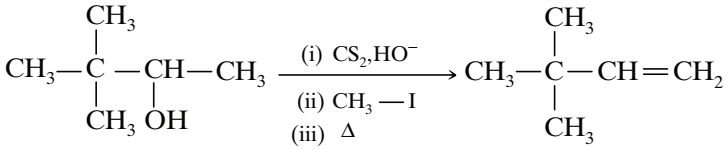


6.15E Pyrolysis of Xanthates or Chugaev Reaction

o-Alkyl-*S*-methyl xanthate is pyrolyzed at 200°C to give an alkene, carbon oxysulphide and methanethiol as the products.



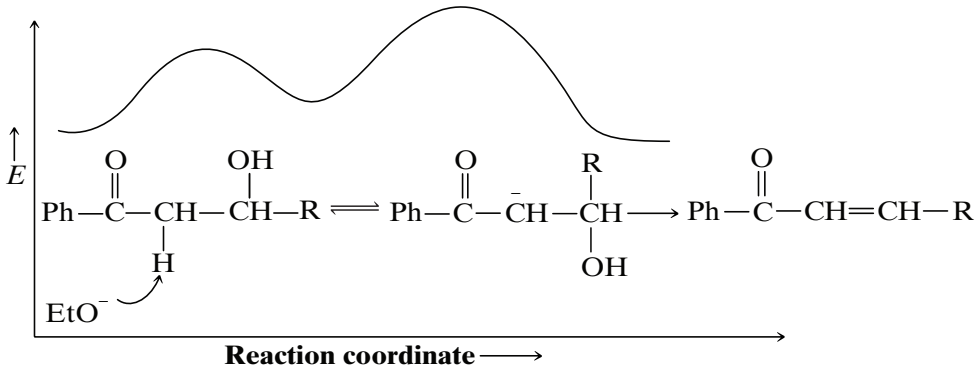
This type of thermal decomposition is called normal Chugaev reaction.



6.15F E_{1CB} (Elimination from Conjugate Base)

In E_{1CB}, the formation of the carbanion intermediate is fast and reversible and the loss of the leaving group is slow and rate limiting. This elimination is bimolecular.

A bimolecular E_{1CB} reaction and its energy profile is given below:



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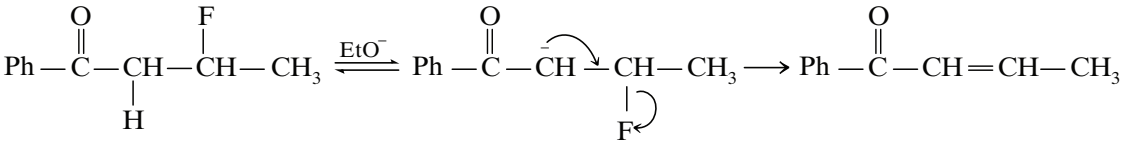
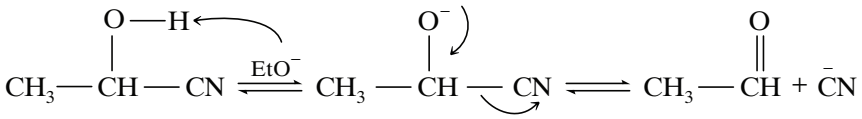
The examples of E_{1CB} are as follows:

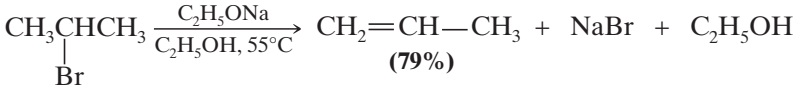


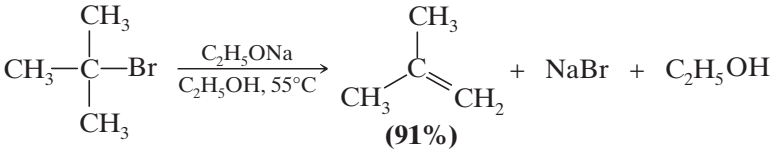
The base induced elimination of cyanohydrin is by E_{1CB}.



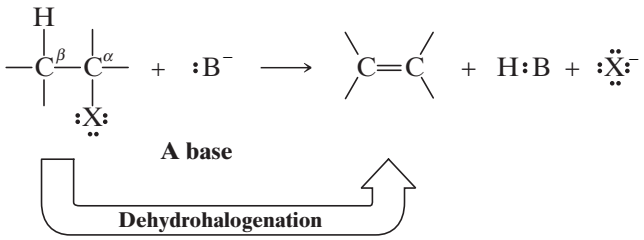
6.15G Dehydrohalogenation

A widely used method for synthesizing alkenes is the elimination of HX from adjacent atoms of an alkyl halide. Heating the alkyl halide with a strong base causes the reaction to take place. The following are two examples:



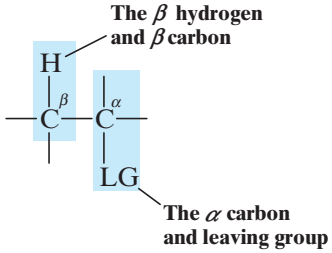


Reactions like these are not limited to the elimination of hydrogen bromide. Chloroalkanes also undergo the elimination of hydrogen chloride, iodoalkanes undergo the elimination of hydrogen iodide, and, in all cases, alkenes are produced. When the elements of a hydrogen halide are eliminated from a haloalkane in this way, the reaction is often called **dehydrohalogenation**:



In these eliminations, as in S_N1 and S_N2 reactions, there is a leaving group and an attacking Lewis base that possesses an electron pair.

Chemists often call the carbon atom that bears the leaving group (e.g., the halogen atom in the previous reaction) the **alpha (α) carbon atom** and any carbon atom adjacent to it a **beta (β) carbon atom**. A hydrogen atom attached to the β carbon atom is called a **β hydrogen atom**. Since the hydrogen atom that is eliminated in dehydrohalogenation is from the β carbon atom, these reactions are often called **β eliminations**. They are also often referred to as **1,2 eliminations**.



We shall have more to say about dehydrohalogenation in Chapter 7, but we can examine several important aspects here.

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6.15H Bases Used in Dehydrohalogenation

Various strong bases have been used for dehydrohalogenations. Potassium hydroxide dissolved in ethanol (KOH/EtOH) is a reagent sometimes used, but the conjugate bases of alcohols, such as sodium ethoxide (EtONa), often offer distinct advantages.

The conjugate base of an alcohol (an alkoxide) can be prepared by treating an alcohol with an alkali metal. For example:

$$2\ R{-}\ddot{O}H + 2\ Na \longrightarrow 2\ R{-}\ddot{O}{:}^{-}\ Na^{+} + H_2$$

Alcohol — **Sodium alkoxide**

This reaction is an **oxidation–reduction reaction**. Metallic sodium reacts with hydrogen atoms that are bonded to oxygen atoms to generate hydrogen gas, sodium cations, and the alkoxide anion. The reaction with water is vigorous and at times explosive.

$$2\ H\ddot{O}H + 2\ Na \longrightarrow 2\ H\ddot{O}{:}^{-}\ Na^{+} + H_2$$

Sodium hydroxide

Sodium alkoxides can also be prepared by allowing an alcohol to react with sodium hydride (NaH). The hydride ion ($H:^-$) is a very strong base. (The pK_a of H_2 is 35.)

$$R{-}\ddot{O}{-}H + Na^{+}{:}H^{-} \longrightarrow R{-}\ddot{O}{:}^{-}\ Na^{+} + H{-}H$$

Sodium (and potassium) alkoxides are usually prepared by using an excess of the alcohol, and the excess alcohol becomes the solvent for the reaction. Sodium ethoxide is frequently prepared in this way using excess ethanol.

$$2\ CH_3CH_2\ddot{O}H + 2\ Na \longrightarrow 2\ CH_3CH_2\ddot{O}{:}^{-}\ Na^{+} + H_2$$

Ethanol (excess) — **Sodium ethoxide dissolved in excess ethanol**

Potassium *tert*-butoxide (*t*-BuOK) is another highly effective dehydrohalogenating reagent. It can be made by the reaction below, or purchased as a solid.

$$2\ \begin{matrix}CH_3\\ |\\ CH_3{-}C{-}\ddot{O}H\\ |\\ CH_3\end{matrix} + 2\ K \longrightarrow 2\ \begin{matrix}CH_3\\ |\\ CH_3{-}C{-}\ddot{O}{:}^{-}\\ |\\ CH_3\end{matrix}\ K^{+} + H_2$$

***tert*-Butanol (excess)** — **Potassium *tert*-butoxide**

6.15I Mechanisms of Dehydrohalogenations

Elimination reactions occur by a variety of mechanisms. With alkyl halides, two mechanisms are especially important because they are closely related to the S_N2 and S_N1 reactions that we have just studied. One mechanism, called the **E2 reaction**, is bimolecular in the rate-determining step; the other mechanism is the **E1 reaction**, which is unimolecular in the rate-determining step.

6.16 | THE E2 REACTION

When isopropyl bromide is heated with sodium ethoxide in ethanol to form propene, the reaction rate depends on the concentration of isopropyl bromide and the concentration of ethoxide ion. The rate equation is first order in each reactant and second order overall:

$$\text{Rate} = k[CH_3CHBrCH_3][C_2H_5O^{-}]$$

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- From the reaction order we infer that the transition state for the rate-determining step must involve both the alkyl halide and the alkoxide ion: The reaction must be bimolecular. We call this type of elimination an E2 reaction.

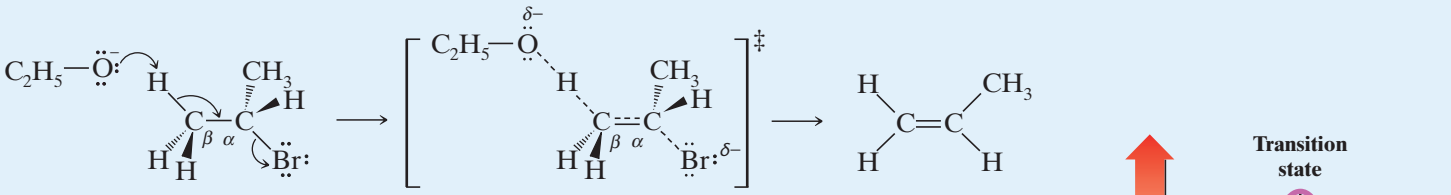
Considerable experimental evidence indicates that an E2 reaction takes place in the following way:

A MECHANISM FOR THE REACTION — Mechanism for the E2 Reaction

Reaction

$$C_2H_5O^- + CH_3CHBrCH_3 \longrightarrow CH_2{=}CHCH_3 + C_2H_5OH + Br^-$$

Mechanism



The basic ethoxide ion begins to remove a proton from the β carbon using its electron pair to form a bond to it. At the same time, the electron pair of the β C—H bond begins to move in to become the π bond of a double bond, and the bromine begins to depart with the electrons that bonded it to the α carbon.

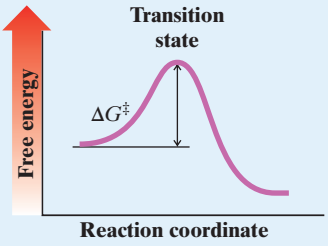
Transition state

Partial bonds in the transition state extend from the oxygen atom that is removing the β hydrogen, through the carbon skeleton of the developing double bond, to the departing leaving group. The flow of electron density is from the base toward the leaving group as an electron pair fills the π bonding orbital of the alkene.

+

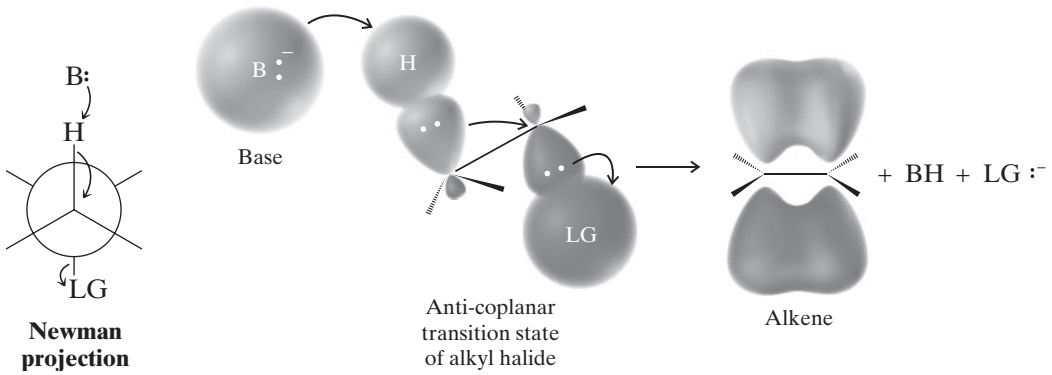
$C_2H_5{-}\ddot{O}H + :\ddot{B}r:^-$

At completion of the reaction, the double bond is fully formed and the alkene has a trigonal planar geometry at each carbon atom. The other products are a molecule of ethanol and a bromide ion.



An E2 reaction has one transition state

When we study the E2 reaction further in Section 7.6D, we shall find that the orientations of the hydrogen atom being removed and the leaving group are not arbitrary and that an orientation where they are all in the same plane, like that shown above and in the example that follows, is required.



Newman projection

Anti-coplanar transition state of alkyl halide

Alkene

Notice that the geometry required here is similar to that of the S_N2 reaction. In the S_N2 reaction (Section 6.6) the nucleophile must push out the leaving group from the **opposite side**. In the E2 reaction the **electron pair of the C—H** bond pushes the leaving group away from the **opposite side** as the base removes the hydrogen. (We shall also find in Section 7.7C that a syn-coplanar E2 transition state is possible, though not as favorable.)

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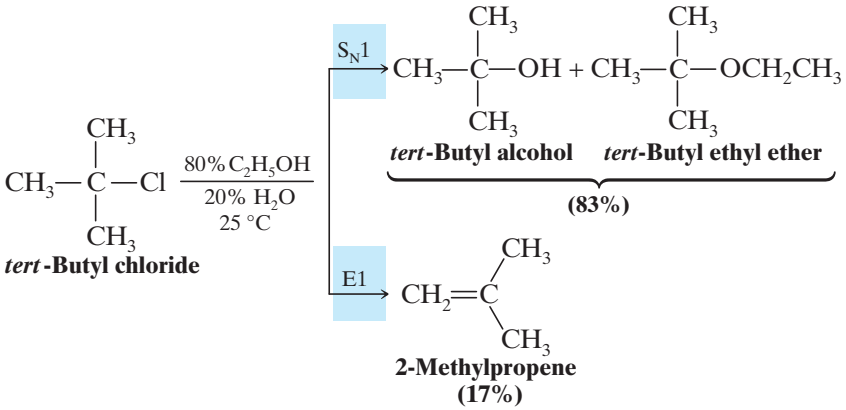
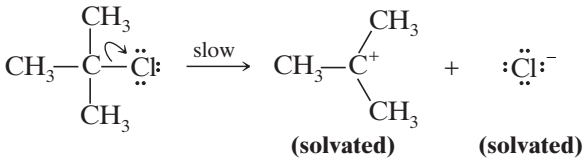
6.17 | THE E1 REACTION

Some elimination reactions follow a pathway that exhibits first-order kinetics. We call these types of eliminations E1 reactions. Treating *tert*-butyl chloride with 80% aqueous ethanol at 25°C, for example, gives *substitution products* in 83% yield and an elimination product (2-methylpropene) in 17% yield:

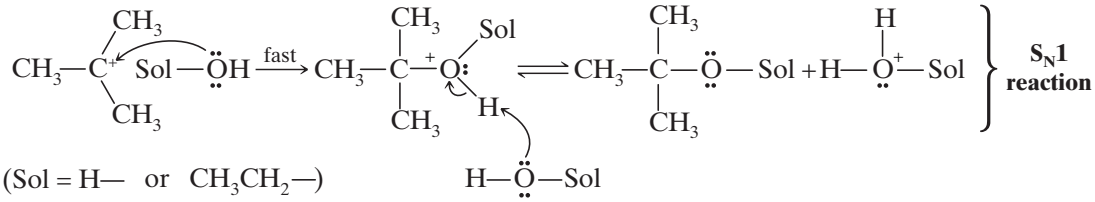


- The initial step for both the substitution and the elimination pathways is the formation of a *tert*-butyl cation as a common intermediate. This is also the slowest step for both reactions; thus both reactions exhibit first-order kinetics and are unimolecular in the rate-determining step.

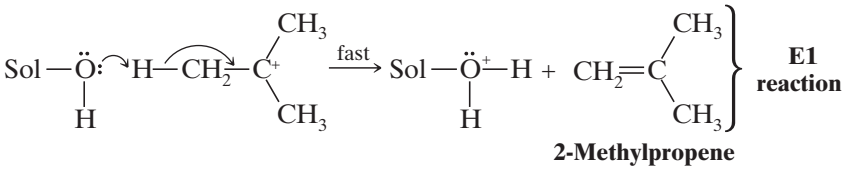


Whether substitution or elimination takes place depends on the next step (the fast step).

- If a solvent molecule reacts as a nucleophile at the positive carbon atom of the *tert*-butyl cation, the product is *tert*-butyl alcohol or *tert*-butyl ethyl ether and the reaction is S_N1:



- If, however, a solvent molecule acts as a base and removes one of the β hydrogen atoms, the product is 2-methylpropene and the reaction is E1.



E1 reactions almost always accompany S_N1 reactions.

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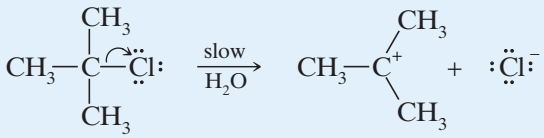
A MECHANISM FOR THE REACTION — Mechanism for the E1 Reaction

Reaction

$$(CH_3)_3CCl + H_2O \longrightarrow CH_2{=}C(CH_3)_2 + H_3O^+ + Cl^-$$

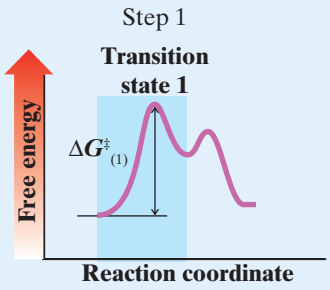
Mechanism

Step 1

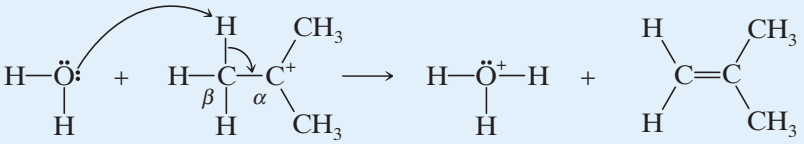


Aided by the polar solvent, a chlorine departs with the electron pair that bonded it to the carbon.

This slow step produces the relatively stable 3° carbocation and a chloride ion. The ions are solvated (and stabilized) by surrounding water molecules.

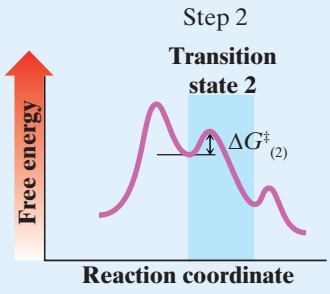


Step 2



A molecule of water removes one of the hydrogens from the β carbon of the carbocation. These hydrogens are acidic due to the adjacent positive charge. At the same time an electron pair moves in to form a double bond between the α and β carbon atoms.

This step produces the alkene and a hydronium ion.



6.18 | HOW TO DETERMINE WHETHER SUBSTITUTION OR ELIMINATION IS FAVORED

All nucleophiles are potential bases and all bases are potential nucleophiles. This is because the reactive part of both nucleophiles and bases is an unshared electron pair. It should not be surprising, then, that nucleophilic substitution reactions and elimination reactions often compete with each other. We shall now summarize factors that influence which type of reaction is favored, and provide some examples.

6.18A S_N2 versus E2

S_N2 and E2 reactions are both favored by a high concentration of a strong nucleophile or base. When the nucleophile (base) attacks a β hydrogen atom, elimination occurs. When the nucleophile attacks the carbon atom bearing the leaving group, substitution results:

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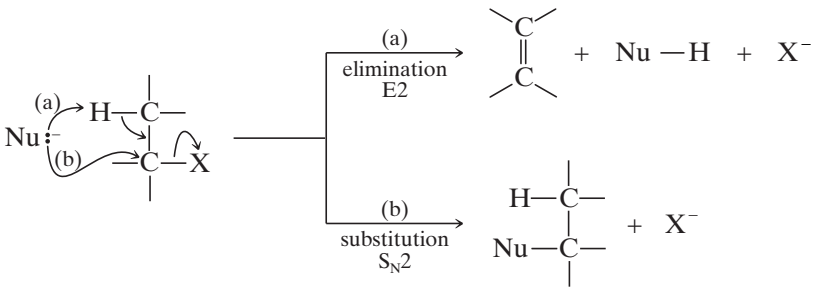
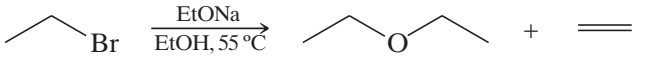


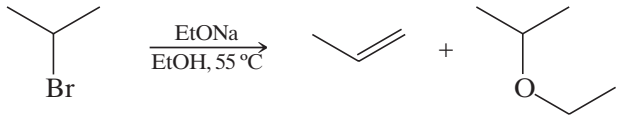
The following examples illustrate the effects of several parameters on substitution and elimination: relative steric hindrance in the substrate (class of alkyl halide), temperature, size of the base/nucleophile (EtONa versus *t*-BuOK), and the effects of basicity and polarizability. In these examples we also illustrate a very common way of writing organic reactions, where reagents are written over the reaction arrow, solvents and temperatures are written under the arrow, and only the substrate and major organic products are written to the left and right of the reaction arrow. We also employ typical shorthand notations of organic chemists, such as exclusive use of bond-line formulas and use of commonly accepted abbreviations for some reagents and solvents.

Primary Substrate When the substrate is a *primary* halide and the base is strong and unhindered, like ethoxide ion, substitution is highly favored because the base can easily approach the carbon bearing the leaving group:



Primary **S_N2 Major (90%)** **E2 Minor (10%)**

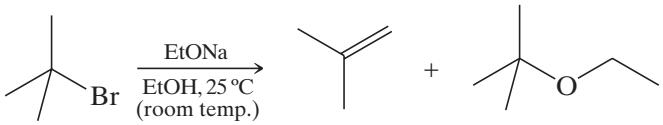
Secondary Substrate With *secondary* halides, however, a strong base favors elimination because steric hindrance in the substrate makes substitution more difficult:



Secondary **E2 Major (79%)** **S_N2 Minor (21%)**

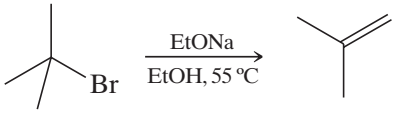
Tertiary Substrate With *tertiary* halides, steric hindrance in the substrate is severe and an S_N2 reaction cannot take place. Elimination is highly favored, especially when the reaction is carried out at higher temperatures. Any substitution that occurs must take place through an S_N1 mechanism:

Without Heating



Tertiary **E2 Major (91%)** **S_N1 Minor (9%)**

With Heating



Tertiary **E2 + E1 Only (100%)**

Temperature Increasing the reaction temperature favors elimination (E1 and E2) over substitution. Elimination reactions have greater free energies of activation than substitution reactions because more bonding changes occur during elimination. When higher temperature is used, the proportion of molecules able to surmount the energy of activation

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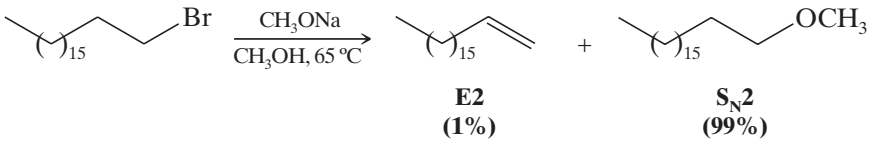
barrier for elimination increases more than the proportion of molecules able to undergo substitution, although the rate of both substitution and elimination will be increased. Furthermore, elimination reactions are entropically favored over substitution because the products of an elimination reaction are greater in number than the reactants. Additionally, because temperature is the coefficient of the entropy term in the Gibbs free-energy equation $\Delta G^\circ = H^\circ - T\Delta S^\circ$, an increase in temperature further enhances the entropy effect.

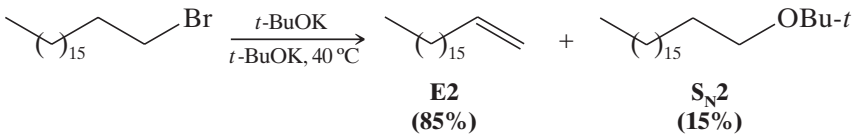
Size of the Base/Nucleophile Increasing the reaction temperature is one way of favorably influencing an elimination reaction of an alkyl halide. Another way is to use a *strong sterically hindered base* such as the *tert*-butoxide ion. The bulky methyl groups of the *tert*-butoxide ion inhibit its reaction by substitution, allowing elimination reactions to take precedence. We can see an example of this effect in the following two reactions. The relatively unhindered methoxide ion reacts with octadecyl bromide primarily by *substitution*, whereas the bulky *tert*-butoxide ion gives mainly *elimination*.

Unhindered (Small) Base/Nucleophile



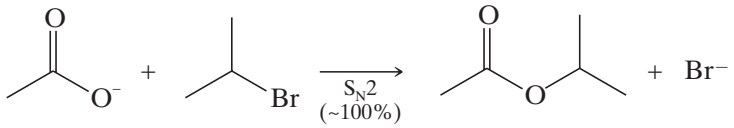
E2 (1%) **S_N2 (99%)**

Hindered Base/Nucleophile



E2 (85%) **S_N2 (15%)**

Basicity and Polarizability Another factor that affects the relative rates of E2 and S_N2 reactions is the relative basicity and polarizability of the base/nucleophile. Use of a strong, slightly polarizable base such as hydroxide ion, amide ion (NH_2^-), or alkoxide ion (especially a hindered one) tends to increase the likelihood of elimination (E2). Use of a weakly basic ion such as a chloride ion (Cl^-) or an acetate ion ($CH_3CO_2^-$) or a weakly basic and highly polarizable one such as Br^-, I^-, or RS^- increases the likelihood of substitution (S_N2). Acetate ion, for example, reacts with isopropyl bromide almost exclusively by the S_N2 path:



The more strongly basic ethoxide ion (Section 6.15B) reacts with the same compound mainly by an E2 mechanism.

6.18B Tertiary Halides: S_N1 versus E1

Because E1 and S_N1 reactions proceed through the formation of a common intermediate, the two types respond in similar ways to factors affecting reactivities. E1 reactions are favored with substrates that can form stable carbocations (i.e., tertiary halides); they are also favored by the use of poor nucleophiles (weak bases) and they are generally favored by the use of polar solvents.

It is usually difficult to influence the relative partition between S_N1 and E1 products because the free energy of activation for either reaction proceeding from the carbocation (loss of a proton or combination with a molecule of the solvent) is very small.

In most unimolecular reactions the S_N1 reaction is favored over the E1 reaction, especially at lower temperatures. *In general, however, substitution reactions of tertiary halides do not find wide use as synthetic methods. Such halides undergo eliminations much too easily.*

Increasing the temperature of the reaction favors reaction by the E1 mechanism at the expense of the S_N1 mechanism.

- **If an elimination product is desired from a tertiary substrate, it is advisable to use a strong base so as to encourage an E2 mechanism over the competing E1 and S_N1 mechanisms.**

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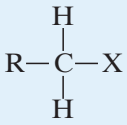
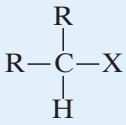
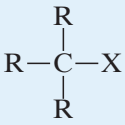
6.19 | OVERALL SUMMARY

The most important reaction pathways for the substitution and elimination reactions of simple alkyl halides are summarized in Table 6.6.

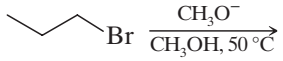
Table 6.6 Overall Summary of S_N1, S_N2, E1, and E2 Reactions

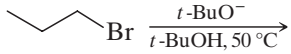
CH_3X			
Methyl	1°	2°	3°
	Bimolecular (S_N2/E2) Reactions Only		**S_N1/E1 or E2**
Gives S_N2 reactions	Gives mainly S_N2 except with a hindered strong base [e.g., $(CH_3)_3CO^-$] and then gives mainly E2.	Gives mainly S_N2 with weak bases (e.g., I^-, $N{\equiv}C^-$, RCO_2^-) and mainly E2 with strong bases (e.g., RO^-).	No S_N2 reaction. In solvolysis gives S_N1/E1, and at lower temperatures S_N1 is favored. When a strong base (e.g., RO^-) is used, E2 predominates.

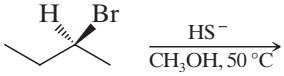
Let us examine several sample exercises that will illustrate how the information in Table 6.6 can be used.

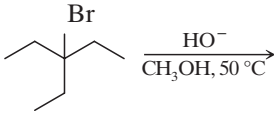
Solved Problem 6.8

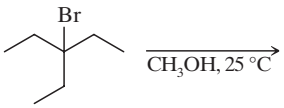
Give the product (or products) that you would expect to be formed in each of the following reactions. In each case give the mechanism (S_N1, S_N2, E1, or E2) by which the product is formed and predict the relative amount of each (i.e., would the product be the only product, the major product, or a minor product?).

(a) 

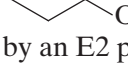
(b) 

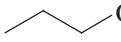
(c) 

(d) 

(e) 

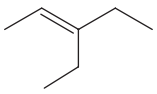
Answer

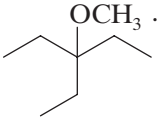
(a) The substrate is a 1° halide. The base/nucleophile is CH_3O^-, a strong base (but not a hindered one) and a good nucleophile. According to Table 6.6, we should expect an S_N2 reaction mainly, and the major product should be  by an E2 pathway.

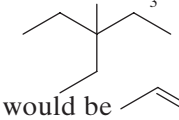
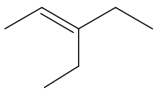
(b) Again the substrate is a 1° halide, but the base/nucleophile, *t*-BuO^-, is a strong hindered base. We should expect, therefore, the major product to be  by an E2 pathway and a minor product to be  by an S_N2 pathway.

(c) The reactant is (*S*)-2-bromobutane, a 2° halide and one in which the leaving group is attached to a chirality center. The base/nucleophile is HS^-, a strong nucleophile but a weak base. We should expect mainly an S_N2 reaction, causing an inversion of configuration at the chirality center and producing the (*R*) stereoisomer:



(d) The base/nucleophile is HO^-, a strong base and a strong nucleophile. The substrate is a 3° halide; therefore, we should not expect an S_N2 reaction. The major product should be  via an E2 reaction.

At this higher temperature and in the presence of a strong base, we should not expect an appreciable amount of the S_N1 solvolysis, product, .

(e) This is solvolysis; the only base/nucleophile is the solvent, CH_3OH, which is a weak base (therefore, no E2 reaction) and a poor nucleophile. The substrate is tertiary (therefore, no S_N2 reaction). At this lower temperature we should expect mainly an S_N1 pathway leading to . A minor product, by an E1 pathway, would be 

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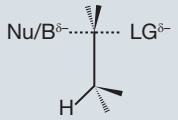
SUMMARY AND REVIEW TOOLS

Mechanism Review: Substitution versus Elimination

S_N2

Primary substrate
Back side attack of Nu: with respect to LG
Strong/polarizable unhindered nucleophile

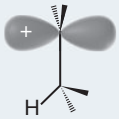
Bimolecular in rate-determining step
Concerted bond forming/bond breaking
Inversion of stereochemistry
Favored by polar aprotic solvent

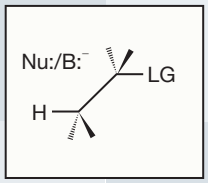


S_N1 and E1

Tertiary substrate
Carbocation intermediate
Weak nucleophile/base (e.g., solvent)

Unimolecular in rate-determining step
Racemization if S_N1
Removal of β-hydrogen if E1
Protic solvent assists ionization of LG
Low temperature (S_N1) / high temperature (E1)





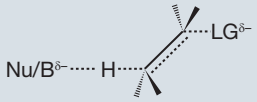
S_N2 and E2

Secondary or primary substrate
Strong unhindered base/nucleophile leads to S_N2
Strong hindered base/nucleophile leads to E2
Low temperature (S_N2) / high temperature (E2)

E2

Tertiary or secondary substrate
Concerted anti-coplanar transition state

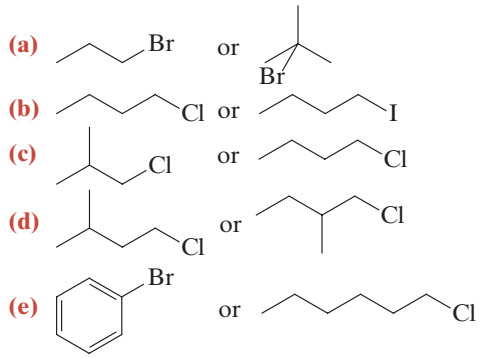
Bimolecular in rate-determining step
Strong hindered base
High temperature



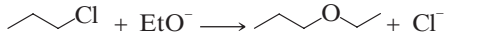
REVIEW PROBLEMS

Relative Rates of Nucleophilic Substitution

6.19 Which alkyl halide would you expect to react more rapidly by an S_N2 mechanism? Explain your answer.



6.20 Which S_N2 reaction of each pair would you expect to take place more rapidly in a protic solvent?

(a) (1) 

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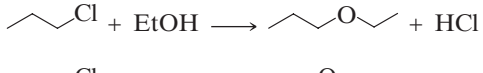
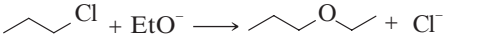
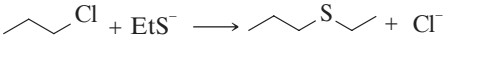
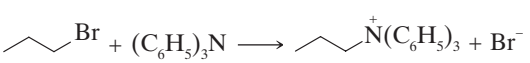
(2) 

(b) (1) 

or

(2) 

(c) (1) 

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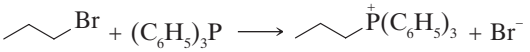
(2) 

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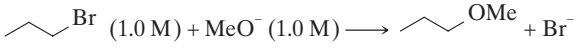
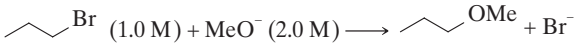
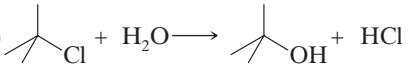
(d) (1)  (1.0 M) + MeO^- (1.0 M) ⟶ + Br^-

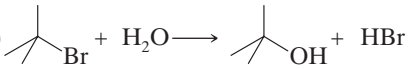
or

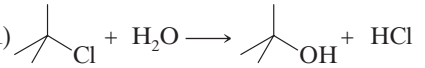
(2)  (1.0 M) + MeO^- (2.0 M) ⟶ + Br^-

6.21 Which S_N1 reaction of each pair would you expect to take place more rapidly? Explain your answer.

(a) (1) 

or

(2) 

(b) (1) 

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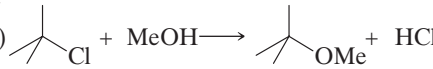
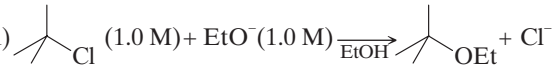
(2) 

(c) (1) 

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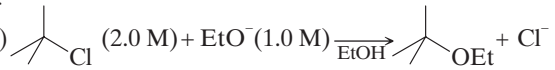
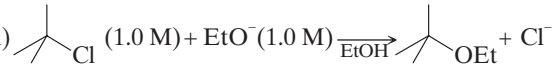
(2) 

(d) (1) 

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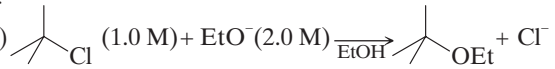
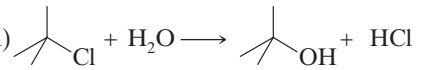
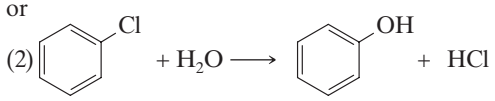
(2) 

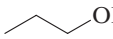
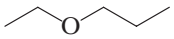
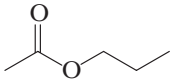
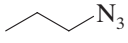
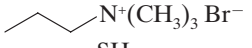
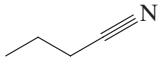
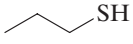
(e) (1) 

or

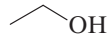
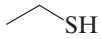
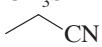
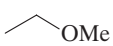
(2) 

Synthesis

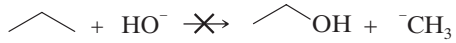
6.22 Show how you might use a nucleophilic substitution reaction of 1-bromopropane to synthesize each of the following compounds. (You may use any other compounds that are necessary.)

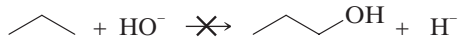
(a) 
(b) 1-Iodopropane
(c) 
(d) $CH_3CH_2CH_2-S-CH_3$
(e) 
(f) 
(g) 
(h) 
(i) 

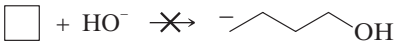
6.23 With methyl, ethyl, or cyclopentyl halides as your organic starting materials and using any needed solvents or inorganic reagents, outline syntheses of each of the following. More than one step may be necessary and you need not repeat steps carried out in earlier parts of this problem.

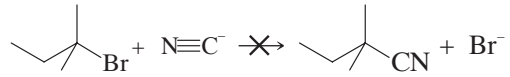
(a) CH_3I
(b) 
(c) CH_3OH
(d) 
(e) CH_3SH
(f) 
(g) CH_3CN
(h) 
(i) CH_3OCH_3
(j) 
(k) 

6.24 Listed below are several hypothetical nucleophilic substitution reactions. None is synthetically useful because the product indicated is not formed at an appreciable rate. In each case provide an explanation for the failure of the reaction to take place as indicated.

(a) 

(b) 

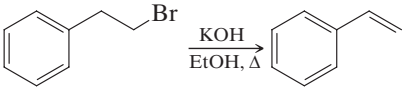
(c) 

(d) 

(e) $NH_3 + CH_3OCH_3 \not\longrightarrow CH_3NH_2 + CH_3OH$

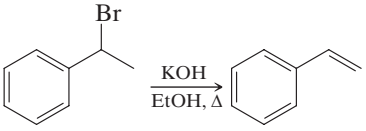
(f) $NH_3 + CH_3\overset{+}{O}H_2 \not\longrightarrow CH_3\overset{+}{N}H_3 + H_2O$

6.25 Your task is to prepare styrene by one of the following reactions. Which reaction would you choose to give the better yield of styrene? Explain your answer.

(1) 

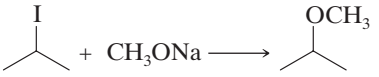
Styrene

or

(2) 

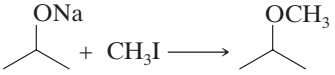
Styrene

6.26 Your task is to prepare isopropyl methyl ether by one of the following reactions. Which reaction would give the better yield? Explain your answer.

(1) 

Isopropyl methyl ether

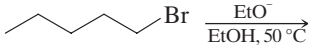
or

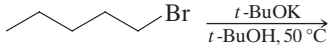
(2) 

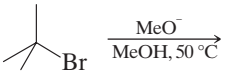
Isopropyl methyl ether

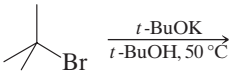
General S_N1, S_N2, and Elimination

6.27 Which product (or products) would you expect to obtain from each of the following reactions? In each part give the mechanism (S_N1, S_N2, E1, or E2) by which each product is formed and predict the relative amount of each product (i.e., would the product be the only product, the major product, a minor product, etc.?).

(a) 

(b) 

(c) 

(d) 

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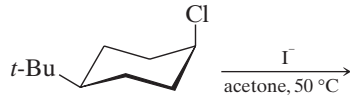
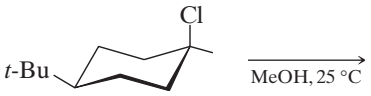
(e) 

(f) 

(g) 3-Chloropentane $\xrightarrow[\text{MeOH, 50 °C}]{\text{MeO}^-}$

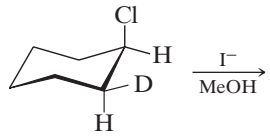
(h) 3-Chloropentane $\xrightarrow[\text{CH}_3\text{CO}_2\text{H, 50 °C}]{\text{CH}_3\text{CO}_2^-}$

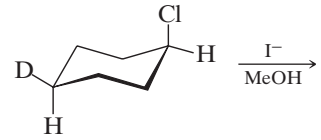
(i) (*R*)-2-bromobutane $\xrightarrow[25\ °C]{HO^-}$

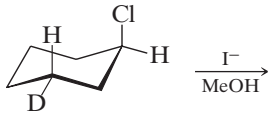
(j) (*S*)-3-Bromo-3-methylhexane $\xrightarrow[\text{MeOH}]{25\ °C}$

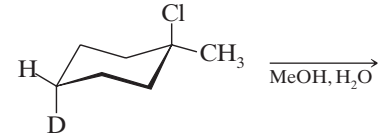
(k) (*S*)-2-Bromooctane $\xrightarrow[\text{MeOH, 50 °C}]{I^-}$

6.28 Write conformational structures for the substitution products of the following deuterium-labeled compounds:

(a) 

(b) 

(c) 

(d) 

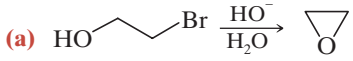
6.29 Consider the reaction of I^- with CH_3CH_2Cl.

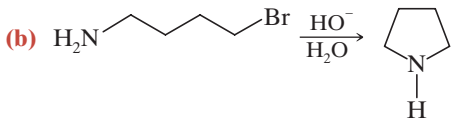
(a) Would you expect the reaction to be S_N1 or S_N2? The rate constant for the reaction at 60°C is 5×10^{-5} L mol^{-1} s^{-1}.
(b) What is the reaction rate if $[I^-] = 0.1$ mol L^{-1} and $[CH_3CH_2Cl] = 0.1$ mol L^{-1}?
(c) If $[I^-] = 0.1$ mol L^{-1} and $[CH_3CH_2Cl] = 0.2$ mol L^{-1}?
(d) If $[I^-] = 0.2$ mol L^{-1} and $[CH_3CH_2Cl] = 0.1$ mol L^{-1}?
(e) If $[I^-] = 0.2$ mol L^{-1} and $[CH_3CH_2Cl] = 0.2$ mol L^{-1}?

6.30 Which reagent in each pair listed here would be the more reactive nucleophile in a polar aprotic solvent?

(a) $CH_3\bar{N}H$ or CH_3NH_2
(b) CH_3O^- or $CH_3CO_2^-$ ($^-$OAc)
(c) CH_3SH or CH_3OH
(d) $(C_6H_5)_3N$ or $(C_6H_5)_3P$
(e) H_2O or H_3O^+
(f) NH_3 or $^+NH_4$
(g) H_2S or HS^-
(h) $CH_3CO_2^-$ ($^-$OAc) or HO^-

6.31 Write mechanisms that account for the products of the following reactions:

(a) 

(b) 

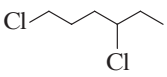
6.32 Draw a three-dimensional representation for the transition state structure in the S_N2 reaction of $N{\equiv}C{:}^-$ (cyanide anion) with bromoethane, showing all nonbonding electron pairs and full or partial charges.

6.33 **(a)** Consider the general problem of converting a tertiary alkyl halide to an alkene, for example, the conversion of *tert*-butyl chloride to 2-methylpropene. What experimental conditions would you choose to ensure that elimination is favored over substitution?
(b) Consider the opposite problem, that of carrying out a substitution reaction on a tertiary alkyl halide. Use as your example the conversion of *tert*-butyl chloride to *tert*-butyl ethyl ether. What experimental conditions would you employ to ensure the highest possible yield of the ether?

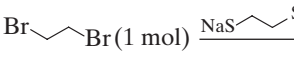
6.34 Give structures for the products of each of the following reactions:

(a) 

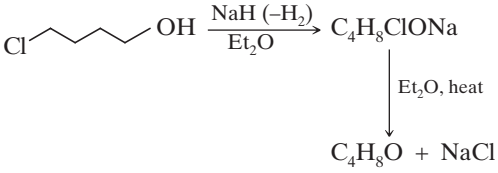
$C_5H_8FI + NaBr$

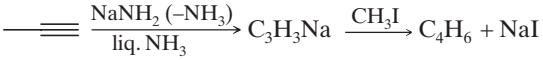
(b) 

$C_6H_{12}ClI + NaCl$

(c) 

$C_4H_8S_2 + 2\ NaBr$

(d) 

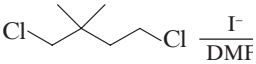
(e) 

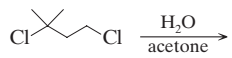
6.35 The reaction of 1° alkyl halides with nitrite salts produces both RNO_2 and RONO. Account for this behavior.

6.36 What would be the effect of increasing solvent polarity on the rate of each of the following nucleophilic substitution reactions?

(a) Nu**:** + R—L⟶R—Nu$^+$ + **:**L$^-$
(b) R—L$^+$⟶R$^+$ + **:**L

6.37 Competition experiments are those in which two reactants at the same concentration (or one reactant with two reactive sites) compete for a reagent. Predict the major product resulting from each of the following competition experiments:

(a) 

(b) 

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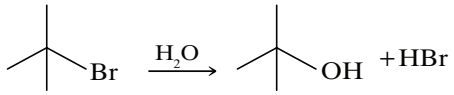
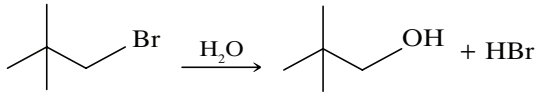
ADDITIONAL OBJECTIVE QUESTIONS

Single Correct Choice Type

1. Which of the following reaction is faster?

(a) 

(b) 

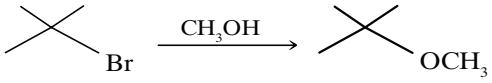
(c) Both are equally fast

(d) Reaction (a) is not possible

2. Strongest nucleophile in polar–protic solvent is

(a) CH_3O^- **(b)** CH_3SH **(c)** $CH_3–S^-$ **(d)** CH_3OH

3. Which of the following would be true for the reaction shown?



(a) The rate of the reaction depends only on the alkyl bromide concentration.

(b) The rate of the reaction depends only on the methanol concentration.

(c) The rate of the reaction depends on both the alkyl halide concentration and the methanol concentration.

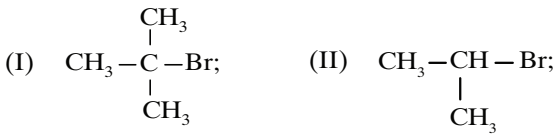
(d) The rate of the reaction depends on the concentration of neither reactant.

4. Consider the compounds (I) R–I; (II) R–Br; (III) R–Cl; (IV) R–F. The rate of S_N1 reaction is

(a) I > II > III > IV **(b)** II > I > III > IV

(c) I = II = III = IV **(d)** IV > III > II > I

5. Consider

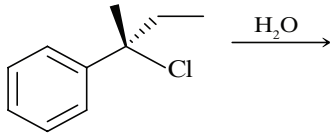


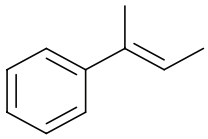
The order of reactivity toward S_N1 reaction is

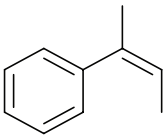
(a) I > II > III **(b)** II > I > III

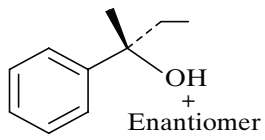
(c) II > III > I **(d)** III > II > I

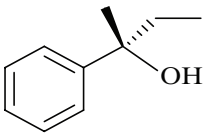
6. What is the major product of the following reaction?



(a) 

(b) 

(c) 

(d) 

7. The order of reactivity of the following alkyl halides for a S_N2 reaction is

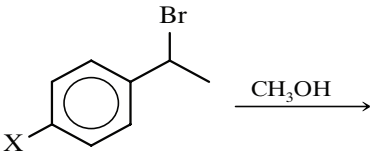
(a) R–F > R–Cl > R–Br > R–I

(b) R–F > R–Br > R–Cl > R–I

(c) R–Cl > R–Br > R–F > R–I

(d) R–I > RBr > R–Cl > R–F

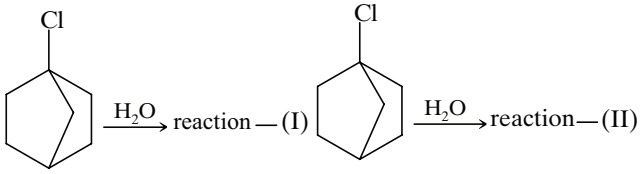
8. Rate of S_N1 is maximum when X is



(a) X = $–OCH_3$ **(b)** X = $–CH_3$

(c) X = $–NO_2$ **(d)** X = –Br

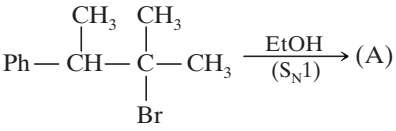
9.



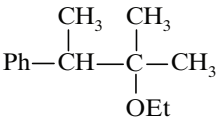
Reaction (I) and reaction (II) are, respectively,

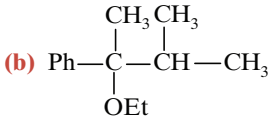
(a) S_N1, S_N1 **(b)** S_N1, S_N2

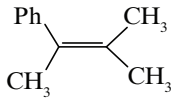
(c) S_N2, S_N1 **(d)** S_N1, no reaction

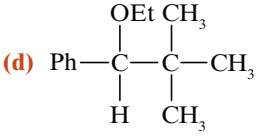
10. 

Major-product (A) is

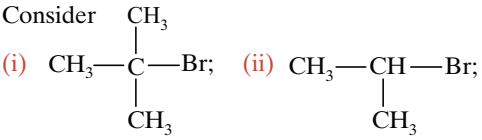
(a) 

(b) 

(c) 

(d) 

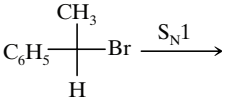
11. Consider



The order of reactivity toward E2 reaction is

(a) (i) > (ii) > (iii) **(b)** (ii) > (i) > (iii)

(c) (ii) > (iii) > (i) **(d)** (iii) > (ii) > (i)

12. 

Maximum racemization takes place when

(a) 100% H_2O

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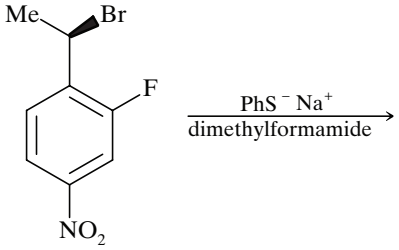
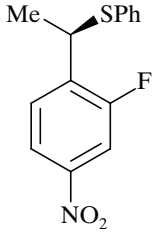
(b) 100% Acetone
(c) 80% H_2O + 20% Acetone
(d) 80% Acetone + 20% H_2O

13. Best leaving group is
(a) F^- **(b)** Cl^- **(c)** Br^- **(d)** I^-

14. The major product of the following reaction is



(a)


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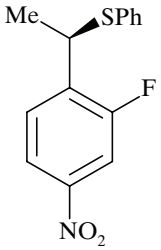
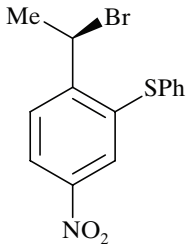
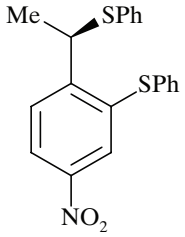
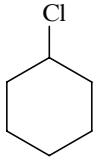
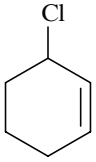


(c)


(d)


15. Which of the following compound will not undergo nucleophilic substitution reaction?

(a)


(b)


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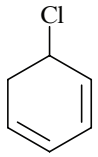

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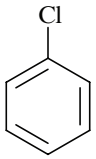
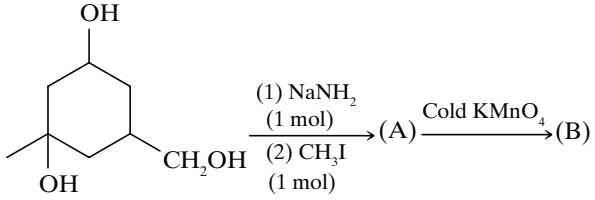
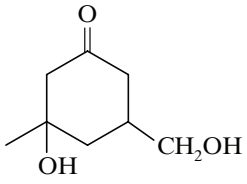
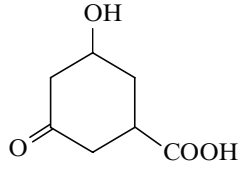
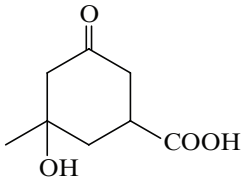


16. Identify the final product (B) in the following reaction.



(a)


(b)


(c)


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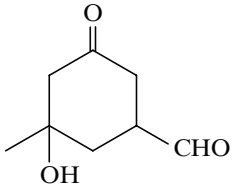
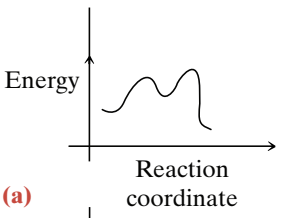
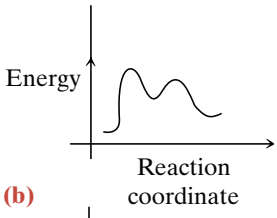


17. The rate of an S_N2 reaction depends upon the
(a) nucleophile. **(b)** carbon skeleton.
(c) leaving group. **(d)** all.

18. Alcoholic solution of KOH is a specific reagent for
(a) dehydration. **(b)** dehydrogenation.
(c) dehydrohalogenations. **(d)** dehalogenation.

19. Energy profile for the following reaction will be
$NH_3 + CH_3 - I \rightarrow CH_3 - {}^+NH_3$

(a)


(b)


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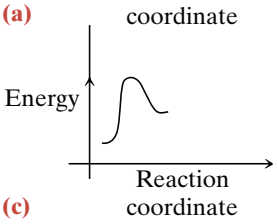

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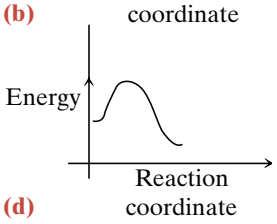
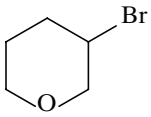
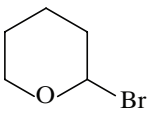
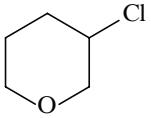


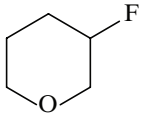
20. Best nucleophile in polar protic solvent is
(a) F^- **(b)** Cl^- **(c)** Br^- **(d)** I^-

21. Which of the following is the most reactive towards S_N1?

(a)


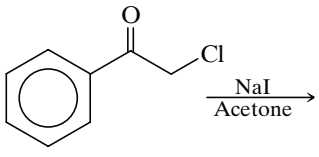
(b)


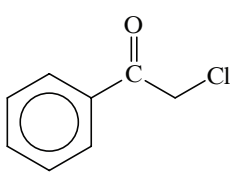
(c)


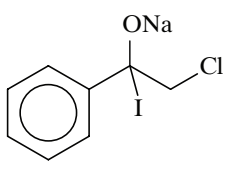
(d)


22. The best leaving group produces a _____ base that is a(n) _____ anion.
(a) weak, stable **(b)** strong, stable
(c) weak, unstable **(d)** strong, unstable

23. What will be the final product?



(a)


(b)


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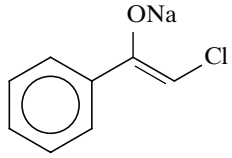
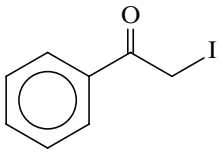
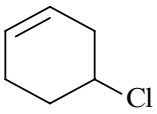
(c) 

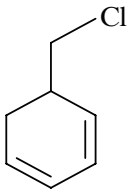
(d) 

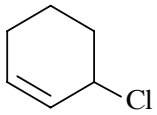
24. Best nucleophile in polar aprotic solvent is

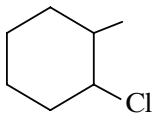
(a) F^- **(b)** Cl^- **(c)** Br^- **(d)** I^-

25. Which of following compounds give same S_N1 and S_N2 product?

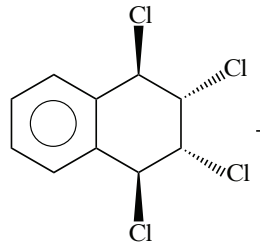
(a) 

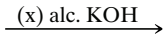
(b) 

(c) 

(d) 

Integer Type

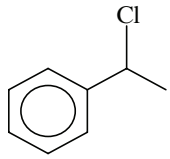
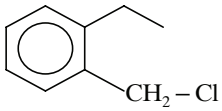
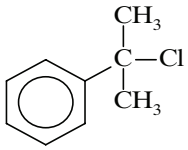
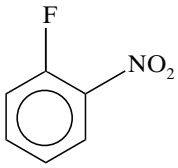
1. 



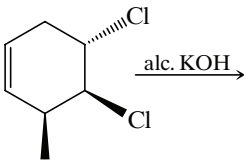
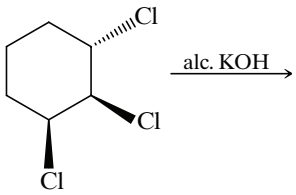
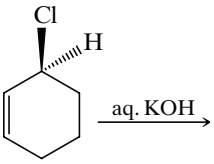
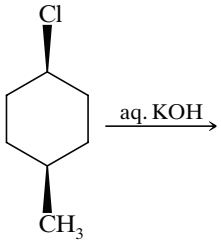
Find the number of moles of alc. KOH consumed in the above reaction.

Matrix Match Type

1.

Column I	Column II
(a) 	**(p)** It will undergo nucleophilic substitution reaction
(b) 	**(q)** It will undergo E2 reaction
(c) 	**(r)** It will undergo E1 reaction
(d) 	**(s)** It will undergo S_N2 reaction
	(t) It will undergo S_N1 reaction

2.

Column I	Column II
(a) 	**(p)** Optically active product
(b) 	**(q)** Optically inactive product
(c) 	**(r)** Second order reaction
(d) 	**(s)** Unimolecular reaction

ANSWER KEY

Single Correct Choice Type

1. (a)	**2.** (c)	**3.** (a)	**4.** (a)
5. (a)	**6.** (c)	**7.** (d)	**8.** (a)
9. (d)	**10.** (b)	**11.** (a)	**12.** (c)
13. (d)	**14.** (a)	**15.** (d)	**16.** (a)

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17. (d) **18.** (c) **19.** (d) **20.** (d)
21. (b) **22.** (a) **23.** (d) **24.** (a)
25. (c)

Integer Type

1. (1)

Matrix Match Type

1. a → (p, q, r, s, t); b → (p, s, t); c → (p, q, r, t); d → (p)
2. a → (p, r); b → (p, r); c → (p, r); d → (q, r)

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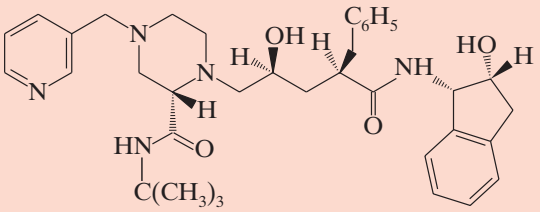
7

Alkenes and Alkynes I

Properties and Synthesis. Elimination Reactions of Alkyl Halides



Crixivan (an HIV protease inhibitor)

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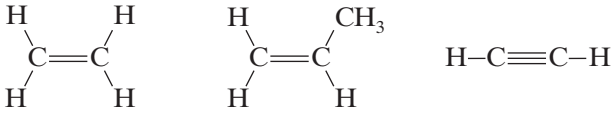
7.1 | Introduction
7.2 | The (*E*)–(*Z*) System for Designating Alkene Diastereomers
7.3 | Relative Stabilities of Alkenes
7.4 | Cycloalkenes
7.5 | Synthesis of Alkenes via Elimination Reactions
7.6 | Dehydrohalogenation of Alkyl Halides
7.7 | Acid-Catalyzed Dehydration of Alcohols
7.8 | Carbocation Stability and the Occurrence of Molecular Rearrangements
7.9 | The Acidity of Terminal Alkynes
7.10 | Synthesis of Alkynes by Elimination Reactions
7.11 | Terminal Alkynes can be Converted to Nucleophiles for Carbon–Carbon Bond Formation
7.12 | Hydrogenation of Alkenes
7.13 | Hydrogenation: The Function of the Catalyst
7.14 | Hydrogenation of Alkynes
7.15 | An Introduction to Organic Synthesis

7.1 | INTRODUCTION

Alkenes are hydrocarbons whose molecules contain a carbon–carbon double bond. An old name for this family of compounds that is still often used is the name **olefins**. Ethene (ethylene), the simplest olefin (alkene), was called olefiant gas (Latin: *oleum,* oil + *facere,* to make) because gaseous ethene (C_2H_4) reacts with chlorine to form $C_2H_4Cl_2$, a liquid (oil).

Hydrocarbons whose molecules contain the carbon–carbon triple bond are called alkynes. The common name for this family is **acetylenes**, after the simplest member, HC≡CH:



Ethene **Propene** **Ethyne**

7.1A Physical Properties of Alkenes and Alkynes

Alkenes and alkynes have physical properties similar to those of corresponding alkanes. Alkenes and alkynes up to four carbons (except 2-butyne) are gases at room temperature. Being relatively nonpolar themselves, alkenes and alkynes dissolve in nonpolar solvents or in solvents of low polarity. Alkenes and alkynes are only *very slightly soluble* in water (with alkynes being slightly more soluble than alkenes). The densities of alkenes and alkynes are lower than that of water.

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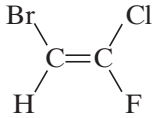
7.2 | THE (*E*)–(*Z*) SYSTEM FOR DESIGNATING ALKENE DIASTEREOMERS

In Section 5.5 we learned to use the terms *cis* and *trans* to designate the stereochemistry of alkene diastereomers (***cis–trans* isomers**). These terms are unambiguous, however, only when applied to disubstituted alkenes. If the alkene is trisubstituted or tetrasubstituted, the terms *cis* and *trans* are either ambiguous or do not apply at all. Consider the following alkene as an example:



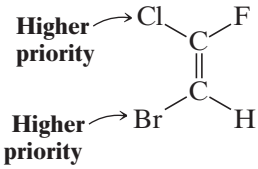
A

It is impossible to decide whether **A** is *cis* or *trans* since no two groups are the same.

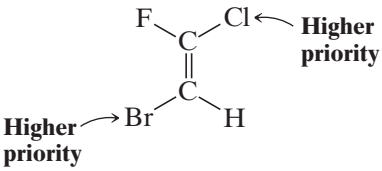
A system that works in all cases is based on the priorities of groups in the Cahn–Ingold–Prelog convention (Section 4.7). This system, called the **(*E*)–(*Z*) system**, applies to alkene diastereomers of all types.

7.2A HOW TO Use The (*E*)–(*Z*) System

1. Examine the two groups attached to one carbon atom of the double bond and decide which has higher priority.
2. Repeat that operation at the other carbon atom:

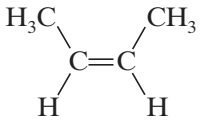


(*Z*)-2-Bromo-1-chloro-1-fluoroethene



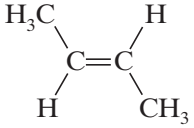
(*E*)-2-Bromo-1-chloro-1-fluoroethene

3. Compare the group of higher priority on one carbon atom with the group of higher priority on the other carbon atom. If the two groups of higher priority are on the same side of the double bond, the alkene is designated (*Z*) (from the German word *zusammen,* meaning together). If the two groups of higher priority are on opposite sides of the double bond, the alkene is designated (*E*) (from the German word *entgegen,* meaning opposite). The following isomers provide another example.



(*Z*)-2-Butene or (*Z*)-but-2-ene (*cis*-2-butene)

$CH_3 > H$



(*E*)-2-Butene or (*E*)-but-2-ene (*trans*-2-butene)

Solved Problem 7.1

The two stereoisomers of 1-bromo-1,2-dichloroethene cannot be designated as *cis* and *trans* in the normal way because the double bond is trisubstituted. They can, however, be given (*E*) and (*Z*) designations. Write a structural formula for each isomer and give each the proper designation.

Answer

We write the structures (below), then note that chlorine has a higher priority than hydrogen, and bromine has a higher priority than chlorine. The group with higher priority on C1 is bromine and the group with higher priority at C2 is chlorine. In the first structure the higher priority chlorine and bromine atoms are on opposite sides of the double bond, and therefore this isomer is (*E*). In the second structure those chlorine and bromine atoms are on the same side, so the latter isomer is (*Z*).

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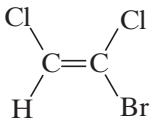
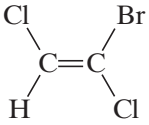


(*E*)-1-Bromo-1,2-dichloroethene

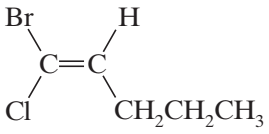
Cl > H
Br > Cl

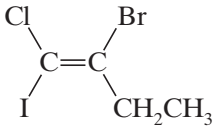


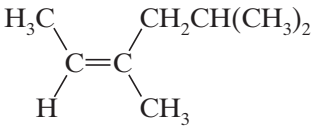
(*Z*)-1-Bromo-1,2-dichloroethene

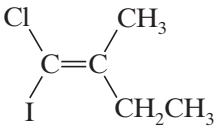
Practice Problem 7.1

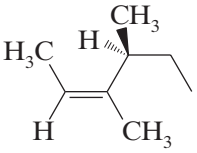
Using the (*E*)–(*Z*) designation [and in parts **(e)** and **(f)** the (*R*)–(*S*) designation as well] give IUPAC names for each of the following:

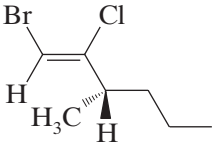
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

7.3 | RELATIVE STABILITIES OF ALKENES

Cis and *trans* isomers of alkenes do not have the same stability.

- Strain caused by crowding of two alkyl groups on the same side of a double bond makes *cis* isomers generally less stable than *trans* isomers (Fig. 7.1).

This effect can be measured quantitatively by comparing thermodynamic data from experiments involving alkenes with related structures, as we shall see later.

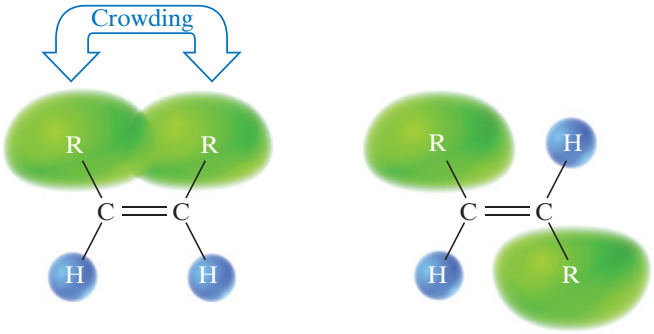
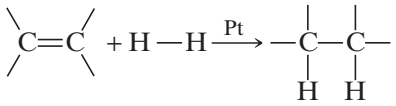


Figure 7.1 Cis and trans alkene isomers. The cis isomer is less stable due to greater strain from crowding by the adjacent alkyl groups.

7.3A Heat of Reaction

The addition of hydrogen to an alkene (**hydrogenation**, Sections 5.16A and 7.13) is an exothermic reaction; the enthalpy change involved is called the **heat of reaction** or, in this specific case, the **heat of hydrogenation**.



$\Delta H^\circ \cong -120$ kJ mol^{-1}

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We can gain a quantitative measure of relative alkene stabilities by comparing the heats of hydrogenation for a family of alkenes that all become the same alkane product on hydrogenation. The results of such an experiment involving platinum-catalyzed hydrogenation of three butene isomers are shown in Fig. 7.2. All three isomers yield the same product—butane—but the heat of reaction is different in each case. On conversion to butane, 1-butene liberates the most heat (127 kJ mol^{-1}), followed by *cis*-2-butene (120 kJ mol^{-1}), with *trans*-2-butene producing the least heat (115 kJ mol^{-1}). These data indicate that the *trans* isomer is more stable than the *cis* isomer, since less energy is released when the *trans* isomer is converted to butane. Furthermore, it shows that the terminal alkene, 1-butene, is less stable than either of the disubstituted alkenes, since its reaction is the most exothermic. Of course, alkenes that do not yield the same hydrogenation products cannot be compared on the basis of their respective heats of hydrogenation. In such cases it is necessary to compare other thermochemical data, such as heats of combustion, although we will not go into analyses of that type here.

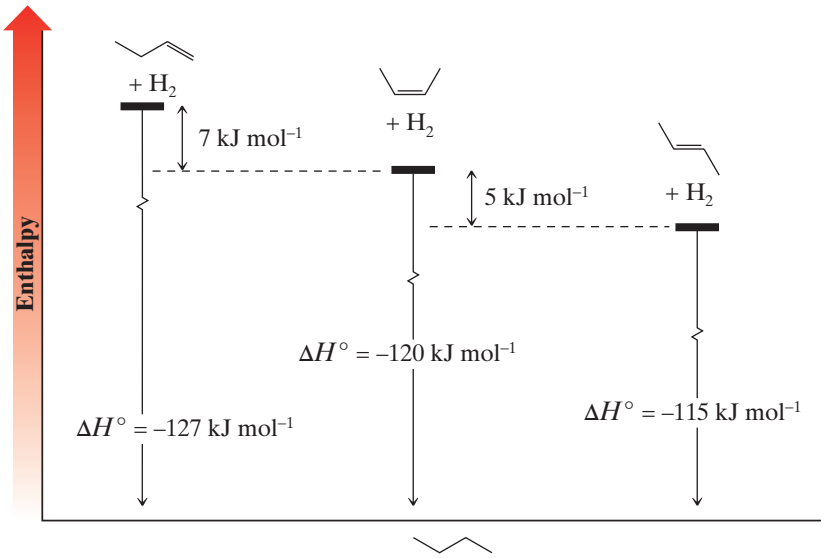


Figure 7.2 An energy diagram for platinum-catalyzed hydrogenation of the three butene isomers. The order of stability based on the differences in their heats of hydrogenation is *trans*-2-butene > *cis*-2-butene > 1-butene.

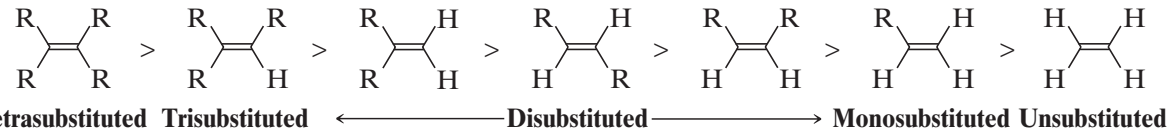
7.3B Overall Relative Stabilities of Alkenes

Studies of numerous alkenes reveal a pattern of stabilities that is related to the number of alkyl groups attached to the carbon atoms of the double bond.

- The greater the number of attached alkyl groups (i.e., the more highly substituted the carbon atoms of the double bond), the greater is the alkene's stability.

This order of stabilities can be given in general terms as follows:*

Relative Stabilities of Alkenes



*This order of stabilities may seem contradictory when compared with the explanation given for the relative stabilities of *cis* and *trans* isomers. Although a detailed explanation of the trend given here is beyond our scope, the relative stabilities of substituted alkenes can be rationalized. Part of the explanation can be given in terms of the electron-releasing effect of alkyl groups (Section 6.11B), an effect that satisfies the electron-withdrawing properties of the sp^2-hybridized carbon atoms of the double bond.

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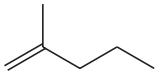
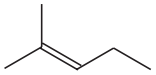
Solved Problem 7.2

Consider the two alkenes 2-methyl-1-pentene and 2-methyl-2-pentene and decide which would be most stable.



2-Methyl-1-pentene (disubstituted, less stable)



2-Methyl-2-pentene (trisubstituted, more stable)

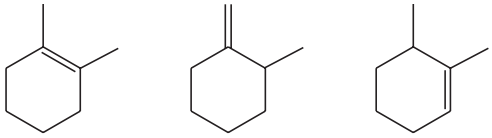
Answer

First write the structures of the two alkenes, then decide how many substituents the double bond of each has.

2-Methyl-2-pentene has three substituents on its double bond, whereas 2-methyl-1-pentene has two, and therefore 2-methyl-2-pentene is the more stable.

Practice Problem 7.2

Rank the following cycloalkenes in order of increasing stability.



Practice Problem 7.3

Heats of hydrogenation of three alkenes are as follows:

2-methyl-1-butene (-119 kJ mol^{-1})
3-methyl-1-butene (-127 kJ mol^{-1})
2-methyl-2-butene (-113 kJ mol^{-1})

(a) Write the structure of each alkene and classify it as to whether its doubly bonded atoms are monosubstituted, disubstituted, trisubstituted, or tetrasubstituted. **(b)** Write the structure of the product formed when each alkene is hydrogenated. **(c)** Can heats of hydrogenation be used to relate the relative stabilities of these three alkenes? **(d)** If so, what is the predicted order of stability? If not, why not? **(e)** What other alkene isomers are possible for these alkenes? Write their structures. **(f)** What are the relative stabilities among just these isomers?

Practice Problem 7.4

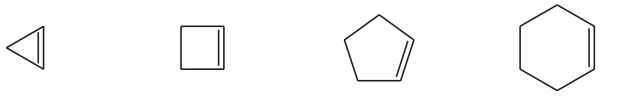
Predict the more stable alkene of each pair: **(a)** 2-methyl-2-pentene or 2,3-dimethyl-2-butene; **(b)** *cis*-3-hexene or *trans*-3-hexene; **(c)** 1-hexene or *cis*-3-hexene; **(d)** *trans*-2-hexene or 2-methyl-2-pentene.

Practice Problem 7.5

How many stereoisomers are possible for 4-methyl-2-hexene, and how many fractions would you obtain if you distilled the mixture?

7.4 | CYCLOALKENES

The rings of cycloalkenes containing five carbon atoms or fewer exist only in the *cis* form (Fig. 7.3). The introduction of a *trans* double bond into rings this small would, if it were possible, introduce greater strain than the bonds of the ring atoms could accommodate.



Cyclopropene **Cyclobutene** **Cyclopentene** **Cyclohexene**

Figure 7.3 *cis*-Cycloalkenes.

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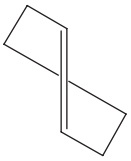
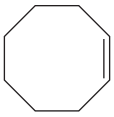


Figure 7.4 Hypothetical *trans*-cyclohexene. This molecule is apparently too strained to exist at room temperature.



***cis*-Cyclooctene**



***trans*-Cyclooctene**

Figure 7.5 The *cis* and *trans* forms of cyclooctene.

(Verify this with handheld molecular models.) *trans*-Cyclohexene might resemble the structure shown in Fig. 7.4. There is evidence that it can be formed as a very reactive short-lived intermediate in some chemical reactions, but it is not isolable as a stable molecule.

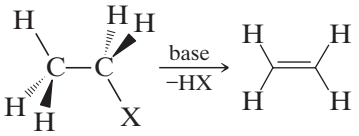
trans-Cycloheptene has been observed spectroscopically, but it is a substance with a very short lifetime and has not been isolated.

trans-Cyclooctene (Fig. 7.5) has been isolated, however. Here the ring is large enough to accommodate the geometry required by a *trans* double bond and still be stable at room temperature. *trans*-Cyclooctene is chiral and exists as a pair of enantiomers. You may wish to verify this using handheld models.

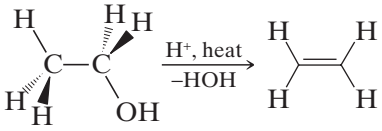
7.5 | SYNTHESIS OF ALKENES VIA ELIMINATION REACTIONS

Elimination reactions are the most important means for synthesizing alkenes. In this chapter we shall study two methods for alkene synthesis based on elimination reactions: dehydrohalogenation of alkyl halides and dehydration of alcohols.

Dehydrohalogenation of Alkyl Halides (Sections 6.15, 6.16, and 7.6)



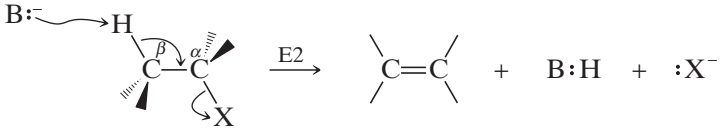
Dehydration of Alcohols (Sections 7.7 and 7.8)



7.6 | DEHYDROHALOGENATION OF ALKYL HALIDES

- The best reaction conditions to use when synthesizing an alkene by **dehydrohalogenation** are those that promote an E2 mechanism.

In an E2 mechanism, a base removes a β hydrogen from the β carbon, as the double bond forms and a leaving group departs from the α carbon.



Reaction conditions that favor elimination by an E1 mechanism should be avoided because the results can be too variable. The carbocation intermediate that accompanies an E1 reaction can undergo rearrangement of the carbon skeleton, as we shall see in Section 7.8, and it can also undergo substitution by an S_N1 mechanism, which competes strongly with formation of products by an E1 path.

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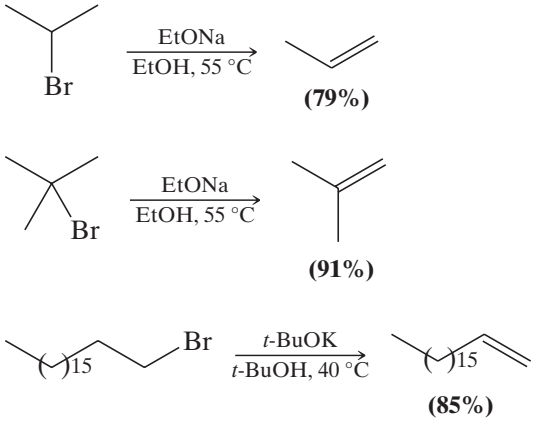
7.6A HOW TO Favor an E2 Mechanism

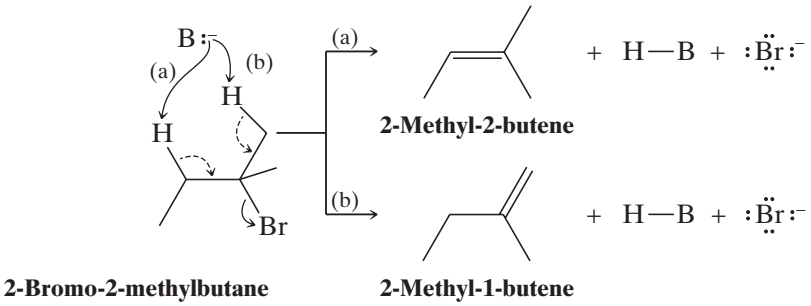
1. **Use a secondary or tertiary alkyl halide if possible.**
   Why? Because steric hindrance in the substrate will inhibit substitution.
2. **When a synthesis must begin with a primary alkyl halide, use a bulky base.**
   Why? Because the steric bulk of the base will inhibit substitution.
3. **Use a high concentration of a strong and nonpolarizable base such as an alkoxide.**
   Why? Because a weak and polarizable base would not drive the reaction toward a bimolecular reaction, thereby allowing unimolecular processes (such as S_N1 or E1 reactions) to compete.
4. **Sodium ethoxide in ethanol (EtONa/EtOH) and potassium *tert*-butoxide in *tert*-butyl alcohol (*t*-BuOK/*t*-BuOH) are bases typically used to promote E2 reactions.**
   Why? Because they meet criterion 3 above. Note that in each case the alkoxide base is dissolved in its corresponding alcohol. (Potassium hydroxide dissolved in ethanol or *tert*-butyl alcohol is also sometimes used, in which case the active base includes both the alkoxide and hydroxide species present at equilibrium.)
5. **Use elevated temperature because heat generally favors elimination over substitution.**
   Why? Because elimination reactions are entropically favored over substitution reactions (because the products are greater in number than the reactants). Hence $\Delta S°$ in the Gibbs free-energy equation, $\Delta G° = \Delta H° - T\Delta S°$ is significant, and $\Delta S°$ will be increased by higher temperature since T is a coefficient, leading to a more negative (favorable) $\Delta G°$.

7.6B Zaitsev's Rule: Formation of the More Substituted Alkene Is Favored with a Small Base

We showed examples in Sections 6.15–6.17 of dehydrohalogenations where only a single elimination product was possible. For example:



Dehydrohalogenation of many alkyl halides, however, yields more than one product. For example, dehydrohalogenation of 2-bromo-2-methylbutane can yield two products: 2-methyl-2-butene and 2-methyl-1-butene, as shown here by pathways (a) and (b), respectively:



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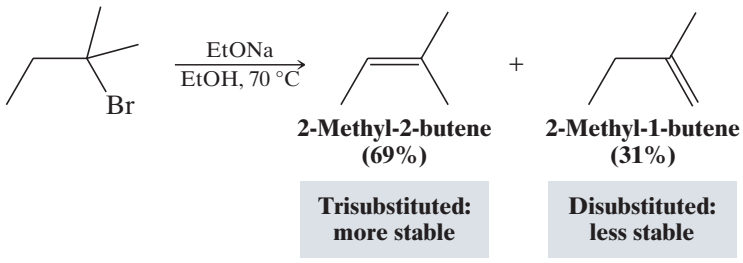
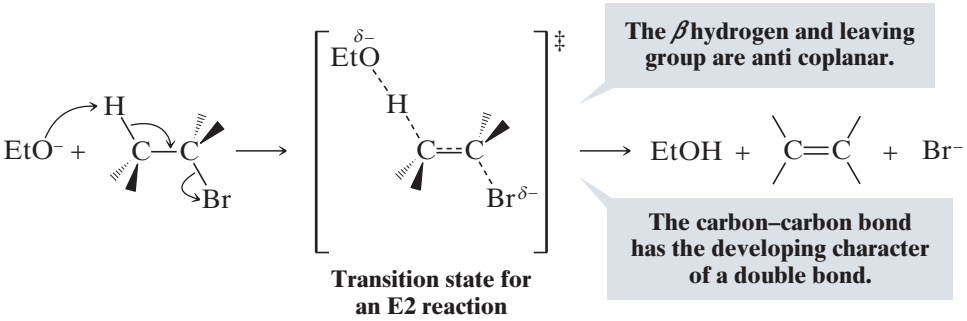
- If we use a small base such as ethoxide or hydroxide, the major product of the reaction will be the more highly substituted alkene (which is also the more stable alkene).



2-Methyl-2-butene is a trisubstituted alkene (three methyl groups are attached to carbon atoms of the double bond), whereas 2-methyl-1-butene is only disubstituted. 2-Methyl-2-butene is the major product.

- Whenever an elimination occurs to give the more stable, more highly substituted alkene, chemists say that the elimination follows **Zaitsev's rule**, named for the nineteenth-century Russian chemist A. N. Zaitsev (1841–1910) who formulated it. (Zaitsev's name is also transliterated as Zaitzev, Saytzeff, Saytseff, or Saytzev.)

The reason for this behavior is related to the double-bond character that develops in the transition state (cf. Section 6.16) for each reaction:



The transition state for the reaction leading to 2-methyl-2-butene (Fig. 7.6) has the developing character of the double bond in a trisubstituted alkene. The transition state for the reaction leading to 2-methyl-1-butene has the

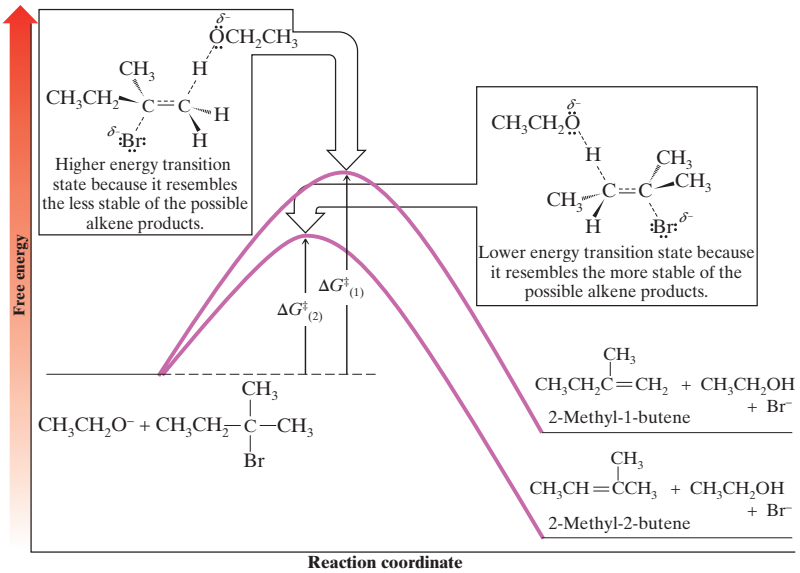


Figure 7.6 Reaction (2) leading to the more stable alkene occurs faster than reaction (1) leading to the less stable alkene; $\Delta G^{\ddagger}_{(2)}$ is less than $\Delta G^{\ddagger}_{(1)}$.

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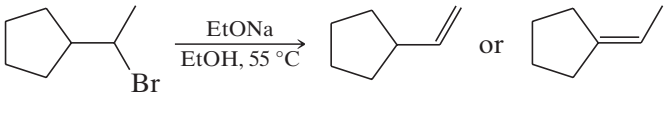
developing character of a double bond in a disubstituted alkene. Because the transition state leading to 2-methyl-2-butene resembles a more stable alkene, this transition state is more stable (recall the Hammond–Leffler postulate, Fig. 6.10). Because this transition state is more stable (occurs at lower free energy), the free energy of activation for this reaction is lower and 2-methyl-2-butene is formed faster. This explains why 2-methyl-2-butene is the major product.

- In general, the preferential formation of one product because the free energy of activation leading to its formation is lower than that for another product, and therefore the rate of its formation faster, is called **kinetic control** of product formation.

Solved Problem 7.3

Using Zaitsev's rule, predict which would be the major product of the following reaction:



A **B**

Answer

Alkene **B** has a trisubstituted double bond whereas the double bond of **A** is only monosubstituted. Therefore, **B** is more stable and, according to Zaitsev's rule, would be the major product.

Practice Problem 7.6

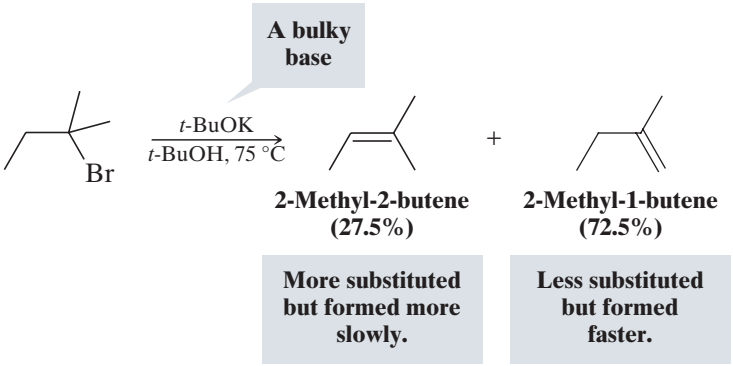
Predict the major product formed when 2-bromobutane is subjected to dehydrobromination using sodium ethoxide in ethanol at 55 °C.

Practice Problem 7.7

List the alkenes that would be formed when each of the following alkyl halides is subjected to dehydrohalogenation with potassium ethoxide in ethanol and use Zaitsev's rule to predict the major product of each reaction: **(a)** 2-bromo-3-methylbutane and **(b)** 2-bromo-2,3-dimethylbutane.

7.6C Formation of the Less Substituted Alkene Using a Bulky Base

- Carrying out dehydrohalogenations with a bulky base such as potassium *tert*-butoxide (*t*-BuOK) in *tert*-butyl alcohol (*t*-BuOH) favors the formation of the **less substituted alkene:**



The reasons for this behavior are related in part to the steric bulk of the base and to the fact that in *tert*-butyl alcohol the base is associated with solvent molecules and thus made even larger. The large *tert*-butoxide ion appears to have difficulty removing one of the internal (2°) hydrogen atoms because of greater crowding at that site in the transition state. It removes one of the more exposed (1°) hydrogen atoms of the methyl group instead.

- When an elimination yields the less substituted alkene, we say that it follows the **Hofmann rule** (see also Section 18.11A).

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Solved Problem 7.4

Your task is the following synthesis. Which base would you use to maximize the yield of this specific alkene?



Answer

Here you want the Hofmann rule to apply (you want the less substituted alkene to be formed). Therefore, use a bulky base such as potassium *tert*-butoxide in *tert*-butyl alcohol.

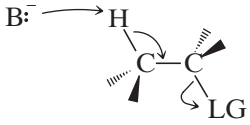
Practice Problem 7.8

Examine Solved Problem 7.3. Your task is to prepare **A** in the highest possible yield by dehydrobromination. Which base would you use?

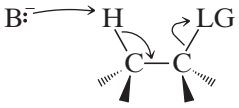
7.6D The Stereochemistry of E2 Reactions: The Orientation of Groups in the Transition State

- The five atoms involved in the transition state of an E2 reaction (including the base) must be **coplanar**, i.e., lie in the same plane.

The requirement for coplanarity of the H—C—C—LG unit arises from a need for proper overlap of orbitals in the developing π bond of the alkene that is being formed (see Section 6.16). There are two ways that this can happen:



Anti coplanar transition state (preferred)



Syn coplanar transition state (only with certain rigid molecules)

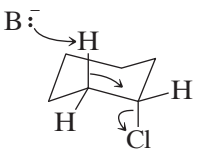
- The **anti coplanar** conformation is the preferred transition state geometry.

The **syn coplanar** transition state occurs only with rigid molecules that are unable to assume the anti arrangement. The reason: the anti coplanar transition state is staggered (and therefore of lower energy), while the syn coplanar transition state is eclipsed. Practice Problem 7.9 will help to illustrate this difference.

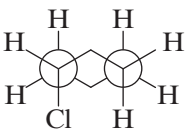
Practice Problem 7.9

Consider a simple molecule such as ethyl bromide and show with Newman projection formulas how the anti coplanar transition state would be favored over the syn coplanar one.

Part of the evidence for the preferred anti coplanar arrangement of groups comes from experiments done with cyclic molecules. Two groups axially oriented on adjacent carbons in a chair conformation of cyclohexane are anti coplanar. If one of these groups is a hydrogen and the other a leaving group, the geometric requirements for an anti coplanar E2 transition state are met. Neither an axial–equatorial nor an equatorial–equatorial orientation of the groups allows formation of an anti coplanar transition state. (Note that there are no syn coplanar groups in a chair conformation, either.)



Here the β hydrogen and the chlorine are both axial. This allows an anti coplanar transition state.



A Newman projection formula shows that the β hydrogen and the chlorine are anti coplanar when they are both axial.

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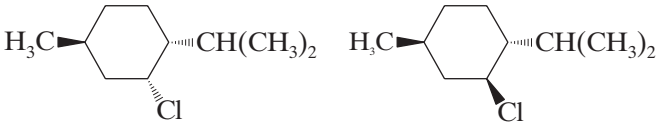
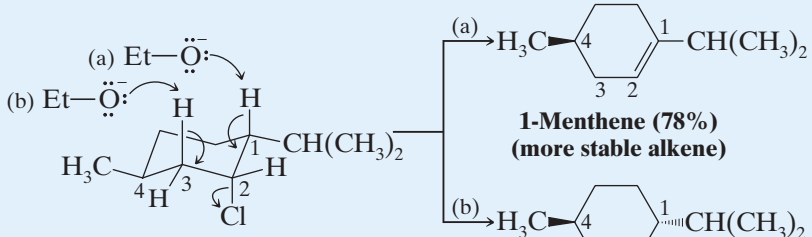
As examples, let us consider the different behavior in E2 reactions shown by two compounds containing cyclohexane rings, neomenthyl chloride and menthyl chloride:



Neomenthyl chloride **Menthyl chloride**

In the more stable conformation of neomenthyl chloride (see the following mechanism), the alkyl groups are both equatorial and the chlorine is axial. There are also axial hydrogen atoms on both C1 and C3. The base can attack either of these hydrogen atoms and achieve an anti coplanar transition state for an E2 reaction. Products corresponding to each of these transition states (2-menthene and 1-menthene) are formed rapidly. In accordance with Zaitsev's rule, 1-menthene (with the more highly substituted double bond) is the major product.

A MECHANISM FOR THE REACTION — E2 Elimination Where There Are Two Axial β Hydrogens



Neomenthyl chloride

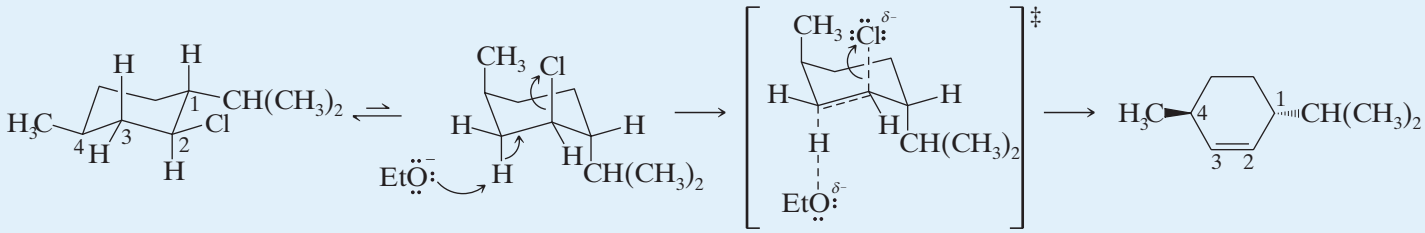
Both green hydrogens are anti to the chlorine in this, the more stable conformation. Elimination by path (a) leads to 1-menthene; by path (b) to 2-menthene.

1-Menthene (78%) (more stable alkene)

2-Menthene (22%) (less stable alkene)

On the other hand, the more stable conformation of menthyl chloride has all three groups (including the chlorine) equatorial. For the chlorine to become axial, menthyl chloride has to assume a conformation in which the large isopropyl group and the methyl group are also axial. This conformation is of much higher energy, and the free energy of activation for the reaction is large because it includes the energy necessary for the conformational change. Consequently, menthyl chloride undergoes an E2 reaction very slowly, and the product is entirely 2-menthene because the hydrogen atom at C1 cannot be anti to the chlorine. This product (or any resulting from an elimination to yield the less substituted alkene) is sometimes called the *Hofmann product* (Sections 7.6C and 18.11A).

A MECHANISM FOR THE REACTION — E2 Elimination Where the Only Axial β Hydrogen Is from a Less Stable Conformer



Menthyl chloride (*more stable conformation*)

Elimination is not possible for this conformation because no hydrogen is anti to the leaving group.

Menthyl chloride (*less stable conformation*)

Elimination is possible from this conformation because the green hydrogen is anti to the chlorine.

The transition state for the E2 elimination is anti coplanar.

2-Menthene (100%)

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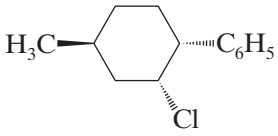
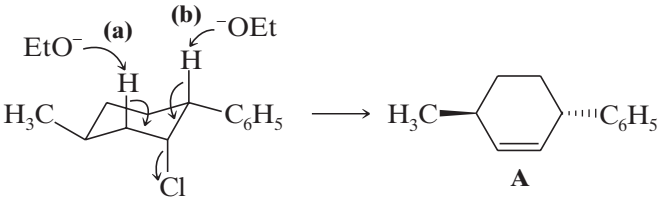
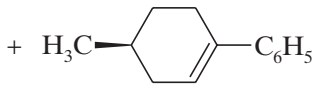
Solved Problem 7.5

Predict the major product formed when the following compound is subjected to dehydrochlorination with sodium ethoxide in ethanol.





Disubstituted, less stable (minor product)



Trisubstituted, more stable (major product)

Answer

We know that for an E2 dehydrochlorination to take place the chlorine will have to be axial. The following conformation has the chlorine axial and has two hydrogen atoms that are anti coplanar to the chlorine. Two products will be formed but **(B)** being more stable should be the major product.

Practice Problem 7.10

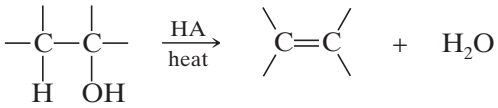
When *cis*-1-bromo-4-*tert*-butylcyclohexane is treated with sodium ethoxide in ethanol, it reacts rapidly; the product is 4-*tert*-butylcyclohexene. Under the same conditions, *trans*-1-bromo-4-*tert*-butylcyclohexane reacts very slowly. Write conformational structures and explain the difference in reactivity of these *cis–trans* isomers.

Practice Problem 7.11

(a) When *cis*-1-bromo-2-methylcyclohexane undergoes an E2 reaction, two products (cycloalkenes) are formed. What are these two cycloalkenes, and which would you expect to be the major product? Write conformational structures showing how each is formed. **(b)** When *trans*-1-bromo-2-methylcyclohexane reacts in an E2 reaction, only one cycloalkene is formed. What is this product? Write conformational structures showing why it is the only product.

7.7 | ACID-CATALYZED DEHYDRATION OF ALCOHOLS

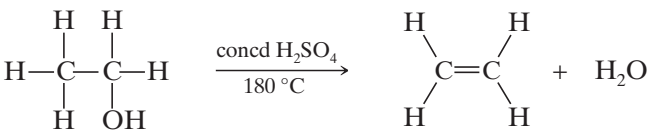
- Most alcohols undergo **dehydration** (lose a molecule of water) to form an alkene when heated with a strong acid.



The reaction is an **elimination** and is favored at higher temperatures (Section 6.18A). The most commonly used acids in the laboratory are Brønsted acids—proton donors such as sulfuric acid and phosphoric acid. Lewis acids such as alumina (Al_2O_3) are often used in industrial, gas-phase dehydrations.

1. **The temperature and concentration of acid required to dehydrate an alcohol depend on the structure of the alcohol substrate.**

   (a) Primary alcohols are the most difficult to dehydrate. Dehydration of ethanol, for example, requires concentrated sulfuric acid and a temperature of 180 °C:



Ethanol (a 1° alcohol) **Ethene**

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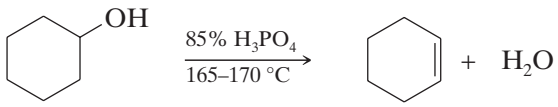
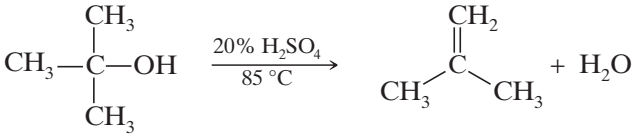
(b) Secondary alcohols usually dehydrate under milder conditions. Cyclohexanol, for example, dehydrates in 85% phosphoric acid at 165–170 °C:



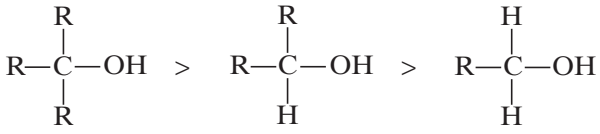
Cyclohexanol — **Cyclohexene (80%)**

(c) Tertiary alcohols are usually so easily dehydrated that relatively mild conditions can be used. *tert*-Butyl alcohol, for example, dehydrates in 20% aqueous sulfuric acid at a temperature of 85 °C:



***tert*-Butyl alcohol** — **2-Methylpropene (84%)**

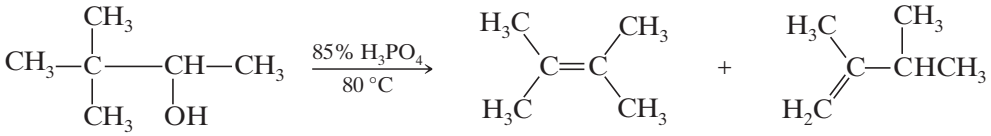
- The relative ease with which alcohols undergo dehydration is 3° > 2° > 1°.



3° Alcohol **2° Alcohol** **1° Alcohol**

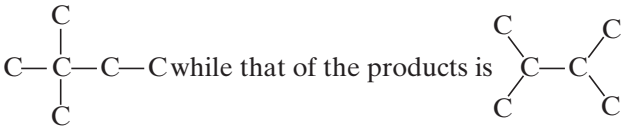
This behavior, as we shall see in Section 7.7B, is related to the relative stabilities of carbocations.

2. **Some primary and secondary alcohols also undergo rearrangements of their carbon skeletons during dehydration.** Such a rearrangement occurs in the dehydration of 3,3-dimethyl-2-butanol:



3,3-Dimethyl-2-butanol — **2,3-Dimethyl-2-butene (80%)** — **2,3-Dimethyl-1-butene (20%)**

Notice that the carbon skeleton of the reactant is



while that of the products is

The carbon skeleton has rearranged

We shall see in Section 7.8 that this reaction involves the migration of a methyl group from one carbon to the next so as to form a more stable carbocation. (Rearrangements to carbocations of approximately equal energy may also be possible with some substrates.)

7.7A Mechanism for Dehydration of Secondary and Tertiary Alcohols: An E1 Reaction

Explanations for these observations can be based on a stepwise mechanism originally proposed by F. Whitmore (of Pennsylvania State University).

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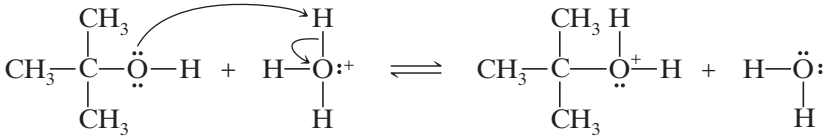
The mechanism is an E1 reaction in which the substrate is a protonated alcohol. Consider the dehydration of *tert*-butyl alcohol as an example:

Step 1

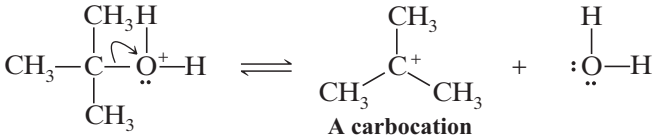


Protonation of the alcohol

In this step, an acid–base reaction, a proton is rapidly transferred from the acid to one of the unshared electron pairs of the alcohol. In dilute sulfuric acid the acid is a hydronium ion; in concentrated sulfuric acid the initial proton donor is sulfuric acid itself. This step is characteristic of all reactions of an alcohol with a strong acid.

The presence of the positive charge on the oxygen of the protonated alcohol weakens all bonds to oxygen, including the carbon–oxygen bond, and in step 2 the carbon–oxygen bond breaks. The leaving group is a molecule of water:

Step 2

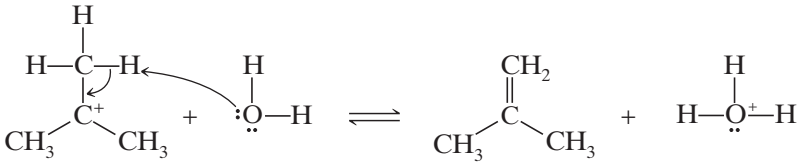


Departure of a water molecule

The carbon–oxygen bond breaks **heterolytically.** The bonding electrons depart with the water molecule and leave behind a carbocation. The carbocation is, of course, highly reactive because the central carbon atom has only six electrons in its valence level, not eight.

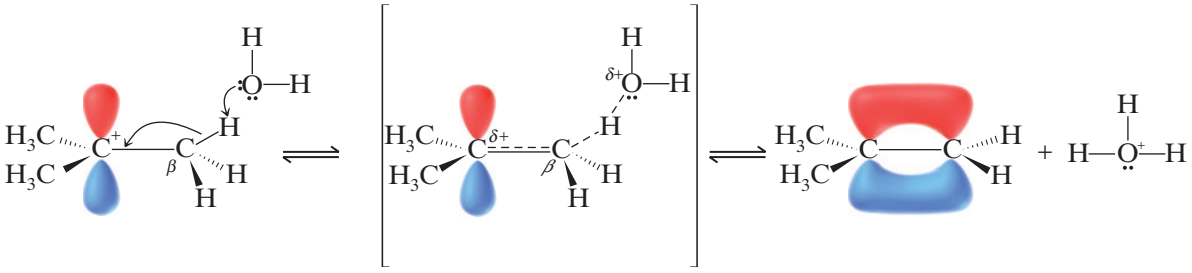
Finally, in step 3, a water molecule removes a proton from the β carbon of the carbocation by the process shown below. The result is the formation of a hydronium ion and an alkene:

Step 3



Removal of a β hydrogen

In step 3, also an acid–base reaction, any one of the nine protons available at the three methyl groups can be transferred to a molecule of water. The electron pair left behind when a proton is removed becomes the second bond of the double bond of the alkene. Notice that this step restores an octet of electrons to the central carbon atom. An orbital representation of this process, with the transition state, is as follows.



Transition state for removal of a proton from the β carbon of the carbocation

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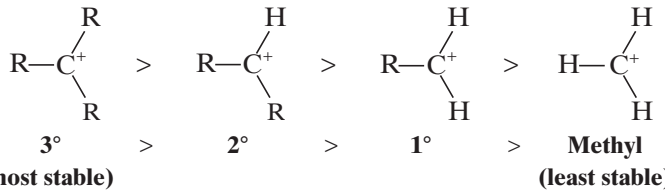
Practice Problem 7.12

Dehydration of 2-propanol occurs in 14 M H_2SO_4 at 100 °C. **(a)** Using curved arrows, write all steps in a mechanism for the dehydration. **(b)** Explain the essential role performed in alcohol dehydrations by the acid catalyst. [*Hint:* Consider what would have to happen if no acid were present.]

7.7B Carbocation Stability and the Transition State

We saw in Section 6.11B that the order of stability of carbocations is tertiary > secondary > primary > methyl:



In the dehydration of secondary and tertiary alcohols the slowest step is formation of the carbocation as shown in step 2 of the "A Mechanism for the Reaction" box in this section. The first and third steps involve simple acid–base proton transfers, which occur very rapidly. The second step involves loss of the protonated hydroxyl as a leaving group, a highly endergonic process (Section 6.7), and hence it is the rate-determining step.

Because step 2 is the rate-determining step, it is this step that determines the overall reactivity of alcohols toward dehydration. With that in mind, we can now understand why tertiary alcohols are the most easily dehydrated. The formation of a tertiary carbocation is easiest because the free energy of activation for step 2 of a reaction leading to a tertiary carbocation is lowest (see Fig. 7.7). Secondary alcohols are not so easily dehydrated because the free energy of activation for their dehydration is higher—a secondary carbocation is less stable. The free energy of activation for dehydration of primary alcohols via a carbocation is so high that they undergo dehydration by another mechanism (Section 7.7C).

The reactions by which carbocations are formed from protonated alcohols are all highly *endergonic*. Based on the Hammond–Leffler postulate (Section 6.13A), there should be a strong resemblance between the transition state and the carbocation in each case.

- ***The transition state that leads to the tertiary carbocation is lowest in free energy because it resembles the carbocation that is lowest in energy.***

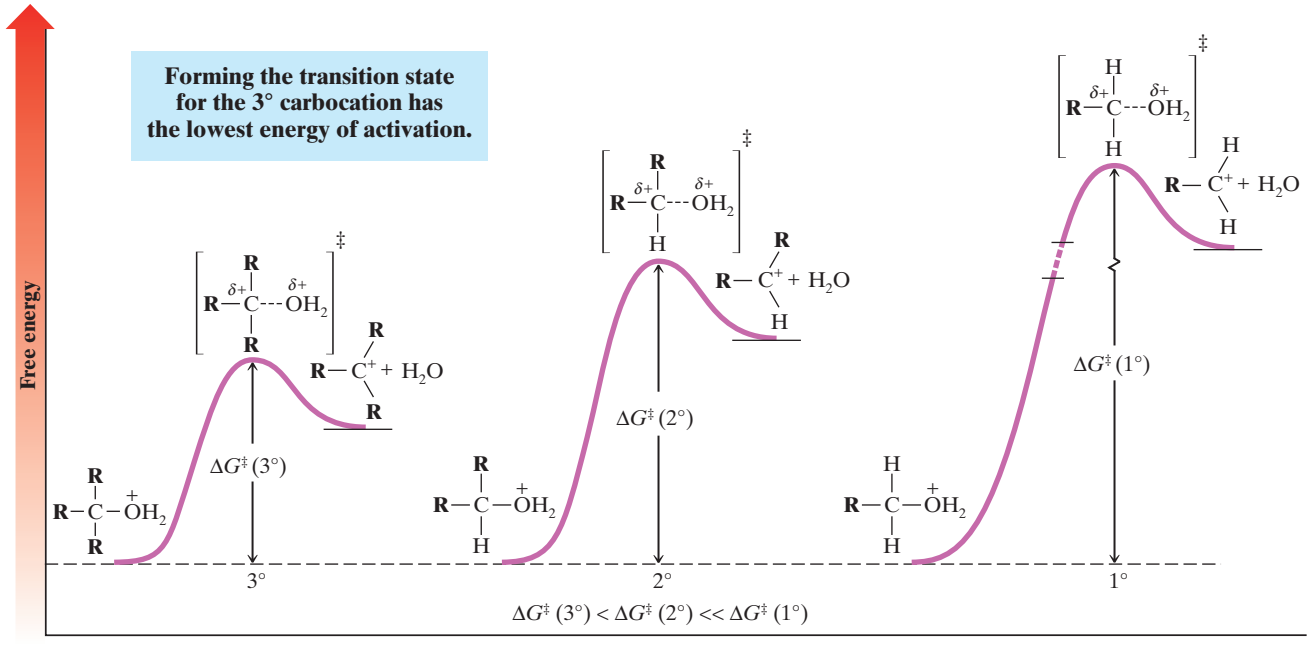


Figure 7.7 Free-energy diagrams for the formation of carbocations from protonated tertiary, secondary, and primary alcohols. The relative free energies of activation are tertiary < secondary ≪ primary.

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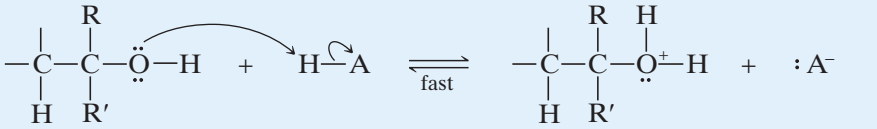
A MECHANISM FOR THE REACTION Acid-Catalyzed Dehydration of Secondary or Tertiary Alcohols: An E1 Reaction

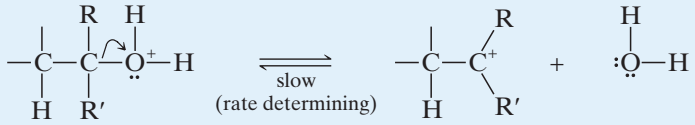
Step 1



2° or 3° Alcohol (R′ may be H) | **Acid catalyst (typically sulfuric or phosphoric acid)** | **Protonated alcohol** | **Conjugate base**

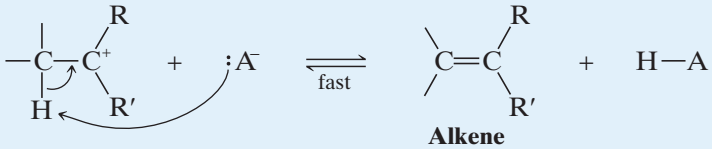
The alcohol accepts a proton from the acid in a fast step.

Step 2



The protonated alcohol loses a molecule of water to become a carbocation. This step is slow and rate determining.

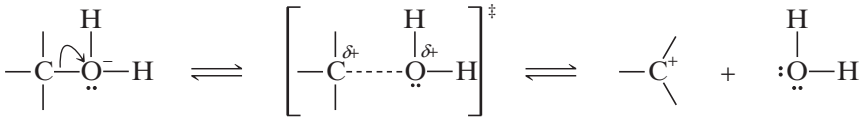
Step 3



Alkene

The carbocation loses a proton to a base. In this step, the base may be another molecule of the alcohol, water, or the conjugate base of the acid. The proton transfer results in the formation of the alkene. Note that the overall role of the acid is catalytic (it is used in the reaction and regenerated).

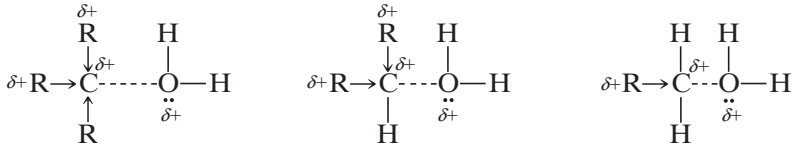
By contrast, the transition state that leads to the primary carbocation occurs at highest free energy because it resembles the carbocation that is highest in energy. In each instance, moreover, the same factor stabilizes the transition state that stabilizes the carbocation itself: **delocalization of the charge**. We can understand this if we examine the process by which the transition state is formed:



Protonated alcohol | **Transition state** | **Carbocation**

The oxygen atom of the protonated alcohol bears a full positive charge. As the transition state develops, this oxygen atom begins to separate from the carbon atom to which it is attached. The carbon atom begins to develop a partial positive charge because it is losing the electrons that bonded it to the oxygen atom. This developing positive charge ***is most effectively delocalized in the transition state leading to a tertiary carbocation because three alkyl groups are present to contribute electron density by hyperconjugation (Section 6.11B) to the developing carbocation***. The positive charge is less effectively delocalized in the transition state leading to a secondary carbocation (*two* electron-releasing groups) and is least effectively delocalized in the transition state leading to a primary carbocation (*one* electron-releasing group). For this reason the dehydration of a primary alcohol proceeds through a different mechanism—an E2 mechanism.

Hyperconjugative stabilization (see Figure 6.7) is greatest for a tertiary carbocation.



Transition state leading to 3° carbocation (most stable) | **Transition state leading to 2° carbocation** | **Transition state leading to 1° carbocation (least stable)**

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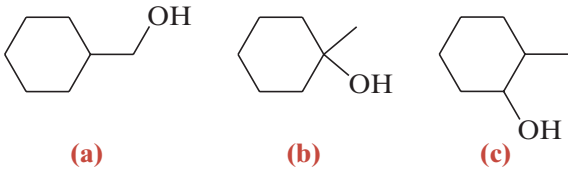
Practice Problem 7.13

Rank the following alcohols in order of increasing ease of acid-catalyzed dehydration.

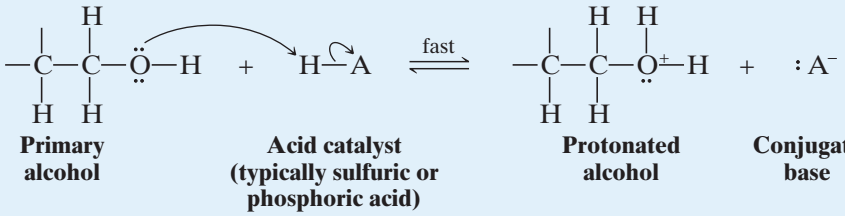


(a) (b) (c)

7.7C A Mechanism for Dehydration of Primary Alcohols: An E2 Reaction

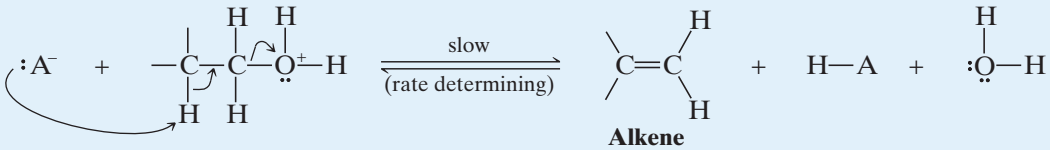
Dehydration of primary alcohols apparently proceeds through an E2 mechanism because the primary carbocation required for dehydration by an E1 mechanism is relatively unstable. The first step in dehydration of a primary alcohol is protonation, just as in the E1 mechanism. Then, with the protonated hydroxyl as a good leaving group, a Lewis base in the reaction mixture removes a β hydrogen simultaneously with formation of the alkene double bond and departure of the protonated hydroxyl group (water).

A MECHANISM FOR THE REACTION — Dehydration of a Primary Alcohol: An E2 Reaction



Primary alcohol | **Acid catalyst (typically sulfuric or phosphoric acid)** | **Protonated alcohol** | **Conjugate base**

The alcohol accepts a proton from the acid in a fast step.



Alkene

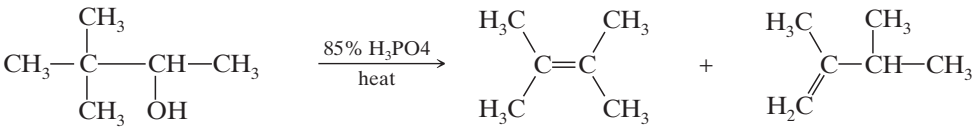
A base removes a hydrogen from the β carbon as the double bond forms and the protonated hydroxyl group departs. The base may be another molecule of the alcohol or the conjugate base of the acid.

7.8 | CARBOCATION STABILITY AND THE OCCURRENCE OF MOLECULAR REARRANGEMENTS

With an understanding of carbocation stability and its effect on transition states, we can now proceed to explain the rearrangements of carbon skeletons that occur in some alcohol **dehydrations**.

7.8A Rearrangements During Dehydration of Secondary Alcohols

Consider again the **rearrangement** that occurs when 3,3-dimethyl-2-butanol is dehydrated:



3,3-Dimethyl-2-butanol | **2,3-Dimethyl-2-butene (major product)** | **2,3-Dimethyl-1-butene (minor product)**

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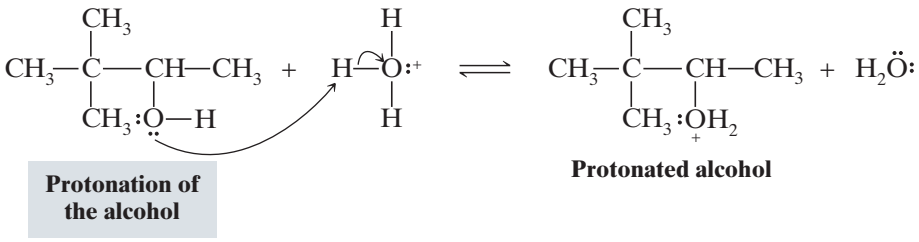
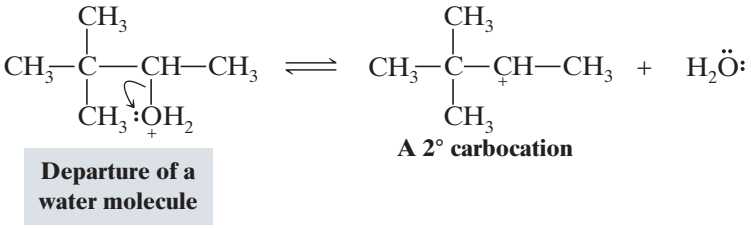
The first step of this dehydration is the formation of the protonated alcohol in the usual way:

Step 1



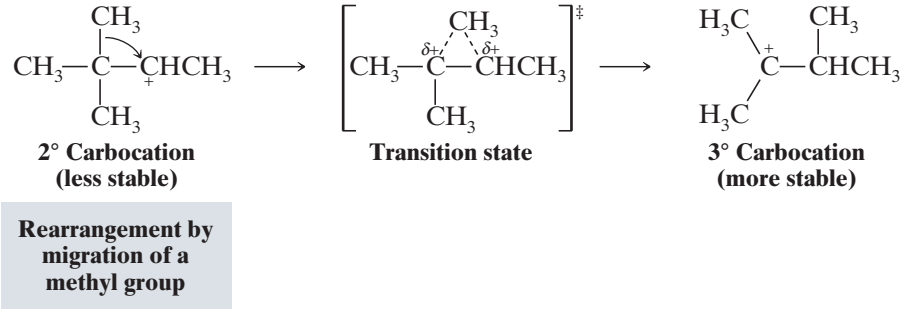
In the second step the protonated alcohol loses water and a secondary carbocation forms:

Step 2



Now the rearrangement occurs. ***The less stable, secondary carbocation rearranges to a more stable tertiary carbocation:***

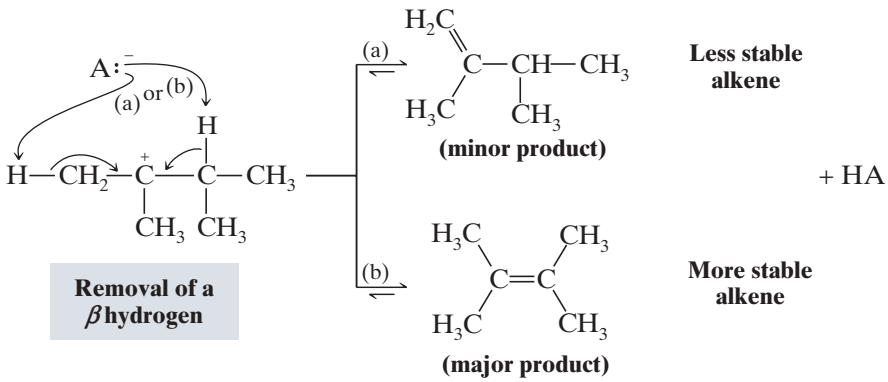
Step 3



The rearrangement occurs through the migration of an alkyl group (methyl) from the carbon atom adjacent to the one with the positive charge. The methyl group migrates **with its pair of electrons** (called a **methanide** shift). In the transition state the shifting methyl is partially bonded to both carbon atoms by the pair of electrons with which it migrates. It never leaves the carbon skeleton. After the migration is complete, the carbon atom that the methyl anion left has become a carbocation, and the positive charge on the carbon atom to which it migrated has been neutralized. Because a group migrates from one carbon to an adjacent one, this kind of rearrangement is also called a **1,2 shift**.

The final step of the reaction is the removal of a proton from the new carbocation (by a Lewis base in the reaction mixture) and the formation of an alkene. This step, however, can occur in two ways:

Step 4



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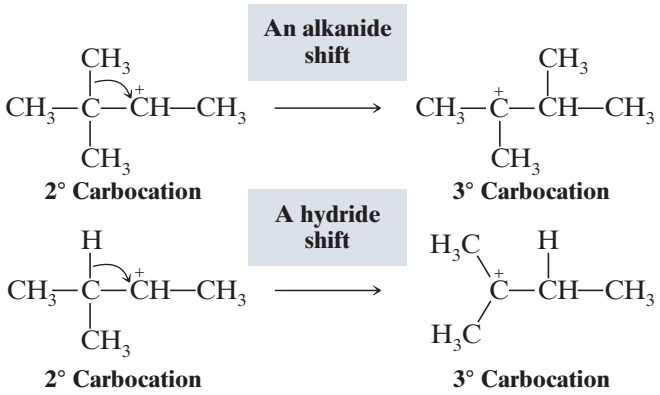
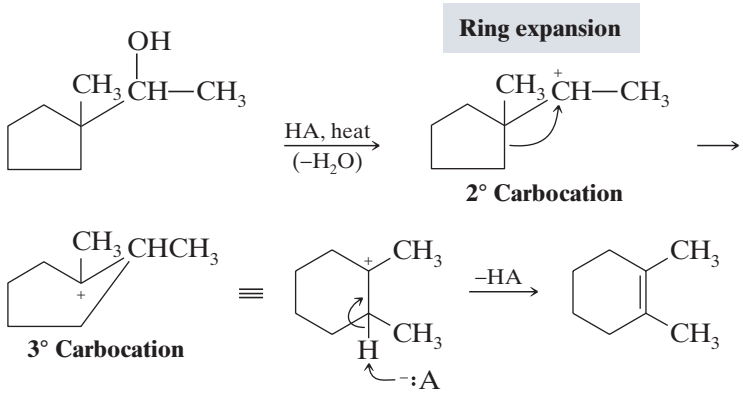
The more favored product is dictated by the stability of the alkene being formed. The conditions for the reaction (heat and acid) allow **equilibrium to be achieved** between the two forms of the alkene, and **the more stable alkene is the major product because it has lower potential energy**. Such a reaction is said to be **under equilibrium** or **thermodynamic control**. Path (b) leads to the highly stable tetrasubstituted alkene and this is the path followed by most of the carbocations. Path (a), on the other hand, leads to a less stable, disubstituted alkene, and because its potential energy is higher, it is the minor product of the reaction.

- **Formation of the more stable alkene is the general rule in acid-catalyzed dehydration of alcohols (Zaitsev's rule).**

Studies of many reactions involving carbocations show that rearrangements like those just described are general phenomena. ***They occur almost invariably when an alkanide shift or hydride shift can lead to a more stable carbocation***. The following are examples:



Rearrangements of carbocations can also lead to a change in ring size, as the following example shows:

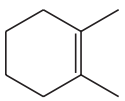


Ring expansion by migration is especially favorable if relief in ring strain occurs.

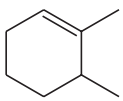
It is important to note that rearrangements to carbocations having approximately equal energy are also possible (e.g., from one secondary carbocation to another), and this can complicate the mixture of products that might be obtained from a reaction.

Solved Problem 7.6

Explain why the major product of the dehydration above is 1,2-dimethylcyclohexene (as shown) and not 2,3-dimethyl-1-cyclohexene.



1,2-Dimethylcyclohexene (major product)



2,3-Dimethyl-1-cyclohexene (minor product)

Answer

We have just learned that dehydration leads mainly to the more stable alkene (when two are possible). We also know that the stability of an alkene is related to the number of alkyl groups that are attached to the carbons of the double bond. 1,2-Dimethylcyclohexene has a tetrasubstituted double bond (and is more stable), while in 2,3-dimethylcyclohexene the double bond is only trisubstituted.

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Practice Problem 7.14

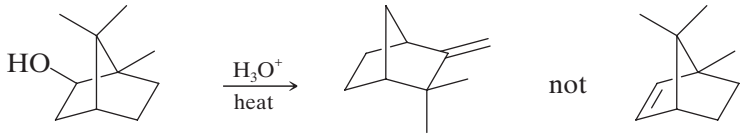
Acid-catalyzed dehydration of neopentyl alcohol, $(CH_3)_3CCH_2OH$, yields 2-methyl-2-butene as the major product. Outline a mechanism showing all steps in its formation.

Practice Problem 7.15

Acid-catalyzed dehydration of either 2-methyl-1-butanol or 3-methyl-1-butanol gives 2-methyl-2-butene as the major product. Write plausible mechanisms that explain these results.

Practice Problem 7.16

When the compound called *isoborneol* is heated with 9 M sulfuric acid, the product of the reaction is the compound called camphene and not bornylene, as one might expect. Using models to assist you, write a step-by-step mechanism showing how camphene is formed.

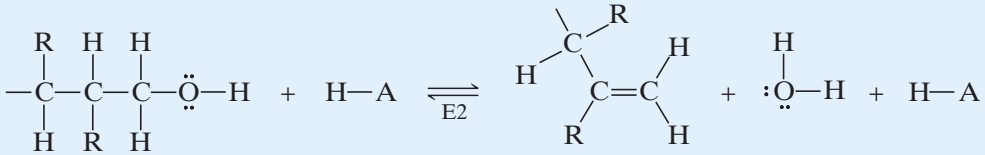


Isoborneol **Camphene** **Bornylene**

7.8B Rearrangement After Dehydration of a Primary Alcohol

Rearrangements also accompany the dehydration of primary alcohols. Since a primary carbocation is unlikely to be formed during dehydration of a primary alcohol, the alkene that is produced initially from a primary alcohol arises by an E2 mechanism, as described in Section 7.7C. However, an alkene can accept a proton to *generate* a carbocation in a process that is essentially the reverse of the *deprotonation* step in the E1 mechanism for dehydration of an alcohol (Section 7.7A). When a terminal alkene does this by using its π electrons to bond a proton at the terminal carbon, a carbocation forms at the second carbon of the chain.* This carbocation, since it is internal to the chain, will be secondary or tertiary, depending on the specific substrate. Various processes that you have already learned can now occur from this carbocation: (1) a different β hydrogen may be removed, leading to a more stable alkene than the initially formed terminal alkene; (2) a hydride or alkanide rearrangement may occur leading to a yet more stable carbocation (e.g., moving from a 2° to a 3° carbocation) or to a carbocation of approximately equal stability, after which the elimination may be completed; or (3) a nucleophile may attack any of these carbocations to form a substitution product. Under the high-temperature conditions for alcohol dehydration the principal products will be alkenes rather than substitution products.

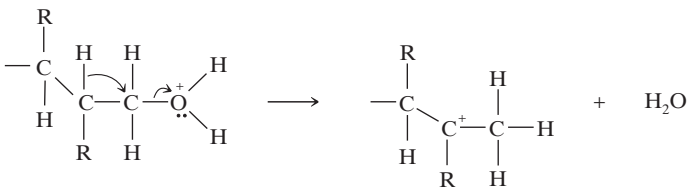
A MECHANISM FOR THE REACTION — Formation of a Rearranged Alkene During Dehydration of a Primary Alcohol



Primary alcohol (R may be H) **Initial alkene**

The primary alcohol initially undergoes acid-catalyzed dehydration by an E2 mechanism (Section 7.7C).

*The carbocation could also form directly from the primary alcohol by a hydride shift from its β carbon to the terminal carbon as the protonated hydroxyl group departs:



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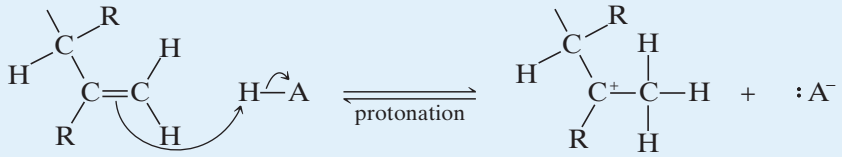
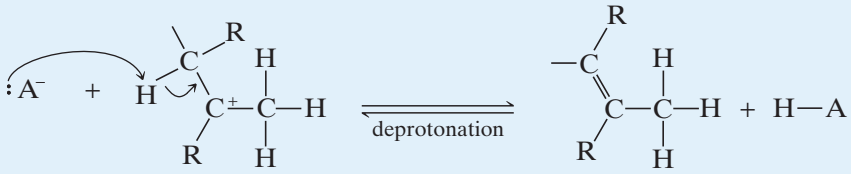


The π electrons of the initial alkene can then be used to form a bond with a proton at the terminal carbon, forming a secondary or tertiary carbocation.*



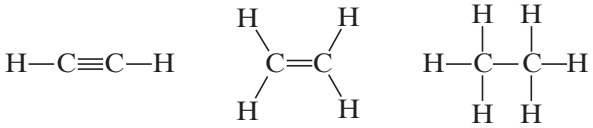
Final alkene

A different β hydrogen can be removed from the carbocation, so as to form a more highly substituted alkene than the initial alkene. This deprotonation step is the same as the usual completion of an E1 elimination. (This carbocation could experience other fates, such as further rearrangement before elimination or substitution by an S_N1 process.)

7.9 | THE ACIDITY OF TERMINAL ALKYNES

The hydrogen bonded to the carbon of a terminal alkyne, called an **acetylenic hydrogen atom**, is considerably more acidic than those bonded to carbons of an alkene or alkane (see Section 3.9A). The pK_a values for ethyne, ethene, and ethane illustrate this point:

A terminal alkyne is ~10^{20} times more acidic than an alkene or alkane.



pK_a = 25 **pK_a = 44** **pK_a = 50**

The order of basicity of their anions is opposite that of their relative acidity:

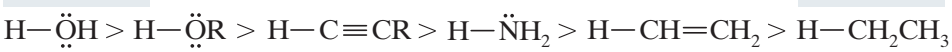
Relative Basicity

$$CH_3CH_2{:}^- > CH_2{=}CH{:}^- > HC{\equiv}C{:}^-$$

If we include in our comparison hydrogen compounds of other first-row elements of the periodic table, we can write the following orders of relative acidities and basicities. This comparison is useful as we consider what bases and solvents to use with terminal alkynes.

Relative Acidity

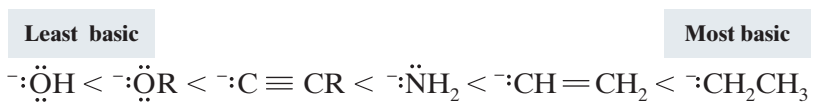
Most acidic **Least acidic**



pK_a 15.7 16–17 25 38 44 50

Relative Basicity

Least basic **Most basic**



We see from the order just given that while terminal alkynes are more acidic than ammonia, they are less acidic than alcohols and are less acidic than water.

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Solved Problem 7.7

As we shall soon see, sodium amide ($NaNH_2$) is useful, especially when a reaction requires a very strong base. Explain why a solvent such as methanol cannot be used to carry out a reaction in which you might want to use sodium amide as a base.

Answer

An alcohol has pK_a = 16–17, and ammonia has pK_a = 38. This means that methanol is a significantly stronger acid than ammonia, and the conjugate base of ammonia (the $^-NH_2$ ion) is a significantly stronger base than an alkoxide ion. Therefore, the following acid–base reaction would take place as soon as sodium amide is added to methanol.

$$\underset{\text{Stronger acid}}{CH_3OH} + \underset{\text{Stronger base}}{NaNH_2} \xrightarrow[CH_3OH]{} \underset{\text{Weaker base}}{CH_3ONa} + \underset{\text{Weaker acid}}{NH_3}$$

With a pK_a difference this large, the sodium amide would convert all of the methanol to sodium methoxide, a much weaker base than sodium amide. (This is an example of what is called the leveling effect of a solvent.)

Practice Problem 7.17

Predict the products of the following acid–base reactions. If the equilibrium would not result in the formation of appreciable amounts of products, you should so indicate. In each case label the stronger acid, the stronger base, the weaker acid, and the weaker base:

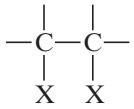
(a) $CH_3CH{=}CH_2 + NaNH_2 \rightarrow$ **(b)** $CH_3C{\equiv}CH + NaNH_2 \rightarrow$ **(c)** $CH_3CH_2CH_3 + NaNH_2 \rightarrow$

(d) $CH_3C{\equiv}C{:}^- + CH_3CH_2OH \rightarrow$ **(e)** $CH_3C{\equiv}C{:}^- + NH_4Cl \rightarrow$

7.10 | SYNTHESIS OF ALKYNES BY ELIMINATION REACTIONS

- Alkynes can be synthesized from alkenes via compounds called vicinal dihalides.

A vicinal dihalide (abbreviated ***vic*-dihalide**) is a compound bearing the halogens on adjacent carbons (*vicinus,* Latin: adjacent). Vicinal dihalides are also called 1,2-dihalides. A vicinal dibromide, for example, can be synthesized by addition of bromine to an alkene (Section 8.1). The *vic*-dibromide can then be subjected to a double dehydrohalogenation reaction with a strong base to yield an alkyne.



A *vic*–dihalide

Vicinal dihalide formation **Double dehydrohalogenation**

$$RCH{=}CHR + Br_2 \longrightarrow \underset{\text{A } \textit{vic}\text{-dibromide}}{R{-}\overset{H}{\overset{|}{C}}{-}\overset{H}{\overset{|}{C}}{-}R} \xrightarrow{2\ NaNH_2} R{-}C{\equiv}C{-}R + 2\ NH_3 + 2\ NaBr$$

The dehydrohalogenations occur in two steps, the first yielding a bromoalkene, and the second, the alkyne.

7.10A Laboratory Application of This Alkyne Synthesis

The two dehydrohalogenations may be carried out as separate reactions, or they may be carried out consecutively in a single mixture. Sodium amide ($NaNH_2$), a very strong base, can be used to cause both reactions in a single mixture. At least two molar equivalents of sodium amide per mole of the dihalide must be used. For example, adding bromine to 1,2-diphenylethene provides the vicinal dihalide needed for a synthesis of 1,2-diphenylethyne:

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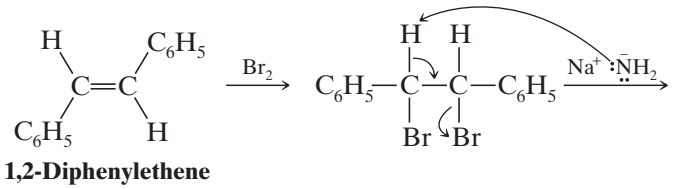
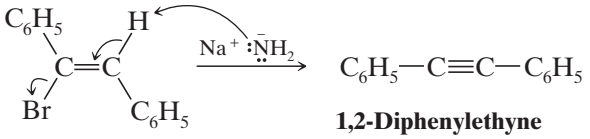


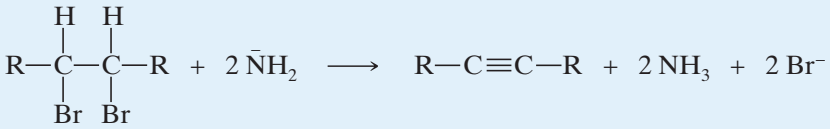
1,2-Diphenylethene



1,2-Diphenylethyne

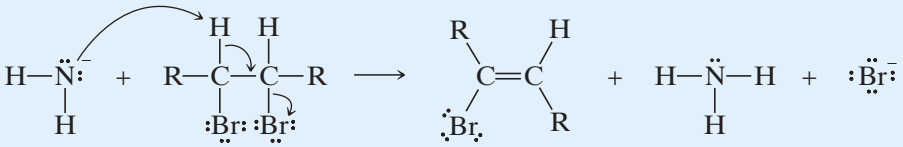
A MECHANISM FOR THE REACTION — Dehydrohalogenation of *vic*-Dibromides to Form Alkynes

Reaction



Mechanism

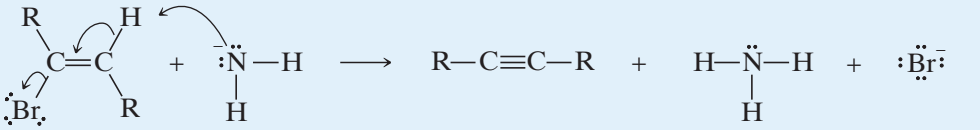
Step 1



Amide ion | ***vic*-Dibromide** | **Bromoalkene** | **Ammonia** | **Bromide ion**

The strongly basic amide ion brings about an E2 reaction.

Step 2



Bromoalkene | **Amide ion** | **Alkyne** | **Ammonia** | **Bromide ion**

A second E2 reaction produces the alkyne.

- If the product is to be an alkyne with a triple bond at the end of the chain (a terminal alkyne) as we show in the example below, then three molar equivalents of sodium amide are required.

Initial dehydrohalogenation of the *vic*-dihalide produces a mixture of two bromoalkenes that are not isolated but that undergo a second dehydrohalogenation. The terminal alkyne that results from this step is deprotonated (because of its acidity) by the third mole of sodium amide (see Section 7.9). To complete the process, addition of ammonium chloride converts the sodium alkynide to the desired product, 1-butyne.

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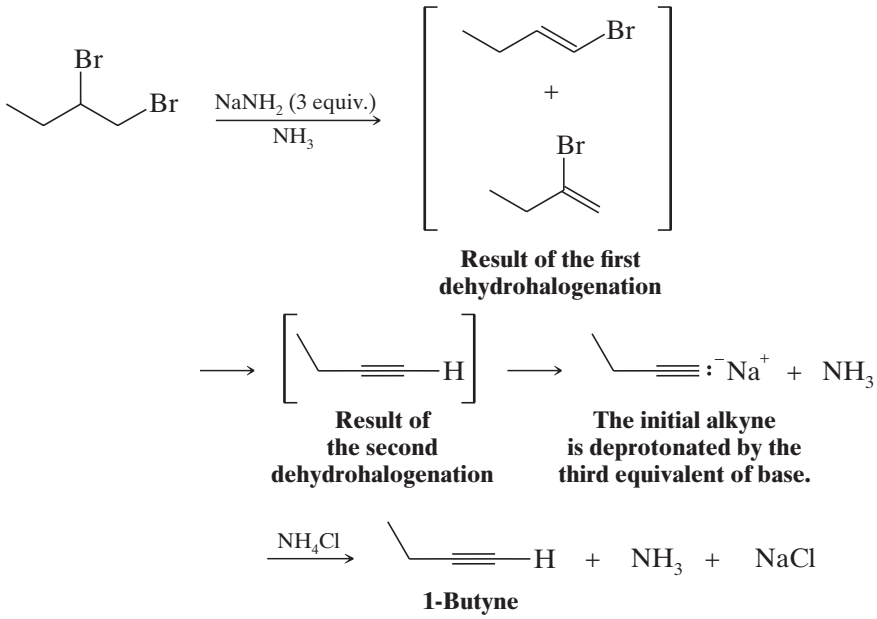
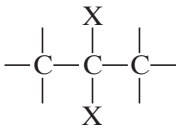
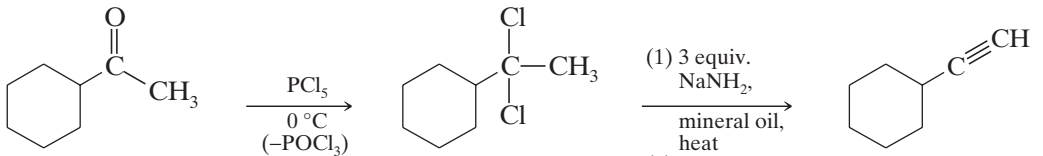


- **Geminal** dihalides can also be converted to alkynes by dehydrohalogenation.

A geminal dihalide (abbreviated ***gem*-dihalide**) has two halogen atoms bonded to the same carbon (*geminus,* Latin: twins). Ketones can be converted to *gem*-dichlorides by reaction with phosphorus pentachloride, and the *gem*-dichlorides can be used to synthesize alkynes.



A *gem*–dihalide



Cyclohexyl methyl ketone → **A *gem*-dichloride (70–80%)** → **Cyclohexylacetylene (46%)**

Practice Problem 7.18

Show how you might synthesize ethynylbenzene from methyl phenyl ketone.

Practice Problem 7.19

Outline all steps in a synthesis of propyne from each of the following:

(a) CH_3COCH_3 **(b)** $CH_3CH_2CHBr_2$ **(c)** $CH_3CHBrCH_2Br$ **(d)** $CH_3CH{=}CH_2$

7.11 | TERMINAL ALKYNES CAN BE CONVERTED TO NUCLEOPHILES FOR CARBON–CARBON BOND FORMATION

- The acetylenic proton of ethyne or any terminal alkyne (pK_a 25) can be removed with a strong base such as sodium amide ($NaNH_2$). The result is an alkynide anion.

$$H{-}C{\equiv}C{-}H + NaNH_2 \xrightarrow[\text{liq. } NH_3]{} H{-}C{\equiv}C{:}^{-}\,Na^{+} + NH_3$$

$$CH_3C{\equiv}C{-}H + NaNH_2 \xrightarrow[\text{liq. } NH_3]{} CH_3C{\equiv}C{:}^{-}\,Na^{+} + NH_3$$

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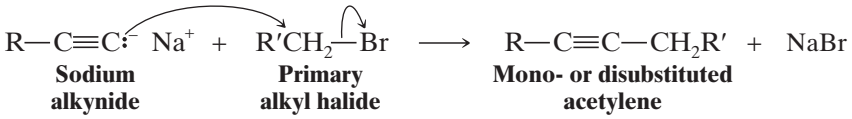
- Alkynide anions are useful nucleophiles for carbon–carbon bond forming reactions with primary alkyl halides or other primary substrates.

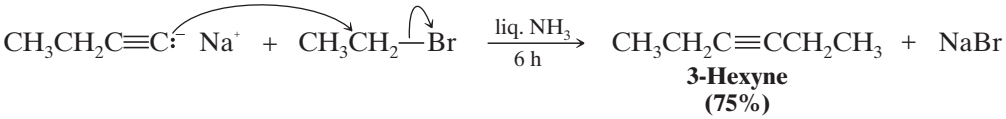
The following are general and specific examples of carbon–carbon bond formation by alkylation of an alkynide anion with a primary alkyl halide.

General Example

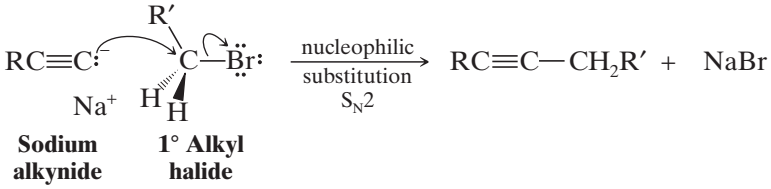


(R or R′ or both may be hydrogen.)

Specific Example

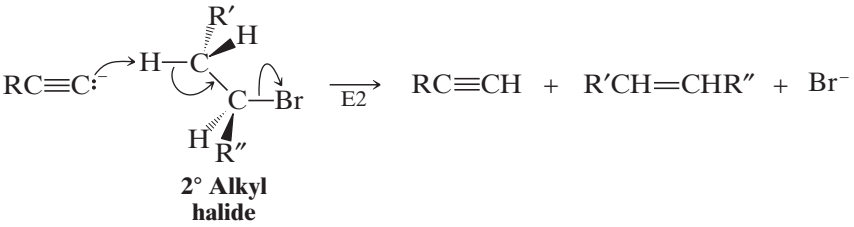


The alkynide anion acts as a nucleophile and displaces the halide ion from the primary alkyl halide. We now recognize this as an S_N2 reaction (Section 6.5).



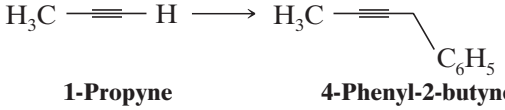
- Primary alkyl halides should be used in the alkylation of alkynide anions, so as to avoid competition by elimination.

Use of a secondary or tertiary substrate causes E2 elimination instead of substitution because the alkynide anion is a strong base as well as a good nucleophile.



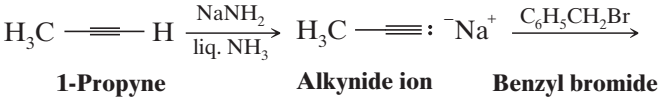
Solved Problem 7.8

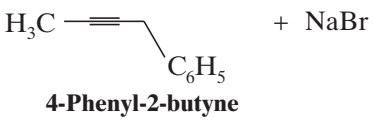
Outline a synthesis of 4-phenyl-2-butyne from 1-propyne.



Answer

Take advantage of the acidity of the acetylenic hydrogen of propyne and convert it to an alkynide anion using sodium amide, a base that is strong enough to remove the acetylenic hydrogen. Then use the akynide ion as a nucleophile in an S_N2 reaction with benzyl bromide.





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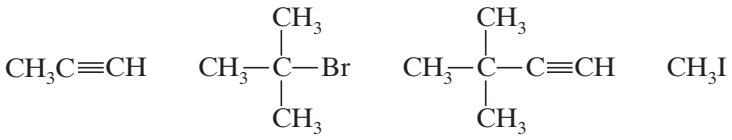
Practice Problem 7.20

Your goal is to synthesize 4,4-dimethyl-2-pentyne. You have a choice of beginning with any of the following reagents:



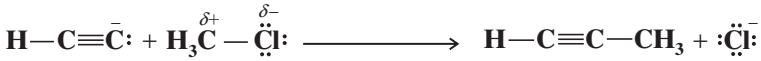
Assume that you also have available sodium amide and liquid ammonia. Outline the best synthesis of the required compound.

7.11A General Principles of Structure and Reactivity Illustrated by the Alkylation of Alkynide Anions

The **alkylation** of alkynide anions illustrates several essential aspects of structure and reactivity that have been important to our study of organic chemistry thus far.

1. Preparation of the alkynide anion involves simple **Brønsted–Lowry acid–base chemistry.** As you have seen (Sections 7.9 and 7.11), the hydrogen of a terminal alkyne is weakly acidic ($pK_a \cong 25$), and with a strong base such as sodium amide it can be removed. The reason for this acidity was explained in Section 3.8A.
2. Once formed, the alkynide anion is a **Lewis base** (Section 3.3) with which the alkyl halide reacts as an electron pair acceptor (a **Lewis acid**). The alkynide anion can thus be called a ***nucleophile*** (Sections 3.4 and 6.3) because of the negative charge concentrated at its terminal carbon—it is a reagent that seeks positive charge.
3. The alkyl halide can be called an ***electrophile*** (Sections 3.4 and 8.1) because of the partial positive charge at the carbon bearing the halogen—it is a reagent that seeks negative charge. Polarity in the alkyl halide is the direct result of the difference in electronegativity between the halogen atom and carbon atom.

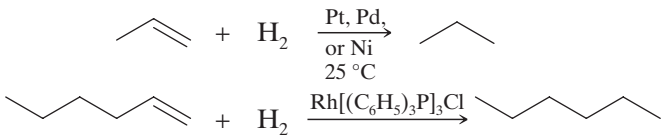
The ethynide anion has strong localization of negative charge at its terminal carbon. Conversely, chloromethane has partial positive charge at the carbon bonded to the electronegative chlorine atom. (The dipole moment for chloromethane is aligned directly along the carbon–chlorine bond.) Thus, acting as a Lewis base, the alkynide anion is attracted to the partially positive carbon of the alkyl halide. Assuming a collision between the two occurs with the proper orientation and sufficient kinetic energy, as the alkynide anion brings two electrons to the alkyl halide to form a new bond, it will displace the halogen from the alkyl halide. The halogen leaves as an anion with the pair of electrons that formerly bonded it to the carbon. This is an S_N2 reaction, of course, akin to others we discussed in Chapter 6.



7.12 | HYDROGENATION OF ALKENES

- Alkenes react with hydrogen in the presence of a variety of metal catalysts to add one hydrogen atom to each carbon atom of the double bond (Sections 5.16A, 4.10A).

Hydrogenation reactions that involve *insoluble* platinum, palladium, or nickel catalysts (Section 5.16A) proceed by **heterogeneous catalysis** because the catalyst is not soluble in the reaction mixture. Hydrogenation reactions that involve soluble catalysts occur by **homogeneous catalysis.** Typical homogeneous hydrogenation catalysts include rhodium and ruthenium complexes that bear various phosphorus and other ligands. One of the most well-known homogeneous hydrogenation catalysts is Wilkinson's catalyst, tris(triphenylphosphine)rhodium chloride, $Rh[(C_6H_5)_3P]_3Cl$. The following are some examples of hydrogenation reactions under heterogeneous and homogeneous catalysis:



Catalytic hydrogenation reactions, like those shown above, are a type of **addition reaction** (versus substitution or elimination), and they are also a type of reduction. This leads to a distinction between compounds that are saturated versus those that are unsaturated.

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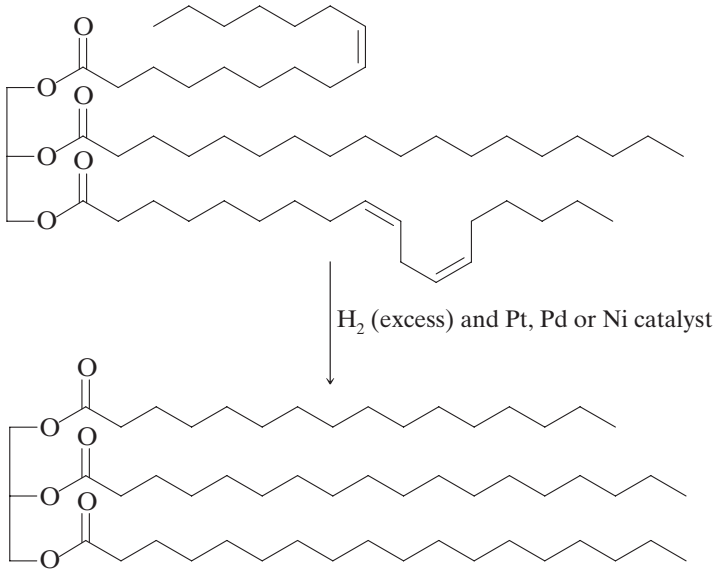
- Compounds containing only carbon–carbon single bonds (alkanes and others) are said to be **saturated compounds** because they contain the maximum number of hydrogen atoms that a given formula can possess.
- Compounds containing carbon–carbon multiple bonds (alkenes, alkynes, and aromatic compounds) are said to be **unsaturated compounds** because they contain fewer than the maximum number of hydrogen atoms possible for a given formula.

Unsaturated compounds can be **reduced** to saturated compounds by **catalytic hydrogenation**. The following example shows conversion of an unsaturated triglyceride to a saturated triglyceride (both are fats), in a catalytic hydrogenation reaction as might be done in the food industry to change the physical properties of a fat.



An unsaturated fat can be hydrogenated to form a saturated fat.

Molecules of a natural unsaturated fat can align less evenly with each other than can molecules of saturated fats due to the "kinks" from the *cis* double bonds in unsaturated fats. Hence intermolecular forces between unsaturated fat molecules are weaker and they have lower melting points than saturated fats. See "The Chemistry of … Hydrogenation in the Food Industry."

The Chemistry of... HYDROGENATION IN THE FOOD INDUSTRY

The food industry makes use of catalytic hydrogenation to convert liquid vegetable oils to semisolid fats in making margarine and solid cooking fats. Examine the labels of many prepared foods and you will find that they contain "partially hydrogenated vegetable oils." There are several reasons why foods contain these oils, but one is that partially hydrogenated vegetable oils have a longer shelf life.

Fats and oils are glyceryl esters of carboxylic acids with long carbon chains, called "fatty acids." Fatty acids are saturated (no double bonds), monounsaturated (one double bond), or polyunsaturated (more than one double bond). Oils typically contain a higher proportion of fatty acids with one or more double bonds than fats do. Partial hydrogenation of an oil converts some of its double bonds to single bonds, and this conversion has the effect of producing a fat with the consistency of margarine or a semisolid cooking fat.

One potential problem that arises from using catalytic hydrogenation to produce partially hydrogenated vegetable oils is that the catalysts used for



Photo by Lisa Gee

A product used in baking that contains oils and mono- and diacylglycerols that are partially hydrogenated.



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No (or zero%) trans fatty acids.

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hydrogenation cause isomerization of some of the double bonds of the fatty acids (some of those that do not absorb hydrogen). In most natural fats and oils, the double bonds of the fatty acids have the *cis* configuration. The catalysts used for hydrogenation convert some of these *cis* double bonds to the unnatural *trans* configuration. The health effects of *trans* fatty acids are still under study, but experiments thus far indicate that they cause an increase in serum levels of cholesterol and triacylglycerols, which in turn increases the risk of cardiovascular disease.

7.13 | HYDROGENATION: THE FUNCTION OF THE CATALYST

Hydrogenation of an alkene is an exothermic reaction ($\Delta H^\circ \cong -120$ kJ mol^{-1}):

$$\text{R—CH=CH—R} + \text{H}_2 \xrightarrow{\text{hydrogenation}} \text{R—CH}_2\text{—CH}_2\text{—R} + \text{heat}$$

Although the process is exothermic, there is usually a high free energy of activation for uncatalyzed alkene hydrogenation, and therefore, the uncatalyzed reaction does not take place at room temperature. However, hydrogenation will take place readily at room temperature in the presence of a catalyst because the catalyst provides a new pathway for the reaction that involves lower free energy of activation (Fig. 7.8).

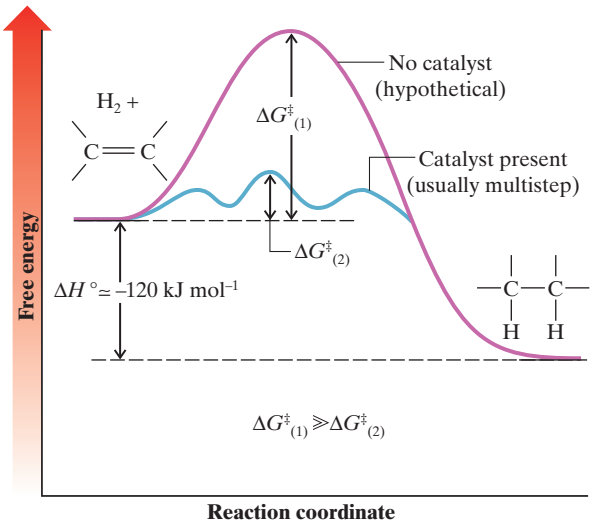

Figure 7.8 Free-energy diagram for the hydrogenation of an alkene in the presence of a catalyst and the hypothetical reaction in the absence of a catalyst. The free energy of activation for the uncatalyzed reaction ($\Delta G^{\ddagger}_{(1)}$) is very much larger than the largest free energy of activation for the catalyzed reaction ($\Delta G^{\ddagger}_{(2)}$). The uncatalyzed hydrogenation reaction does not occur.

Heterogeneous hydrogenation catalysts typically involve finely divided platinum, palladium, nickel, or rhodium deposited on the surface of powdered carbon (charcoal). Hydrogen gas introduced into the atmosphere of the reaction vessel adsorbs to the metal by a chemical reaction where unpaired electrons on the surface of the metal *pair* with the electrons of hydrogen (Fig. 7.9*a*) and bind the hydrogen to the surface. The collision of an alkene with the surface

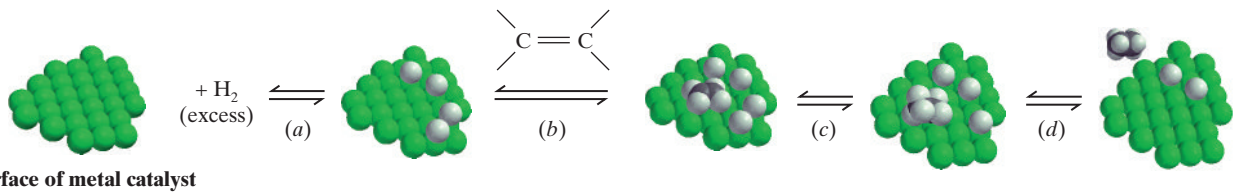

Figure 7.9 The mechanism for the hydrogenation of an alkene as catalyzed by finely divided platinum metal: (*a*) hydrogen adsorption; (*b*) adsorption of the alkene; (*c*, *d*) stepwise transfer of both hydrogen atoms to the same face of the alkene (syn addition).

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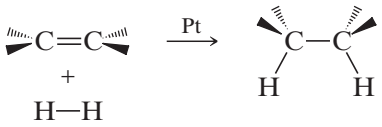
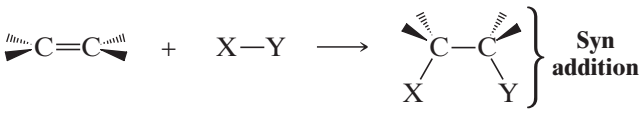
bearing adsorbed hydrogen causes adsorption of the alkene as well (Fig. 7.9*b*). A stepwise transfer of hydrogen atoms takes place, and this produces an alkane before the organic molecule leaves the catalyst surface (Figs. 7.10*c, d*). As a consequence, *both hydrogen atoms usually add from the same side of the molecule.* This mode of addition is called a **syn** addition (Section 7.14A):



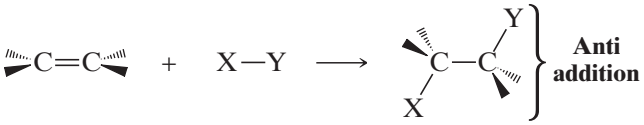
Catalytic hydrogenation is a syn addition.

7.13A Syn and Anti Additions

An addition that places the parts of the adding reagent on the same side (or face) of the reactant is called **syn addition**. We have just seen that the platinum-catalyzed addition of hydrogen (X = Y = H) is a syn addition:



The opposite of a syn addition is an **anti addition**. An anti addition places the parts of the adding reagent on opposite faces of the reactant.



In Chapter 8 we shall study a number of important syn and anti additions.

7.14 | HYDROGENATION OF ALKYNES

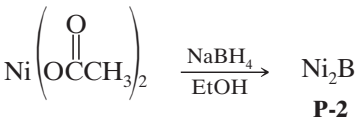
Depending on the conditions and the catalyst employed, one or two molar equivalents of hydrogen will add to a carbon–carbon triple bond. When a platinum catalyst is used, the alkyne generally reacts with two molar equivalents of hydrogen to give an alkane:

$$CH_3C{\equiv}CCH_3 \xrightarrow{Pt,\ H_2} [CH_3CH{=}CHCH_3] \xrightarrow{Pt,\ H_2} CH_3CH_2CH_2CH_3$$

However, **hydrogenation** of an alkyne to an alkene can be accomplished through the use of special catalysts or reagents. Moreover, these special methods allow the preparation of either (*E*)- or (*Z*)-alkenes from disubstituted alkynes.

7.14A Syn Addition of Hydrogen: Synthesis of *cis*-Alkenes

A **heterogeneous catalyst** that permits hydrogenation of an alkyne to an alkene is the nickel boride compound called P-2 catalyst. The P-2 catalyst can be prepared by the reduction of nickel acetate with sodium borohydride:



- Hydrogenation of alkynes in the presence of P-2 catalyst causes **syn addition of hydrogen**. The alkene formed from an internal alkyne has the (*Z*) or *cis* configuration.

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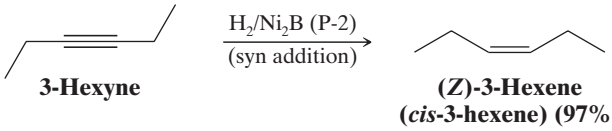
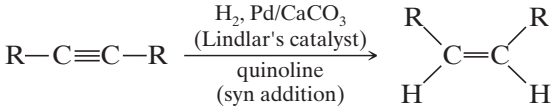
The hydrogenation of 3-hexyne illustrates this method. The reaction takes place on the surface of the catalyst (Section 7.14), accounting for the syn addition:

Syn addition of hydrogen to an alkyne



3-Hexyne → **(*Z*)-3-Hexene (*cis*-3-hexene) (97%)**

Other specially conditioned catalysts can be used to prepare *cis*-alkenes from disubstituted alkynes. Metallic palladium deposited on calcium carbonate can be used in this way after it has been conditioned with lead acetate and quinoline (an amine, see Section 18.1B). This special catalyst is known as **Lindlar's catalyst**:

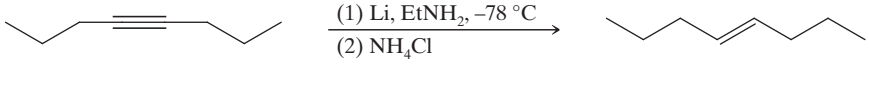


7.14B Anti Addition of Hydrogen: Synthesis of *trans*-Alkenes

- **Anti addition** of hydrogen to the triple bond of alkynes occurs when they are treated with lithium or sodium metal in ammonia or ethylamine at low temperatures.

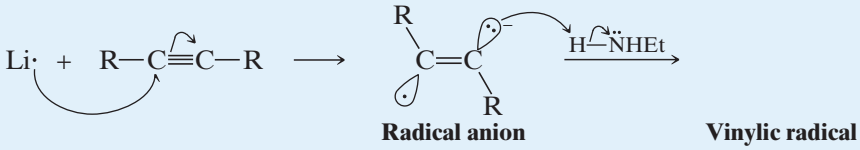
This reaction, called a **dissolving metal reduction,** takes place in solution and produces an (*E*)- or *trans*-alkene. The mechanism involves radicals, which are molecules that have unpaired electrons (see Chapter 9).

Anti addition of hydrogen to an alkyne.



4-Octyne → **(anti addition)** → **(*E*)-4-Octene (*trans*-4-octene) (52%)**

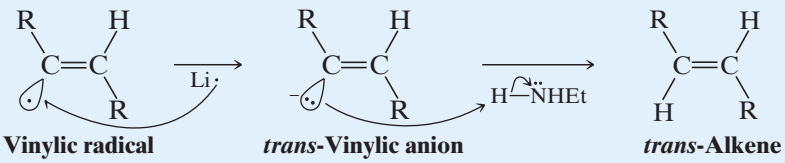
A MECHANISM FOR THE REACTION — The Dissolving Metal Reduction of an Alkyne



Radical anion — **Vinylic radical**

A lithium atom donates an electron to the π bond of the alkyne. An electron pair shifts to one carbon as the hybridization states change to sp^2.

The radical anion acts as a base and removes a proton from a molecule of ethylamine.



Vinylic radical — ***trans*-Vinylic anion** — ***trans*-Alkene**

A second lithium atom donates an electron to the vinylic radical.

The anion acts as a base and removes a proton from a second molecule of ethylamine.

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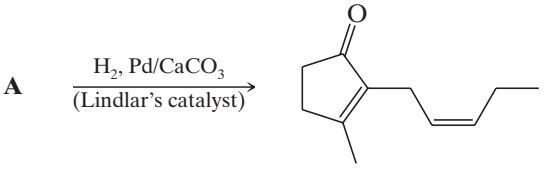
The mechanism for this reduction, shown in the preceding box, involves successive electron transfers from lithium (or sodium) atoms and proton transfers from amines (or ammonia). In the first step, a lithium atom transfers an electron to the alkyne to produce an intermediate that bears a negative charge and has an unpaired electron, called a **radical anion.** In the second step, an amine transfers a proton to produce a **vinylic radical.** Then, transfer of another electron gives a **vinylic anion.** It is this step that determines the stereochemistry of the reaction. The *trans*-vinylic anion is formed preferentially because it is more stable; the bulky alkyl groups are farther apart. Protonation of the *trans*-vinylic anion leads to the *trans*-alkene.

Practice Problem 7.21

Write the structure of compound **A**, used in this synthesis of the perfume ingredient (*Z*)-jasmone.



(*Z*)-Jasmone

Practice Problem 7.22

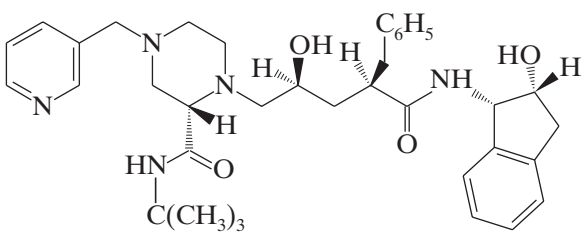
How would you convert 2-nonyne into (*E*)-2-nonene?

7.15 | AN INTRODUCTION TO ORGANIC SYNTHESIS

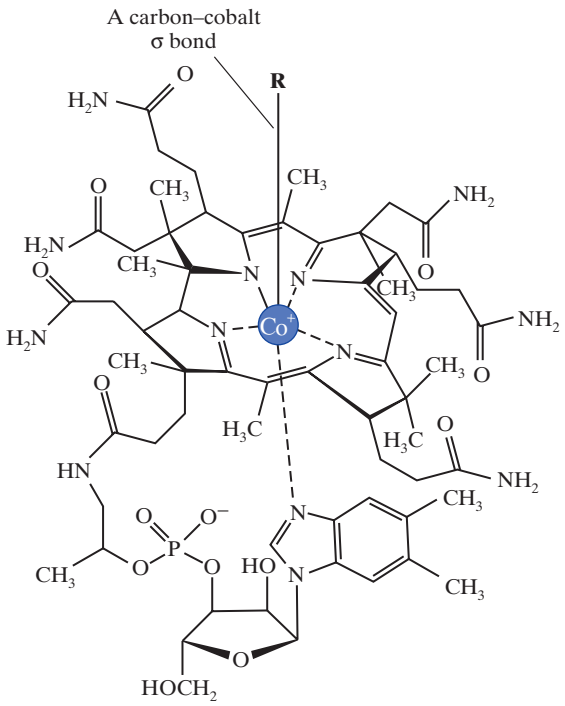
You have learned quite a few tools that are useful for organic synthesis, including nucleophilic substitution reactions, elimination reactions, and the hydrogenation reactions covered in Sections 7.12–7.14. Now we will consider the logic of organic synthesis and the important process of retrosynthetic analysis. Then we will apply nucleophilic substitution (in the specific case of alkylation of alkynide anions) and **hydrogenation** reactions to the synthesis of some simple target molecules.

7.15A Why Do Organic Synthesis?

Organic synthesis is the process of building organic molecules from simpler precursors. Syntheses of organic compounds are carried out for many reasons. Chemists who develop new drugs carry out organic syntheses in order to discover molecules with structural attributes that enhance certain medicinal effects or reduce undesired side effects. Crixivan, whose structure is shown below, was designed by small-scale synthesis in a research laboratory and then quickly moved to large-scale synthesis after its approval as a drug. In other situations, organic synthesis may be needed to test a hypothesis about a reaction mechanism or about how a certain organism metabolizes a compound. In cases like these we often will need to synthesize a particular compound "labeled" at a certain position (e.g., with deuterium, tritium, or an isotope of carbon).



Crixivan (an HIV protease inhibitor)



Vitamin B_{12}

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A very simple organic synthesis may involve only one chemical reaction. Others may require from several to 20 or more steps. A landmark example of organic synthesis is that of vitamin B_{12}, announced in 1972 by R. B. Woodward (Harvard) and A. Eschenmoser (Swiss Federal Institute of Technology). Their synthesis of vitamin B_{12} took 11 years, required more than 90 steps, and involved the work of nearly 100 people. We will work with much simpler examples, however.

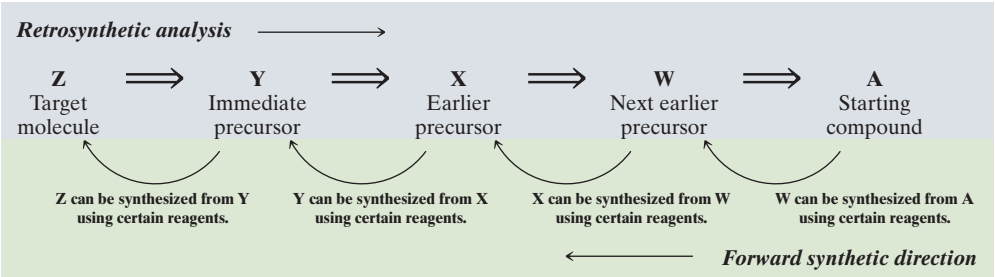
An organic synthesis typically involves two types of transformations:

1. reactions that convert functional groups from one to another
2. reactions that create new carbon–carbon bonds.

You have studied examples of both types of reactions already. For example, hydrogenation transforms the carbon–carbon double- or triple-bond functional groups in alkenes and alkynes to single bonds (actually removing a functional group in this case), and alkylation of alkynide anions forms carbon–carbon bonds. Ultimately, at the heart of organic synthesis is the orchestration of functional group interconversions and carbon–carbon bond-forming steps. Many methods are available to accomplish both of these things.

7.15B Retrosynthetic Analysis—Planning an Organic Synthesis

Sometimes it is possible to visualize from the start all the steps necessary to synthesize a desired (target) molecule from obvious precursors. Often, however, the sequence of transformations that would lead to the desired compound is too complex for us to "see" a path from the beginning to the end. In this case, since we know where we want to finish (the target molecule) but not where to start, we envision the sequence of steps that is required in a backward fashion, one step at a time. We begin by identifying immediate precursors that could react to make the target molecule. Once these have been chosen, they in turn become new intermediate target molecules, and we identify the next set of precursors that could react to form them, and so on, and so on. This process is repeated until we have worked backward to compounds that are sufficiently simple that they are readily available in a typical laboratory:



- The process we have just described is called **retrosynthetic analysis**.
- The open arrow is called a **retrosynthesis arrow,** and means that a molecule can be synthesized from its most immediate precursor by some chemical reaction.

Although some of the earliest organic syntheses likely required some type of analytical planning, it was E. J. Corey who first formalized a set of global principles for chemical synthesis, a process which he termed retrosynthetic analysis, that enabled anyone to plan a complex molecule synthesis. Once retrosynthetic analysis has been completed, to actually carry out the synthesis we conduct the sequence of reactions from the beginning, starting with the simplest precursors and working step by step until the target molecule is achieved.

- When doing retrosynthetic analysis it is necessary to generate as many possible precursors, and hence different synthetic routes, as possible (Fig. 7.11).

We evaluate all the possible advantages and disadvantages of each path and in so doing determine the most efficient route for synthesis. The prediction of which route is most feasible is usually based on specific restrictions or limitations of reactions in the sequence, the availability of materials, or other factors. We shall see an example of this in Section 7.16C. In actuality more than one route may work well. In other cases it may be necessary to try several approaches in the laboratory in order to find the most efficient or successful route.

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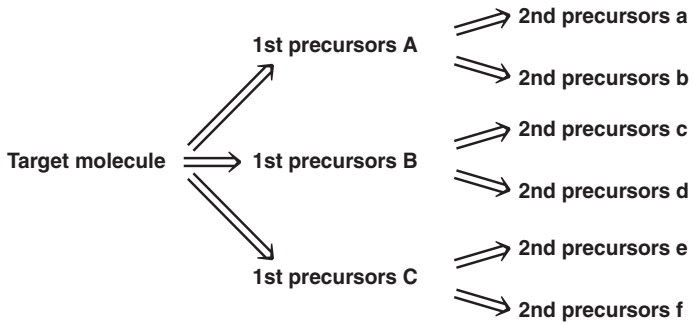


Figure 7.11 Retrosynthetic analysis often discloses several routes from the target molecule back to varied precursors.

7.15C Identifying Precursors

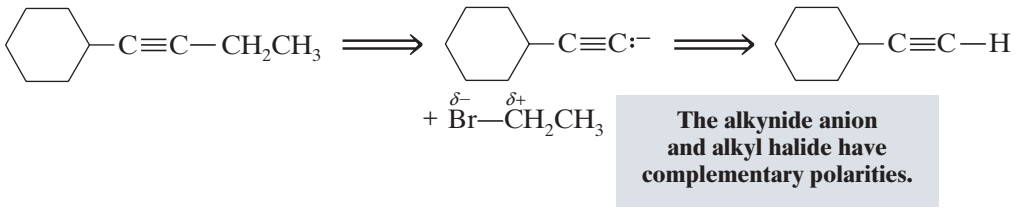
In the case of functional groups we need to have a toolbox of reactions from which to choose those we know can convert one given functional group into another. You will develop such a toolbox of reactions as you proceed through your study of organic chemistry. Similarly, with regard to making carbon–carbon bonds in synthesis, you will develop a repertoire of reactions for that purpose. In order to choose the appropriate reaction for either purpose, you will inevitably consider basic principles of structure and reactivity.

As we stated in Sections 3.3A and 7.12:

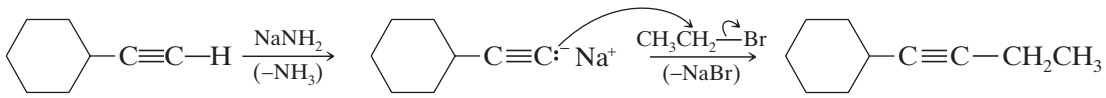
- Many organic reactions depend on the interaction of molecules that have complementary full or partial charges.

One very important aspect of retrosynthetic analysis is being able to identify those atoms in a target molecule that could have had complementary (opposite) charges in synthetic precursors. Consider, for example, the synthesis of 1-cyclohexyl-1-butyne. On the basis of reactions learned in this chapter, you might envision an alkynide anion and an alkyl halide as precursors having complementary polarities that when allowed to react together would lead to this molecule:

Retrosynthetic Analysis



Synthesis



Sometimes, however, it will not at first be obvious where the retrosynthetic bond disconnections are in a target molecule that would lead to oppositely charged or complementary precursors. The synthesis of an alkane would be such an example. An alkane does not contain carbon atoms that could directly have had opposite charges in precursor molecules. However, if one supposes that certain carbon–carbon single bonds in the alkane could have arisen by hydrogenation of a corresponding alkyne (a functional group interconversion), then, in turn, two atoms of the alkyne could have been joined from precursor molecules that had complementary charges (i.e., an alkynide anion and an alkyl halide).

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The Chemistry of... FROM THE INORGANIC TO THE ORGANIC

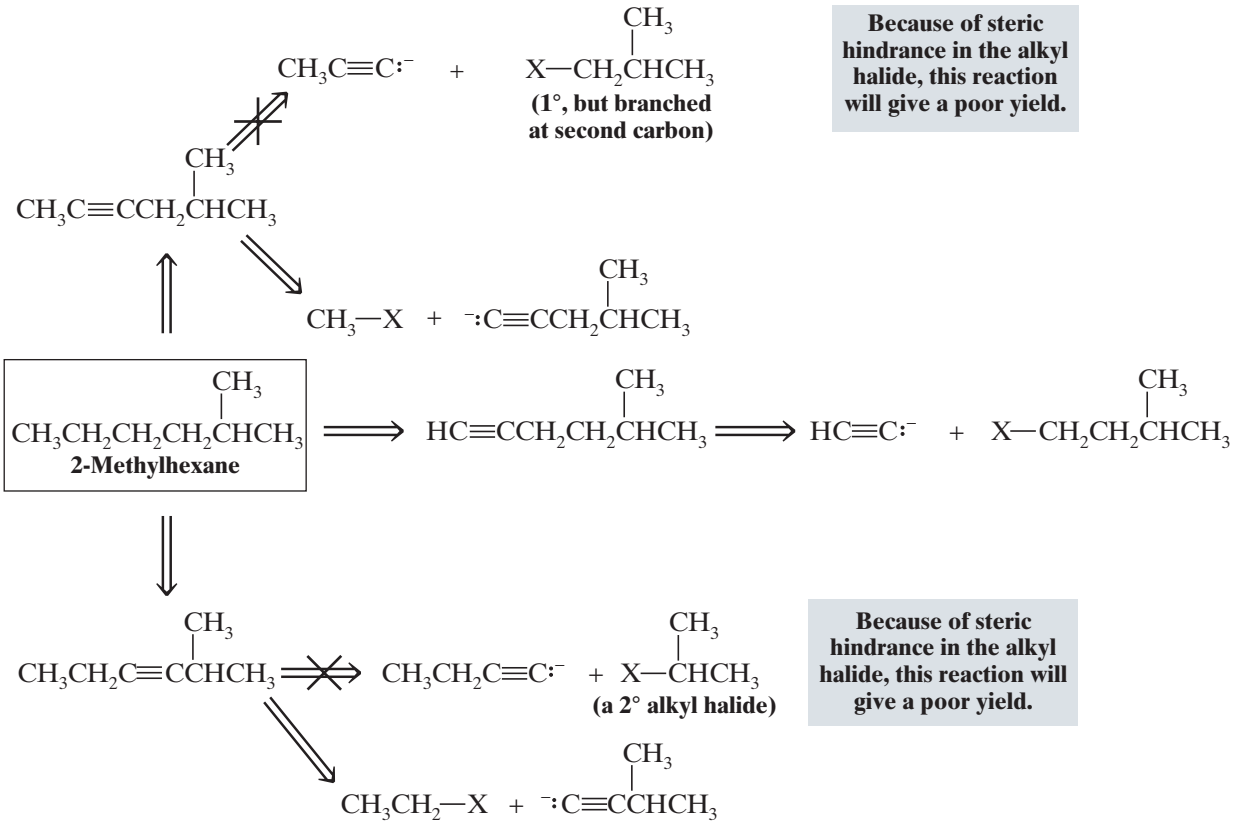
In 1862, Friedrich Wöhler discovered calcium carbide (CaC_2) by heating carbon with an alloy of zinc and calcium. He then synthesized acetylene by allowing the calcium carbide to react with water:

$$C \xrightarrow{\text{Zinc-calcium, alloy, heat}} CaC_2 \xrightarrow{2H_2O} HC{\equiv}CH + Ca(OH)_2$$

Acetylene produced this way burned in lamps of some lighthouses and in old-time miners' headlamps. From the standpoint of organic synthesis, it is theoretically possible to synthesize anything using reactions of alkynes to form carbon–carbon bonds and to prepare other functional groups. Thus, while Wöhler's 1828 conversion of ammonium cyanate to urea was the first synthesis of an organic compound from an inorganic precursor his discovery of calcium carbide and its reaction with water to form acetylene gives us a formal link from inorganic materials to the entire realm of organic synthesis.

Consider the following retrosynthetic analysis for **2-methylhexane:**

Retrosynthetic Analysis



As indicated in the retrosynthetic analysis above, we must bear in mind the limitations that exist for the reactions that would be applied in the synthetic (forward) direction. In the example above, two of the pathways have to be discarded because they involve the use of a 2° alkyl halide or a primary halide branched at the second (beta) carbon (Sections 6.13A, 7.11).

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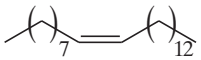
Solved Problem 7.9

Outline a retrosynthetic pathway that leads from 'muscalure', the sex attractant pheromone of the common housefly back to the simplest alkyne, ethyne (acetylene). Then show the synthesis. You may use any inorganic compounds, or solvents, you need and alkyl halides of any length necessary.

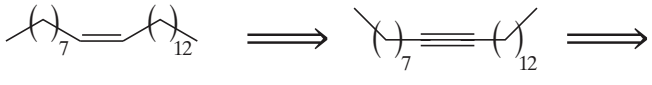


Muscalure

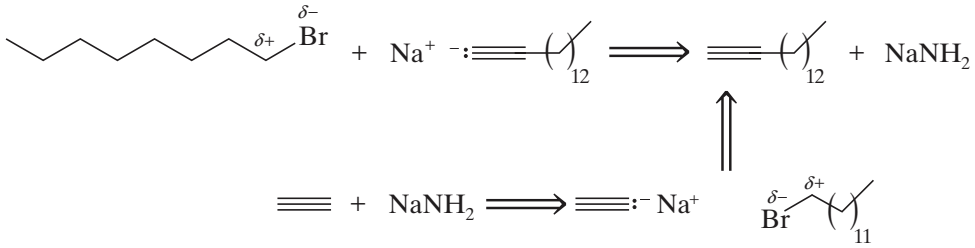
Answer

We make use of two reactions that we have just studied in this chapter: syn addition of hydrogen to an alkyne, and alkylation of alkynide ions.

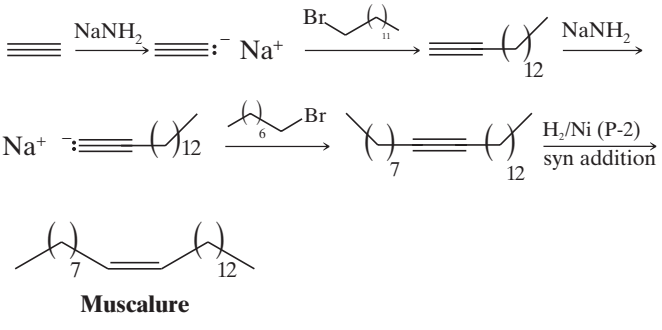
Retrosynthetic Analysis



Muscalure **+ H_2, syn addition**



Synthesis



Muscalure

Practice Problem 7.23

Referring to the retrosynthetic analysis for 2-methylhexane in this section, write reactions for those synthesis routes that are feasible.

Practice Problem 7.24

(a) Devise retrosynthetic schemes for all conceivable alkynide anion alkylation syntheses of the insect pheromones undecane and 2-methylheptadecane. **(b)** Write reactions for two feasible syntheses of each pheromone.

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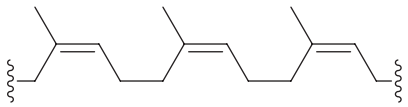
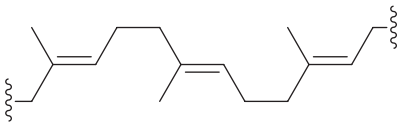
ALKENE GEOMETRY, RUBBER, AND THE CHEMISTRY OF VISION

WHY Do These Topics Matter?

The (*E*) or (*Z*) configurations of substituted double bonds is not just a matter for exercise sets and exams. In the real world, they define the properties of many compounds. For example, natural rubber, which can be obtained from the sap of certain trees, has all (*Z*) configurations about its trisubstituted double bonds. Some other trees make the all (*E*) version, a compound known as gutta percha. While gutta percha is also a latex-like material, the change in stereochemistry actually makes it inelastic so that it does not have the same useful properties as natural rubber.



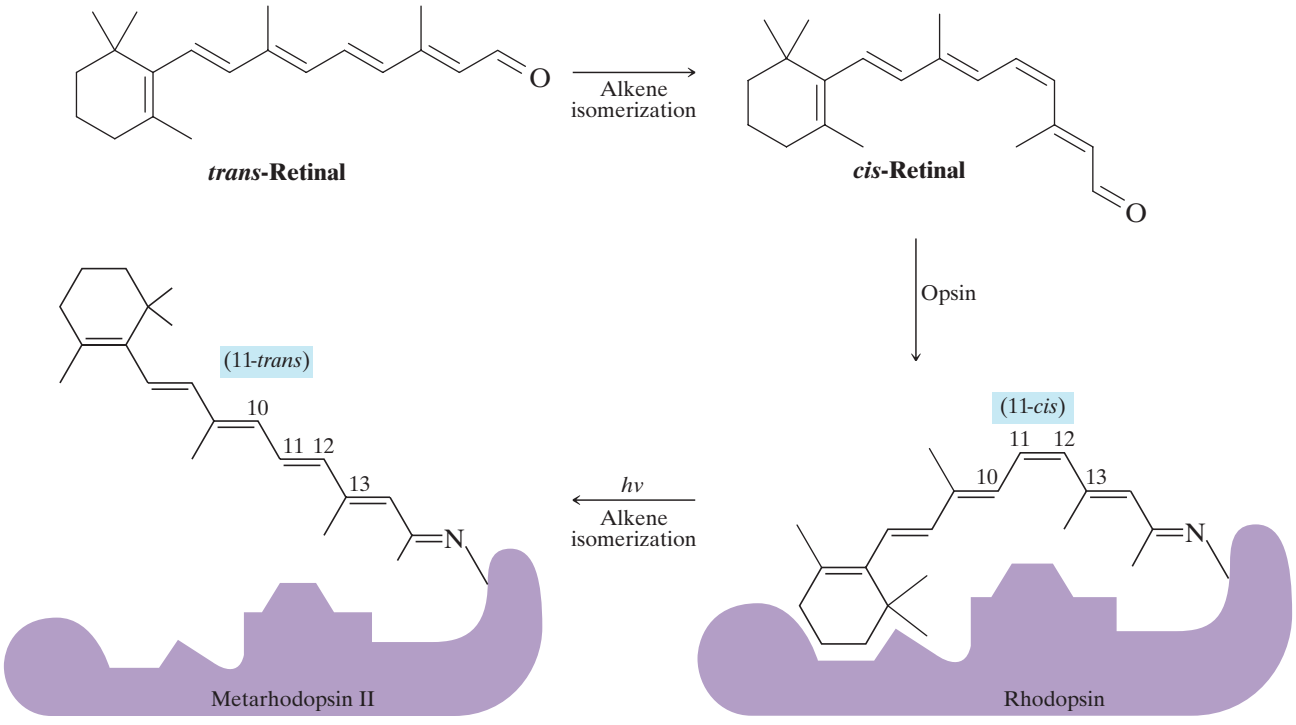
Natural rubber (*Z* configuration)



Gutta percha (*E* configuration)

Alkene stereochemistry is also critical to our ability to see. In our eyes, the key molecule is a compound called *trans*-retinal, a material that can be synthesized in our bodies and that comes from our diets through foods like carrots.

In order for retinal to participate in the vision process, one particular double bond within it must first be isomerized from *trans* to *cis* through a process that breaks the π-bond, rotates about a single bond, and reforms the π-bond. This new stereochemical orientation places several carbon atoms in a different orientation than they were in the *trans* configuration. The value of that change, however, is that the new spatial orientation of *cis*-retinal allows it to fit into a receptor in a protein known as opsin in our retinas and merge with it through a general reaction process we will learn more about in Chapter 15; this step generates a new complex known as rhodopsin. The key thing to understand for now, however, is that when rhodopsin is exposed to light of a certain wavelength (of which we will learn more in Chapter 12), the *cis* double bond isomerizes back to the more stable all *trans* configuration through a series of steps to become metarhodopsin II as shown below. It is believed that the repositioning of the cyclohexene ring within the retinal portion of metarhodopsin II following this isomerization induces some further conformational changes within the protein. These changes ultimately lead to a nerve impulse that is interpreted by our brains as vision. The picture shown here is but a small part in the overall process, but these initial, critical steps are based solely on alkene stereochemistry. As such, it really does matter whether a double bond is *cis* or trans, (*E*) or (*Z*)!



***trans*-Retinal** ***cis*-Retinal**

SUMMARY AND REVIEW TOOLS

Reaction Summary of E2 and E1 elimination

E2 via small base

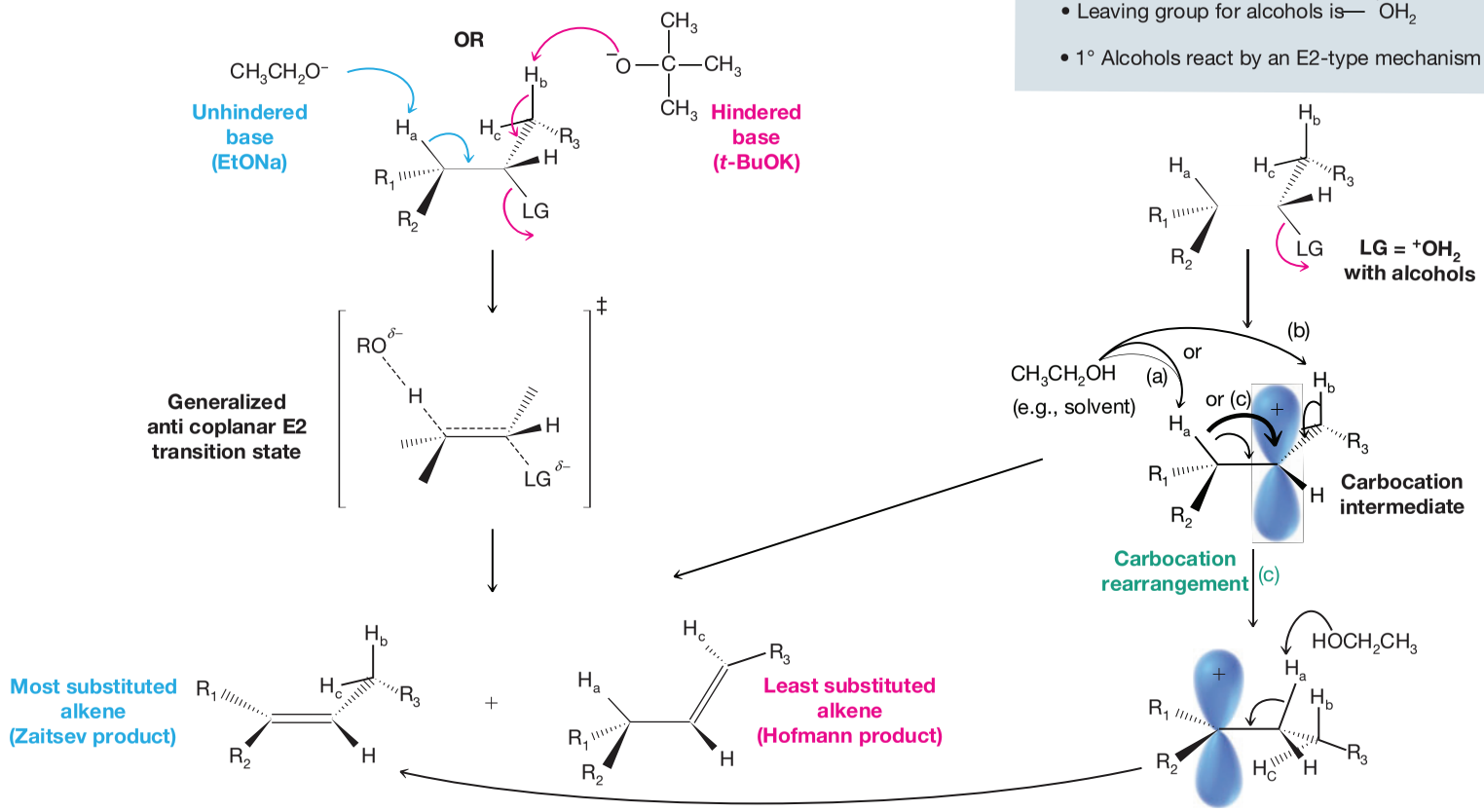
- Strong **unhindered base** e.g., CH_3CH_2ONa (EtONa), HO^-
- Predominant formation of **most substituted alkene** (Zaitsev product)
- Anti coplanar transition state
- Bimolecular in rate-determining step

E2 via bulky base

- Strong **hindered base**, e.g. $(CH_3)_3COK$ (*t*-BuOK)
- Predominant formation of **least substituted alkene** (Hofmann product)
- Anti coplanar transition state
- Bimolecular in rate-determining step

E1 (including Alcohol Dehydration)

- Absence of strong base (solvent is often the base)
- Alcohols require **strong acid catalyst**
- Carbocation formation is unimolecular rate-determining step
- Carbocation **may rearrange**
- Predominant formation of most substituted alkene (Zaitsev product)
- Leaving group for alcohols is $-{}^+OH_2$
- 1° Alcohols react by an E2-type mechanism



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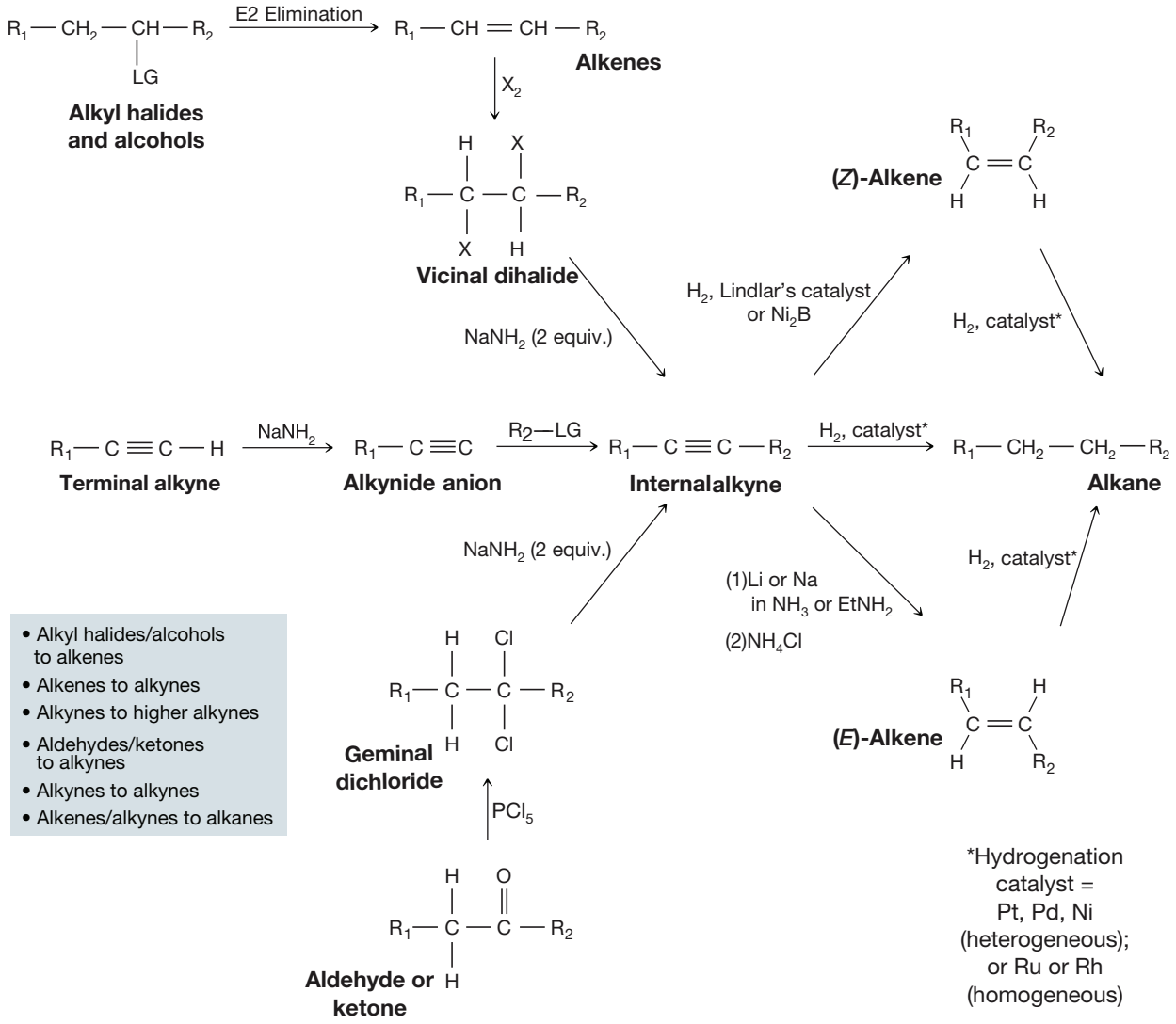
SUMMARY AND REVIEW TOOLS

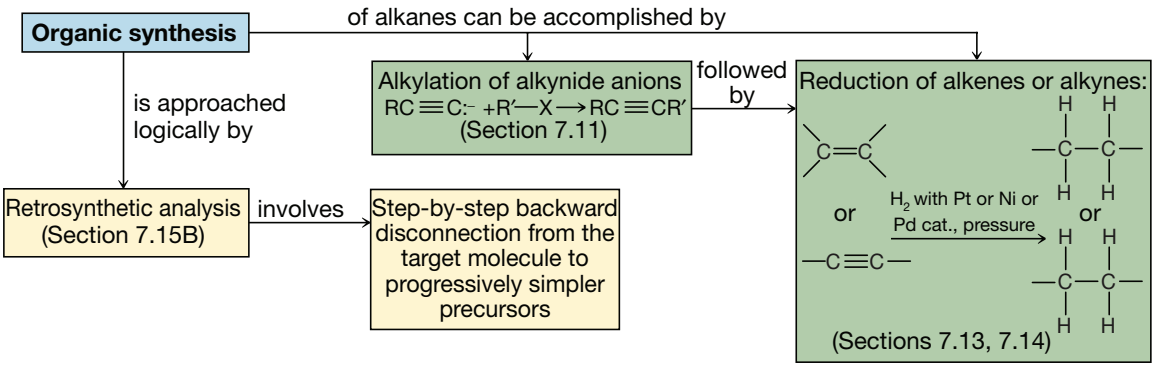
Synthetic Connections of Alkynes, Alkenes, Alkyl Halides, and Alcohols



- Alkyl halides/alcohols to alkenes
- Alkenes to alkynes
- Alkynes to higher alkynes
- Aldehydes/ketones to alkynes
- Alkynes to alkynes
- Alkenes/alkynes to alkanes

*Hydrogenation catalyst = Pt, Pd, Ni (heterogeneous); or Ru or Rh (homogeneous)

CONCEPT MAP



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REVIEW PROBLEMS

Structure and Nomenclature

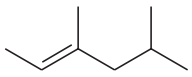
7.25 Each of the following names is incorrect. Give the correct name and explain your reasoning.
- **(a)** *trans*-3-Pentene
- **(b)** 1,1-Dimethylethene
- **(c)** 2-Methylcyclohexene
- **(d)** 4-Methylcyclobutene
- **(e)** (*Z*)-3-Chloro-2-butene
- **(f)** 5,6-Dichlorocyclohexene

7.26 Write a structural formula for each of the following:
- **(a)** 3-Methylcyclobutene
- **(b)** 1-Methylcyclopentene
- **(c)** 2,3-Dimethyl-2-pentene
- **(d)** (*Z*)-3-Hexene
- **(e)** (*E*)-2-Pentene
- **(f)** 3,3,3-Tribromopropene
- **(g)** (*Z*,4*R*)-4-Methyl-2-hexene
- **(h)** (*E*,4*S*)-4-Chloro-2-pentene
- **(i)** (*Z*)-1-Cyclopropyl-1-pentene
- **(j)** 5-Cyclobutyl-1-pentene
- **(k)** (*R*)-4-Chloro-2-pentyne
- **(l)** (*E*)-4-Methylhex-4-en-1-yne

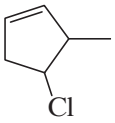
7.27 Write three-dimensional formulas for and give names using (*R*)–(*S*) and (*E*)–(*Z*) designations for the isomers of:
- **(a)** 4-Bromo-2-hexene
- **(b)** 3-Chloro-1,4-hexadiene
- **(c)** 2,4-Dichloro-2-pentene
- **(d)** 2-Bromo-4-chlorohex-2-en-5-yne

7.28 Give the IUPAC names for each of the following:

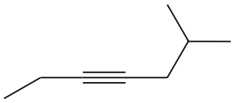
(a)



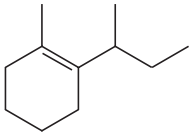
(b)



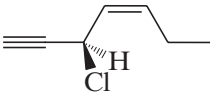
(c)



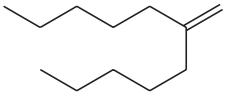
(d)



(e)



(f)



7.29 Without consulting tables, arrange the following compounds in order of decreasing acidity:

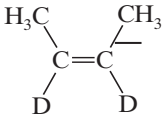
Pentane 1-Pentene 1-Pentyne 1-Pentanol

Synthesis

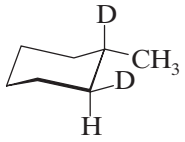
7.30 Outline a synthesis of propene from each of the following:
- **(a)** Propyl chloride
- **(b)** Isopropyl chloride
- **(c)** Propyl alcohol
- **(d)** Isopropyl alcohol
- **(e)** 1,2-Dibromopropane
- **(f)** Propyne

7.31 Outline a synthesis of cyclopentene from each of the following:
- **(a)** Bromocyclopentane
- **(b)** Cyclopentanol

7.32 Starting with ethyne, outline syntheses of each of the following. You may use any other needed reagents, and you need not show the synthesis of compounds prepared in earlier parts of this problem.
- **(a)** Propyne
- **(b)** 1-Butyne
- **(c)** 2-Butyne
- **(d)** *cis*-2-Butene
- **(e)** *trans*-2-Butene
- **(f)** 1-Pentyne
- **(g)** 2-Hexyne
- **(h)** (*Z*)-2-Hexene
- **(i)** (*E*)-2-Hexene
- **(j)** 3-Hexyne
- **(k)** $CH_3CH_2C{=}CD$
- **(l)**

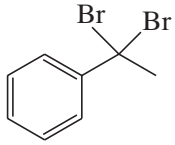


7.33 Starting with 1-methylcyclohexene and using any other needed reagents, outline a synthesis of the following deuterium-labeled compound:

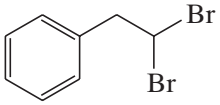


7.34 Outline a synthesis of phenylethyne from each of the following:

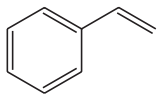
(a)



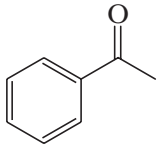
(b)



(c)



(d)



Dehydrohalogenation and Dehydration

7.35 Write a three-dimensional representation for the transition state structure leading to formation of 2-methyl-2-butene from reaction of 2-bromo-2-methylbutane with sodium ethoxide.

7.36 When *trans*-2-methylcyclohexanol (see the following reaction) is subjected to acid-catalyzed dehydration, the major product is 1-methylcyclohexene:

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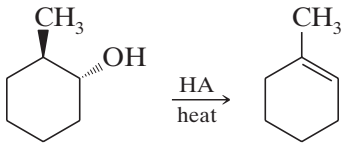
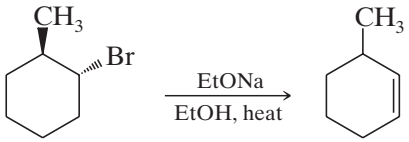
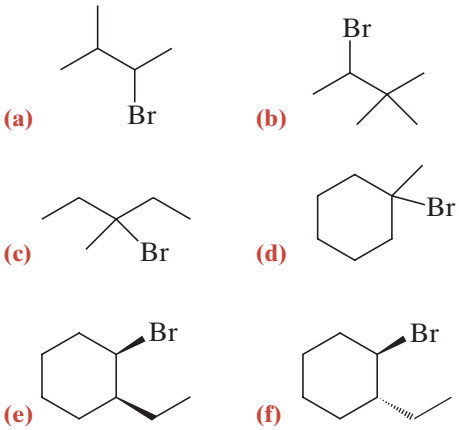


However, when *trans*-1-bromo-2-methylcyclohexane is subjected to dehydrohalogenation, the major product is 3-methylcyclohexene:

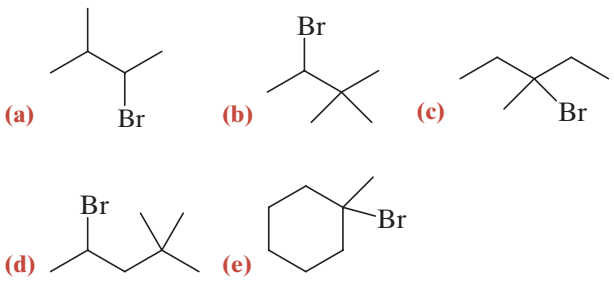


Account for the different products of these two reactions.

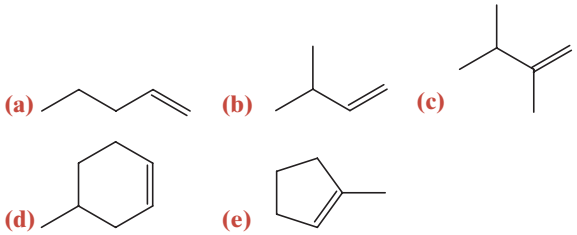
7.37 Write structural formulas for all the products that would be obtained when each of the following alkyl halides is heated with sodium ethoxide in ethanol. When more than one product results, you should indicate which would be the major product and which would be the minor product(s). You may neglect *cis–trans* isomerism of the products when answering this question.



7.38 Write structural formulas for all the products that would be obtained when each of the following alkyl halides is heated with potassium *tert*-butoxide in *tert*-butyl alcohol. When more than one product results, you should indicate which would be the major product and which would be the minor product(s). You may neglect *cis–trans* isomerism of the products when answering this question.



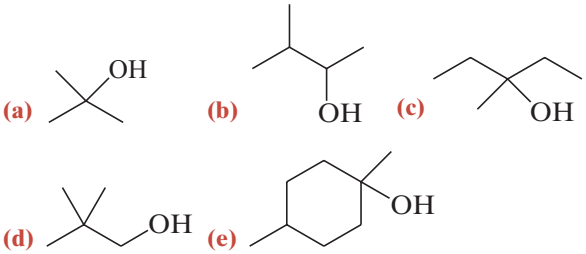
7.39 Starting with an appropriate alkyl halide and base, outline syntheses that would yield each of the following alkenes as the major (or only) product:



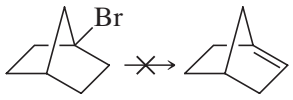
7.40 Arrange the following alcohols in order of their reactivity toward acid-catalyzed dehydration (with the most reactive first):

1-Pentanol 2-Methyl-2-butanol 3-Methyl-2-butanol

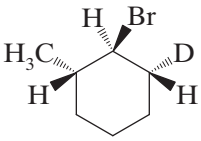
7.41 Give the products that would be formed when each of the following alcohols is subjected to acid-catalyzed dehydration. If more than one product would be formed, designate the alkene that would be the major product. (Neglect *cis–trans* isomerism.)



7.42 1-Bromobicyclo[2.2.1]heptane does not undergo elimination (below) when heated with a base. Explain this failure to react. (Construction of molecular models may help.)

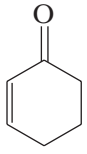


7.43 When the deuterium-labeled compound shown at right is subjected to dehydrohalogenation using sodium ethoxide in ethanol, the only alkene product is 3-methylcyclohexene. (The product contains no deuterium.) Provide an explanation for this result.



Index of Hydrogen Deficiency

7.44 What is the index of hydrogen deficiency (IHD) (degree of unsaturation) for each of the following compounds?

(a) 

(b) $C_6H_8Br_4$

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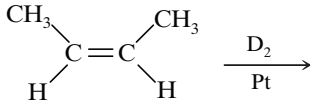
ADDITIONAL OBJECTIVE QUESTIONS

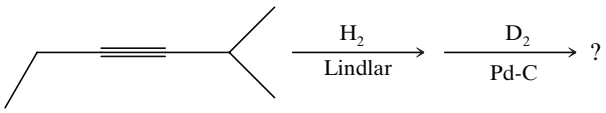
Single Correct Choice Type

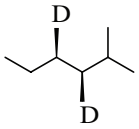
1. Major product of the following reaction is

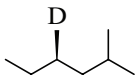


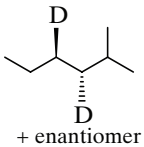
(a) racemic mixture. **(b)** diastereomer.
(c) meso compound. **(d)** structural isomer.

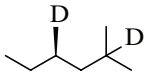
2. Select the major product from the following reaction sequence.



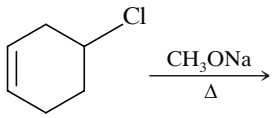
(a)  + enantiomer

(b)  + enantiomer

(c)  + enantiomer

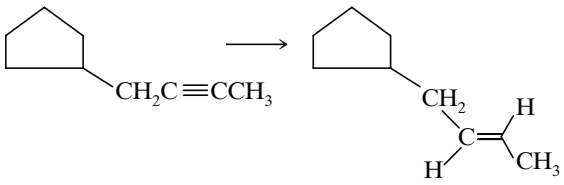
(d)  + enantiomer

3. The following reaction proceeds by which mechanism?



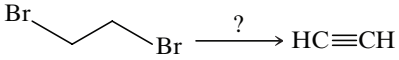
(a) S_N1 **(b)** S_N2 **(c)** E_2 **(d)** E_1

4. Reagent used to carry out following conversion from alkyne to alkene is



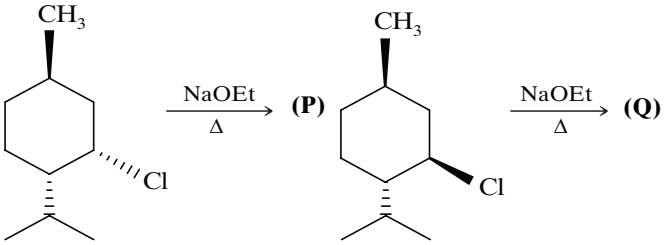
(a) $Pd–C/H_2$ **(b)** Na/NH_3
(c) Pt/H_2 **(d)** Ni/H_2

5. The reagent(s) for the following conversion is/are

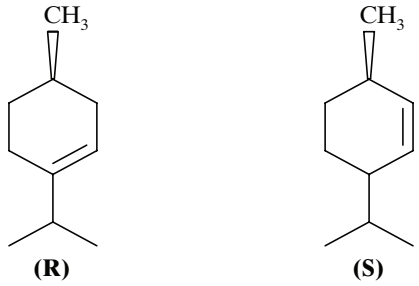


(a) alc. KOH
(b) alc. KOH followed by $NaNH_2$
(c) aq. KOH followed by $NaNH_2$
(d) Zn/CH_3OH

6. Consider the following reaction:



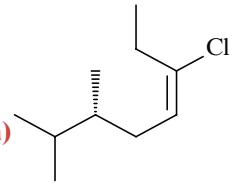
Identify products (P) and (Q) from the following compounds:

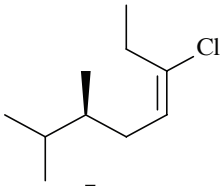


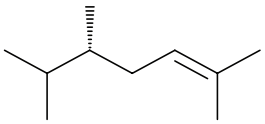
(R) **(S)**

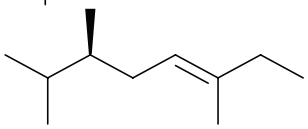
(a) P=R, Q=S **(b)** P=S, Q=S
(c) P=S, Q=R **(d)** P=R, Q=R

7. Choose the compound with the (*S*) chiral carbon and the (*Z*) double bond configuration

(a) 

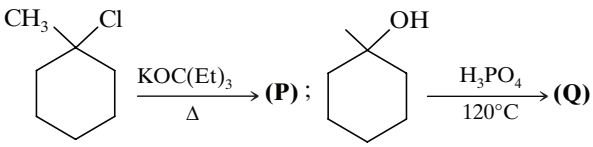
(b) 

(c) 

(d) 

8. The synthesis of 3-octyne is achieved by adding a bromoalkane into a mixture of sodium amide and an alkyne. The bromoalkane and alkyne, respectively, are

(a) $BrCH_2CH_2CH_2CH_3$ and $CH_3CH_2C{\equiv}CH$
(b) $BrCH_2CH_2CH_3$ and $CH_3CH_2CH_2C{\equiv}CH$
(c) $BrCH_2CH_2CH_2CH_2CH_3$ and $CH_3C{\equiv}CH$
(d) $BrCH_2CH_2CH_2CH_3$ and $CH_3CH_2C{\equiv}CH$

9. 

Products (P) and (Q) are

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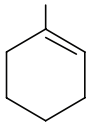
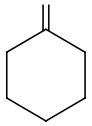
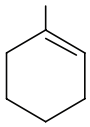
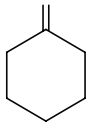
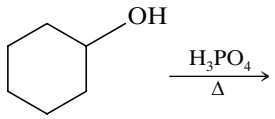
(a)  (b) 

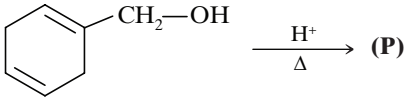
(c)  (d) 

10. The following reaction proceeds by which mechanism?

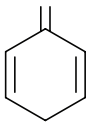
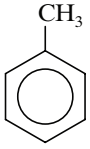
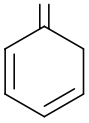
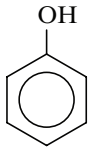


(a) S_N1 **(b)** S_N2 **(c)** E_2 **(d)** E_1

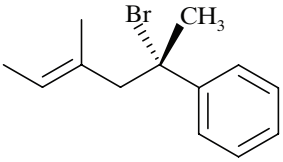
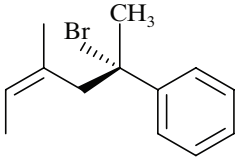
11. Consider the following reaction:

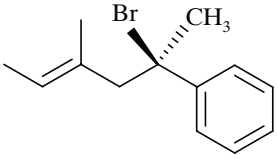
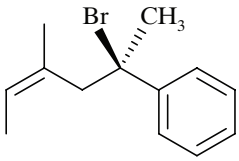


If (P) on heating isomerizes to (Q). What is the structure of (Q)?

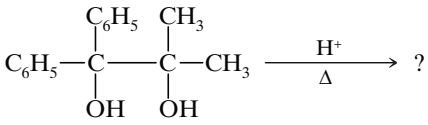
(a)  (b)  (c)  (d) 

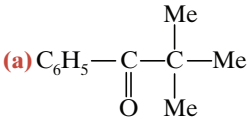
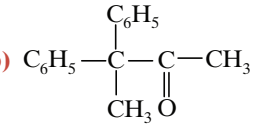
12. Choose the structure that has the name (*R*, *Z*)-2-bromo-4-methyl-2-phenylhex-4-ene.

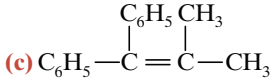
(a)  (b) 

(c)  (d) 

13. Identify the final product in the reaction



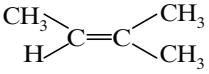
(a)  (b) 

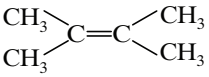
(c)  (d) Stilbene

14. Which of the following alkene is most stable?

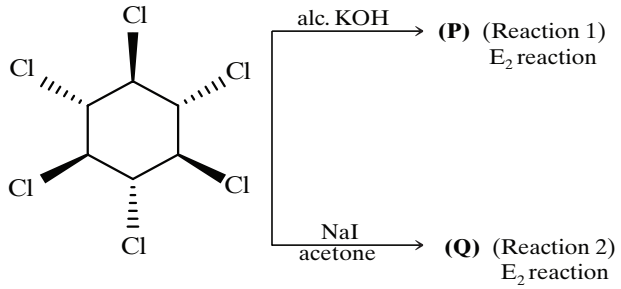
(a) $CH_3—CH_2—CH=CH_2$

(b) $CH_3—CH(CH_3)—CH=CH_2$

(c) 

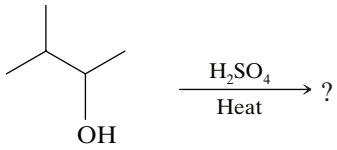
(d) 

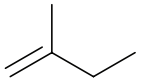
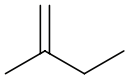
15. How many halogen atoms will be removed in the following E_2 reaction?

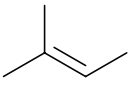
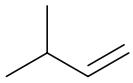


(a) 4 **(b)** 6 **(c)** 8 **(d)** 10

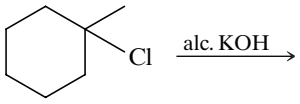
16. What is the major product of the following reaction?



(a)  (b) 

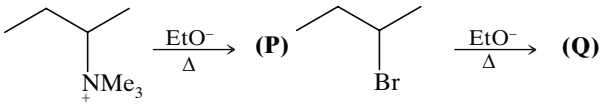
(c)  (d) 

17. The following reaction proceeds by which mechanism?

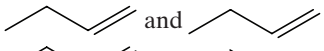


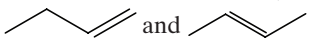
(a) S_N1 **(b)** S_N2 **(c)** E2 **(d)** E1

18. Consider the following reactions:

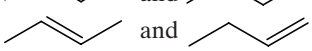


The products (P) and (Q) are

(a) 

(b) 

(c) 

(d) 

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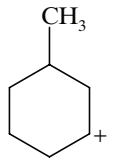
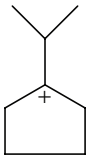
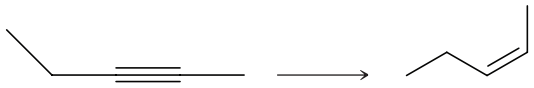
19. Which of the following carbocation will undergo rearrangement?

(a) 

(b) 

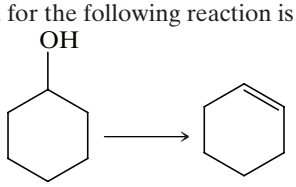
(c) $CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-\overset{+}{C}=O$ **(d)** $CH_3-NH-\overset{+}{C}H-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_3$

20. What reagent is needed for the following reaction?



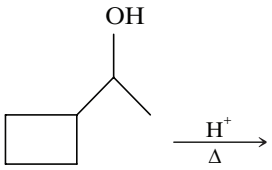
(a) H_2/Lindlar's Catalyst **(b)** 1) Li in NH_3 2) NH_4Cl
(c) H_2/Ni_2B **(d)** (a) and (c)

21. Best method for the following reaction is

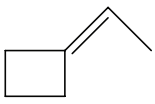


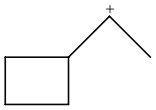
(a) conc. HCl + $ZnCl_2$ **(b)** conc. H_3PO_4
(c) HBr **(d)** conc. HCl

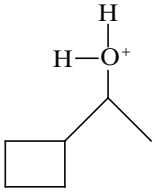
22.

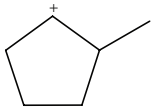


Which of the following is not an intermediate of the reaction?

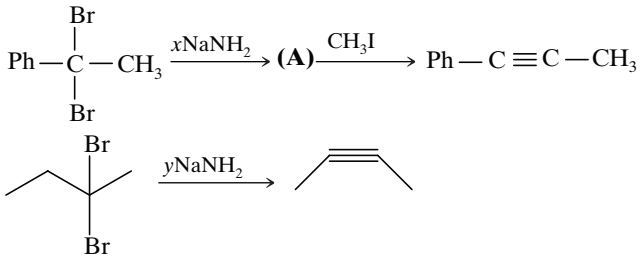
(a) 

(c) 

(b) 

(d) 

23.



The sum of x and y is
(a) 2 **(b)** 4 **(c)** 5 **(d)** 6

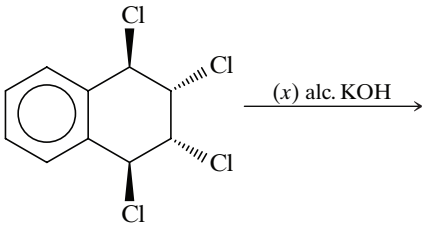
24. The most reactive conformation for an E2 reaction is
(a) syn periplanar. **(b)** anti periplanar.
(c) gauche staggered. **(d)** gauche eclipsed.

25. In the following sequence of reactions

$$CH_3CH_2CH_2Br \xrightarrow{KOH(alc)} (A) \xrightarrow{HBr} (B) \xrightarrow{KOH(aq).} (C),$$

The product (C) is
(a) propan-2-ol. **(b)** propan-1-ol.
(c) propyne. **(d)** propene.

26. For the following reaction,



the moles (x) of alc. KOH consumed are
(a) 0 **(b)** 1 **(c)** 2 **(d)** 3

27. Which of the reactions can not be used to synthesize propyne?

(a) $CH_3-CH=CH-Br \xrightarrow[t\text{-ButOH}]{t\text{-ButO}^-/\Delta}$
(b) $CH\equiv CNa + CH_3-I \longrightarrow$
(c) $HC\equiv CH + CH_3Na \longrightarrow$
(d) $CH_3-CHBrCHBr \xrightarrow[(2)H^+]{(1)NaNH_2(excess)}$

28. Consider the following compounds

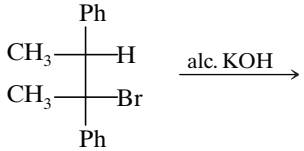
(I) $CH_3-\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-Br$

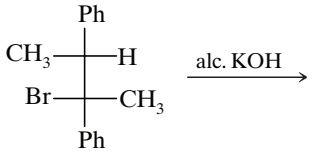
(II) $CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-Br$

(III) $CH_3-CH_2-CH_2Br$

Their reactivity toward E1 is
(a) I > II > III **(b)** II > I > III
(c) II > III > I **(d)** III > II > I

29. Consider the following two reactions:

(I) 

(II) 

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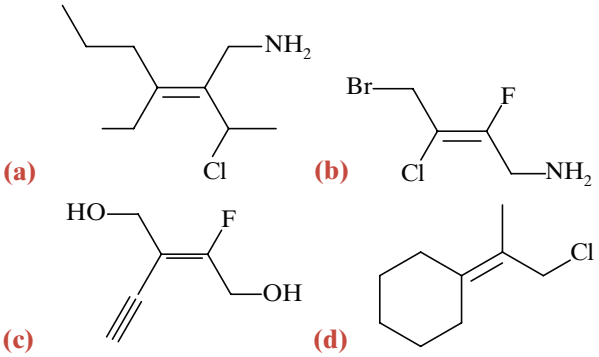
Products of reactions (I) and (II) are

(a) *cis, cis* **(b)** *cis, trans* **(c)** *trans, cis* **(d)** *trans, trans*

Multiple Correct Choice Type

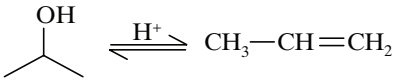
1. Which of the following alkenes has the ***Z*** configuration along the double bond?



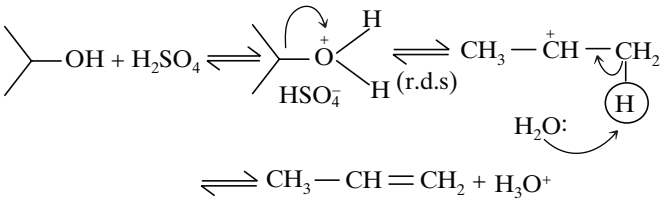
Linked Comprehension Type

Paragraph for Questions 1 to 4

Dehydration of alcohols requires an acid catalyst to protonate the hydroxy group of the alcohol and convert it into a good leaving group. Loss of water followed by a loss of a proton givens the alkene, and an equilibrium is established between the reactants and the products.



Mechanism:

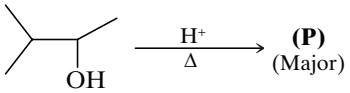


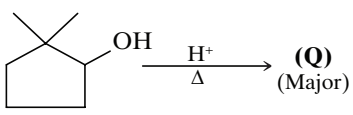
1. To improve yield of the above reaction, which of the following is correct?

(a) Heating high at temperature **(b)** Distillation

(c) Addition of H_2O **(d)** Both (a) and (b)

2. Consider the following reactions

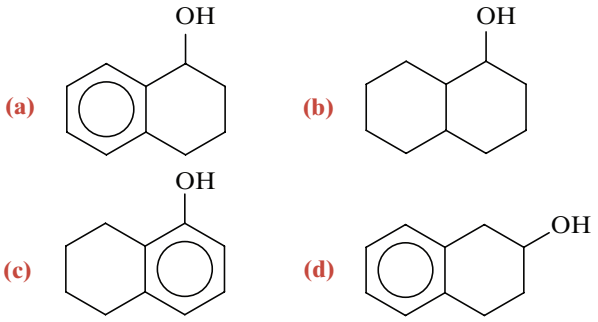




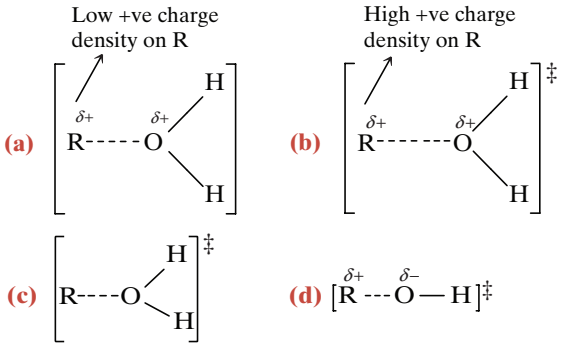
The total number of α-hydrogens in P + Q is

(a) 13 **(b)** 15 **(c)** 17 **(d)** 19

3. Which alcohol is most reactive toward dehydration of alcohol in acid catalyzed reaction?

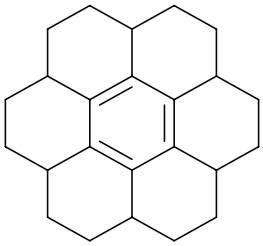


4. Most appropriate transition state in dehydration of alcohol (in acidic medium) is

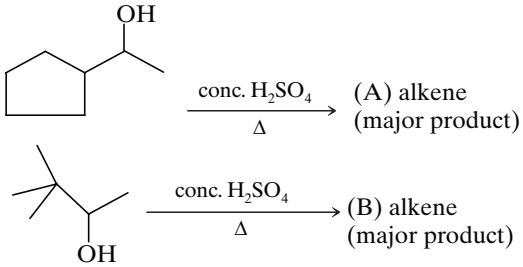


Integer Type

1. Total number of α-hydrogen in the following compound is ____.

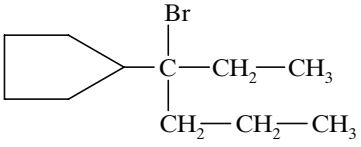


2.



Sum of α-hydrogens in A + B is

3.



Find the total number of products obtained when this substrate is subjected to E2 reaction will be (including stereoisomer).

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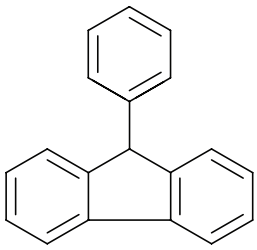
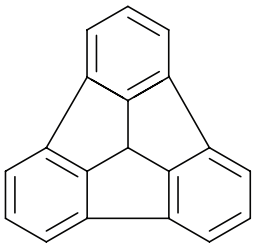
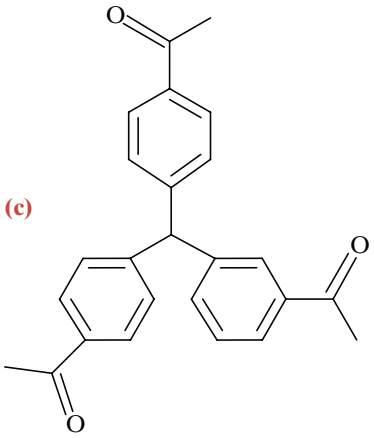
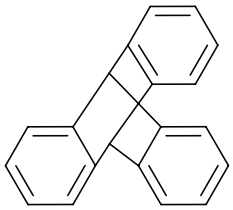
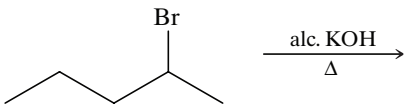
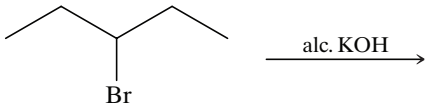
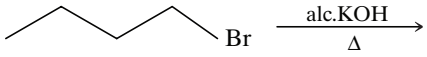
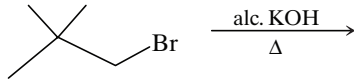
Matrix Match Type

1.

Column I Compound	Column II Index of Hydrogen Deficiency
(a) 	(p) 11
(b) 	(q) 12
(c) 	(r) 13
(d) 	(s) 14
	(t) 15

2.

Column I E2 reaction (elimination bimolecular)	Column II No. of possible products, (including stereoisomerism)
(a) 	(p) 0
(b) 	(q) 1
(c) 	(r) 2
(d) 	(s) 3

ANSWER KEY

Single Correct Choice Type

1. (c)	**2.** (c)	**3.** (c)	**4.** (b)	**5.** (b)
6. (a)	**7.** (d)	**8.** (d)	**9.** (b)	**10.** (d)
11. (b)	**12.** (d)	**13.** (b)	**14.** (d)	**15.** (b)

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16. (c) **17.** (c) **18.** (b) **19.** (b) **20.** (d)
21. (b) **22.** (a) **23.** (c) **24.** (b) **25.** (a)
26. (b) **27.** (c) **28.** (a) **29.** (c)

Multiple Correct Choice Type

1. (a), (c)

Linked Comprehension Type

1. (d) **2.** (d) **3.** (d) **4.** (c)

Integer Type

1. (6) **2.** (19) **3.** (5)

Matrix Match Type

1. a→(r); b→(t); c→(t); d→(s)
2. a→(r); b→(s); c→(q); d→(p)

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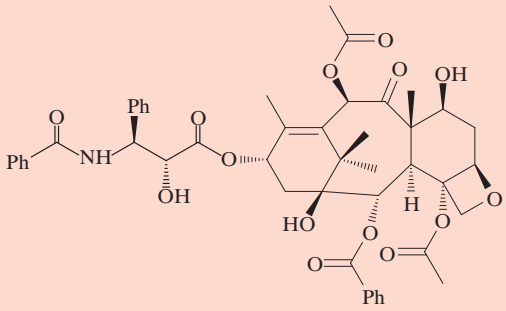
8

Alkenes and Alkynes II

Addition Reactions



Taxol

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8.5 | Alcohols from Alkenes through Oxymercuration–Demercuration: Markovnikov Addition
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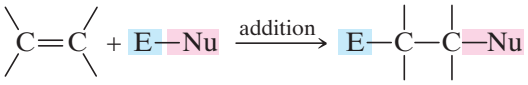
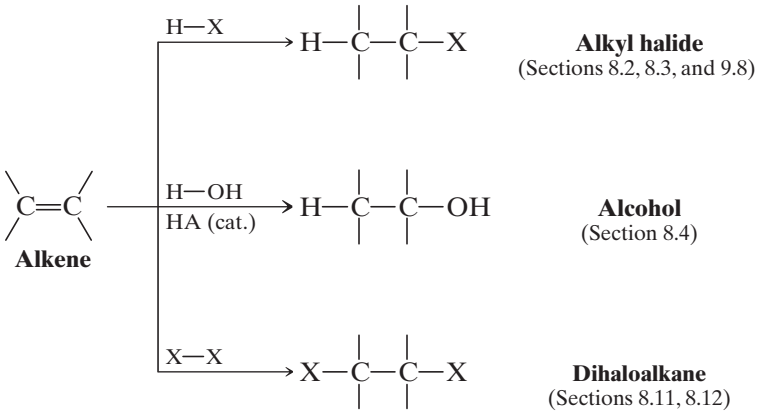
8.20 | Dimerization of Alkene
8.21 | Prins Reaction

8.1 | ADDITION REACTIONS OF ALKENES

We have already studied one addition reaction of alkenes—hydrogenation—in which a hydrogen atom is added at each end of a double (or triple) bond. In this chapter we shall study other alkene addition reactions that do not involve the same mechanism as hydrogenation. We can depict this type of reaction generally, using E for an electrophilic portion of a reagent and Nu for a nucleophilic portion, as follows.



Some specific reactions of this type that we shall study in this chapter include addition of hydrogen halides, sulfuric acid, water (in the presence of an acid catalyst), and halogens. Later we shall also study some specialized reagents that undergo addition reactions with alkenes.



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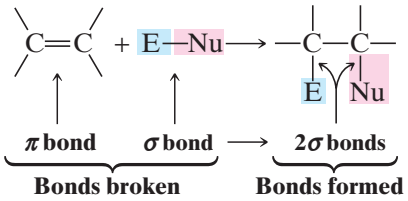
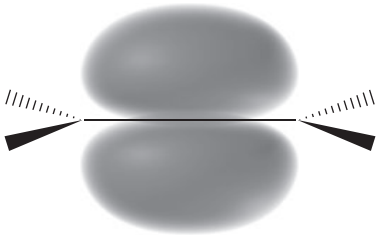
8.1A HOW TO Understand Additions to Alkenes

Two characteristics of the double bond help us understand why these addition reactions occur:

1. An addition reaction results in the conversion of one π bond and one σ bond (Sections 1.7 and 1.8) into two σ bonds. The result of this change is usually energetically favorable. The energy released in making two σ bonds exceeds that needed to break one σ bond and one π bond (because π bonds are weaker), and, therefore, addition reactions are usually exothermic:



2. The electrons of the π bond are exposed. Because the π bond results from overlapping p orbitals, the π electrons lie above and below the plane of the double bond:



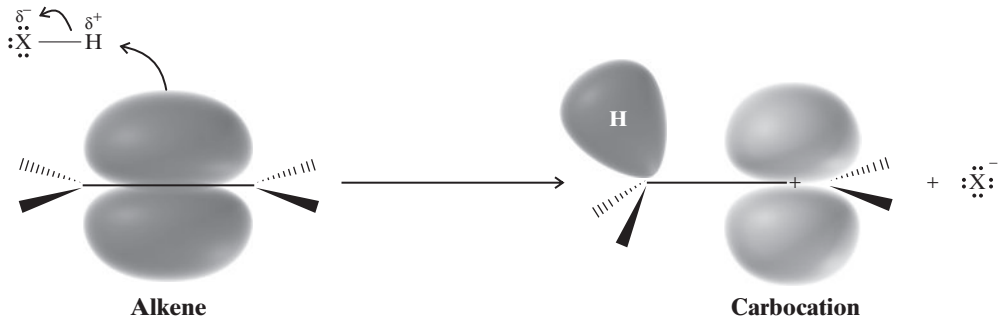
The electron pair of the π bond is distributed throughout both lobes of the π molecular orbital.

Electrophilic Addition

- Electrons in the π bond of alkenes react with electrophiles.
- **Electrophiles** are electron-seeking reagents. They have the property of being **electrophilic**.

Electrophiles include proton donors such as Brønsted–Lowry acids, neutral reagents such as bromine (because it can be polarized so that one end is positive), and Lewis acids such as BH_3, BF_3, and $AlCl_3$. Metal ions that contain vacant orbitals—the silver ion (Ag^+), the mercuric ion (Hg^{2+}), and the platinum ion (Pt^{2+}), for example—also act as electrophiles.

Hydrogen halides, for example, react with alkenes by accepting a pair of electrons from the π bond to form a σ bond between the hydrogen and one of the carbon atoms, with loss of the halide ion. This leaves a vacant p orbital and a + charge on the other carbon. The overall result is the formation of a carbocation and a halide ion from the alkene and HX:



Being highly reactive, the carbocation may then combine with the halide ion by accepting one of its electron pairs:

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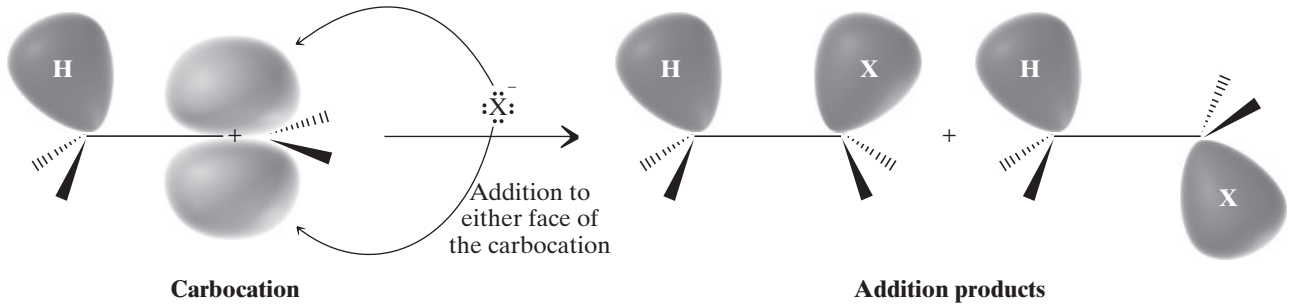
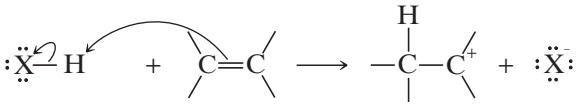
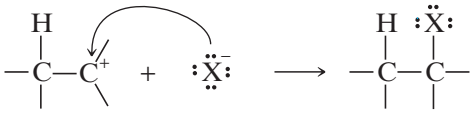


Electrophiles Are Lewis Acids Electrophiles are molecules or ions that can accept an electron pair. Nucleophiles are molecules or ions that can furnish an electron pair (i.e., Lewis bases). Any reaction of an electrophile also involves a nucleophile. In the protonation of an alkene the electrophile is the proton donated by an acid; the nucleophile is the alkene:

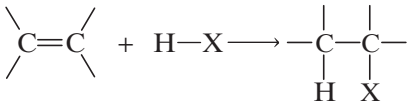


In the next step, the reaction of the carbocation with a halide ion, the carbocation is the electrophile and the halide ion is the nucleophile:



8.2 | ELECTROPHILIC ADDITION OF HYDROGEN HALIDES TO ALKENES: MECHANISM AND MARKOVNIKOV'S RULE

Hydrogen halides (HI, HBr, HCl, and HF) add to the double bond of alkenes:



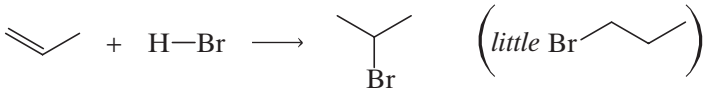
These additions are sometimes carried out by dissolving the hydrogen halide in a solvent, such as acetic acid or CH_2Cl_2, or by bubbling the gaseous hydrogen halide directly into the alkene and using the alkene itself as the solvent. HF is prepared as polyhydrogen fluoride in pyridine.

- The order of reactivity of the hydrogen halides in alkene addition is

$$HI > HBr > HCl > HF$$

Unless the alkene is highly substituted, HCl reacts so slowly that the reaction is not one that is useful as a preparative method. HBr adds readily, but as we shall learn in Section 9.8, unless precautions are taken, the reaction may follow an alternate course.

The addition of HX to an unsymmetrical alkene could conceivably occur in two ways. In practice, however, one product usually predominates. The addition of HBr to propene, for example, could conceivably lead to either 1-bromopropane or 2-bromopropane. The main product, however, is 2-bromopropane:



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When 2-methylpropene reacts with HBr, the main product is 2-bromo-2-methylpropane, not 1-bromo-2-methylpropane:

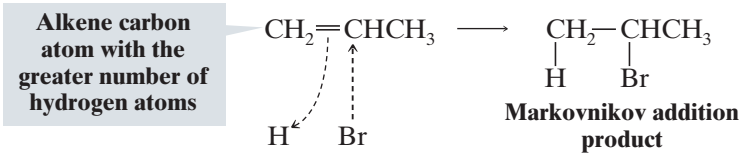


2-Methylpropene **2-Bromo-2-methylpropane** **1-Bromo-2-methylpropane**

Consideration of many examples like this led the Russian chemist Vladimir Markovnikov in 1870 to formulate what is now known as Markovnikov's rule.

- One way to state **Markovnikov's rule** is to say that ***in the addition of* HX *to an alkene, the hydrogen atom adds to the carbon atom of the double bond that already has the greater number of hydrogen atoms.***

The addition of HBr to propene is an illustration:

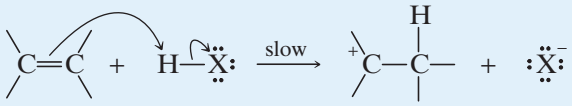


Reactions that illustrate Markovnikov's rule are said to be *Markovnikov additions*.

A mechanism for addition of a hydrogen halide to an alkene involves the following two steps:

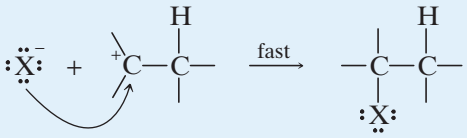
A MECHANISM FOR THE REACTION — Addition of a Hydrogen Halide to an Alkene

Step 1



The π electrons of the alkene form a bond with a proton from HX to form a carbocation and a halide ion.

Step 2



The halide ion reacts with the carbocation by donating an electron pair; the result is an alkyl halide.

The important step—because it is the **rate-determining step**—is step 1. In step 1 the alkene donates a pair of electrons to the proton of the hydrogen halide and forms a carbocation. This step (Fig. 8.1) is highly endergonic and has a high free energy of activation. Consequently, it takes place slowly. In step 2 the highly reactive carbocation stabilizes itself by combining with a halide ion. This exergonic step has a very low free energy of activation and takes place very rapidly.

8.2A Theoretical Explanation of Markovnikov's Rule

If the alkene that undergoes addition of a hydrogen halide is an unsymmetrical alkene such as propene, then step 1 could conceivably lead to two different carbocations:

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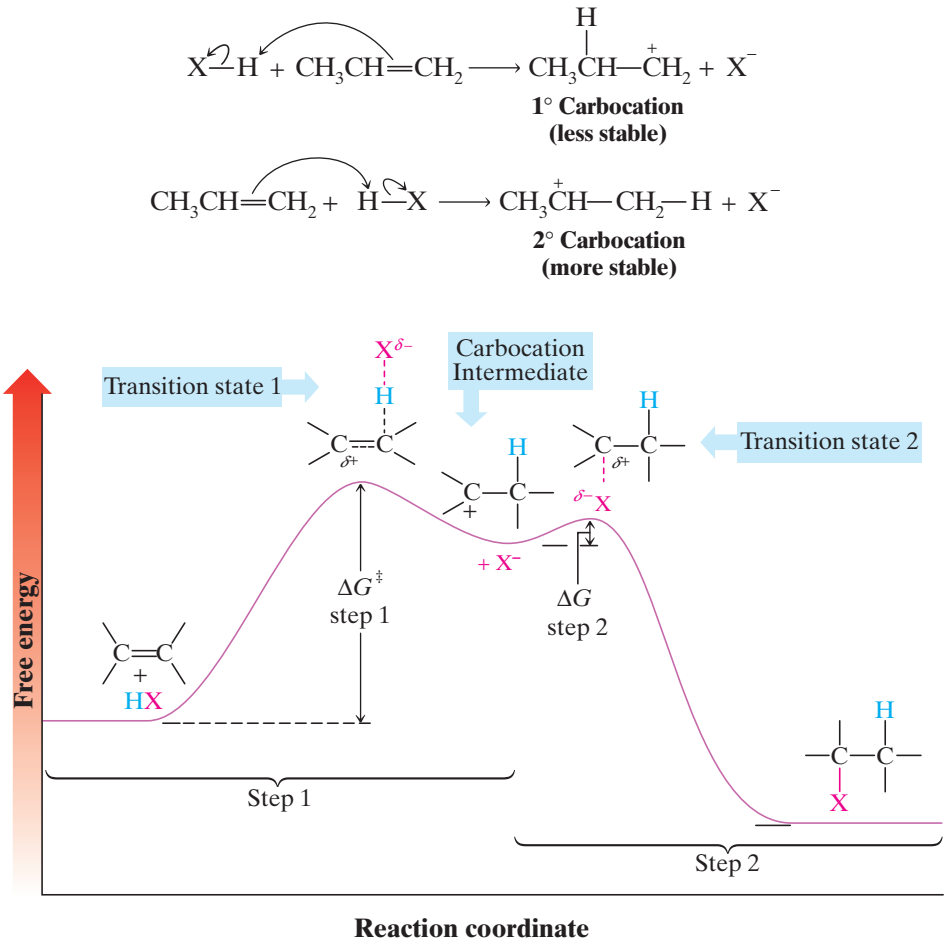
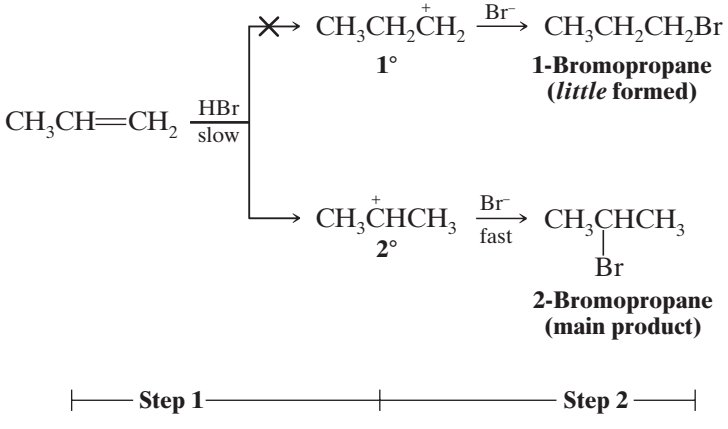


Figure 8.1 Free-energy diagram for the addition of HX to an alkene. The free energy of activation for step 1 is much larger than that for step 2.

These two carbocations are not of equal stability, however. The secondary carbocation is *more stable*, and it is the greater stability of the secondary carbocation that accounts for the correct prediction of the overall addition by Markovnikov's rule. In the addition of HBr to propene, for example, the reaction takes the following course:



The chief product of the reaction is 2-bromopropane because the more stable secondary carbocation is formed preferentially in the first step.

- The more stable carbocation predominates because it is formed faster.

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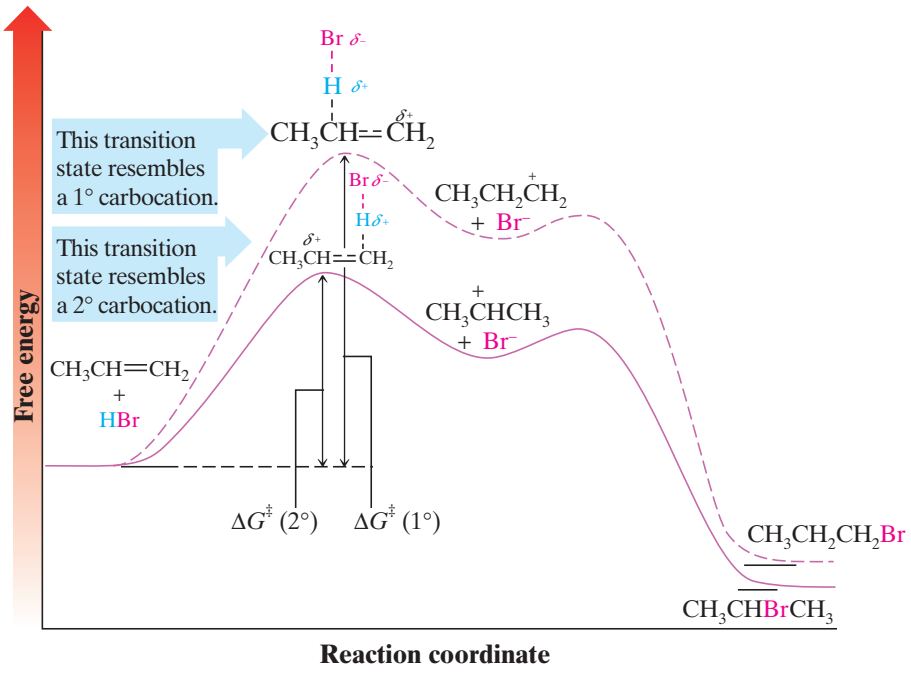


Figure 8.2 Free-energy diagrams for the addition of HBr to propene. $\Delta G^{\ddagger}$ (2°) is less than $\Delta G^{\ddagger}$ (1°).

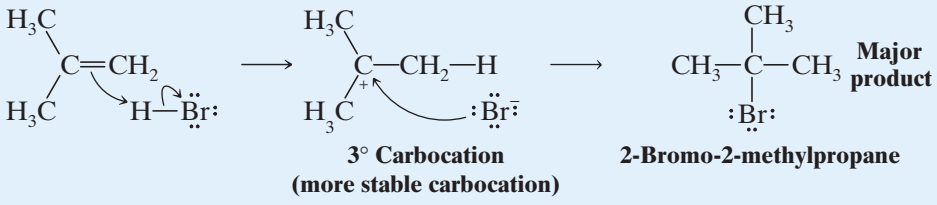
We can understand why this is true if we examine the free-energy diagrams in Fig. 8.2.

- The reaction leading to the secondary carbocation (and ultimately to 2-bromopropane) has the lower free energy of activation. This is reasonable because its transition state resembles the more stable carbocation.
- The reaction leading to the primary carbocation (and ultimately to 1-bromopropane) has a higher free energy of activation because its transition state resembles a less stable primary carbocation. This second reaction is much slower and does not compete appreciably with the first reaction.

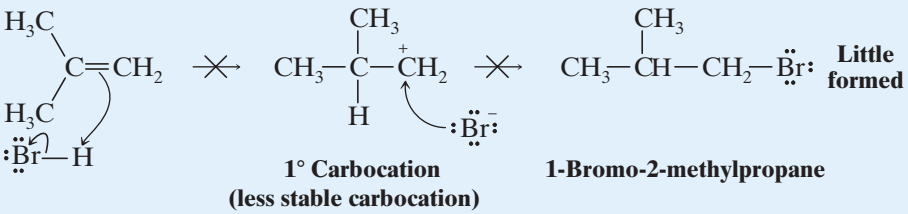
The reaction of HBr with 2-methylpropene produces only 2-bromo-2-methylpropane, for the same reason regarding carbocations stability. Here, in the first step (i.e., the attachment of the proton) the choice is even more pronounced—between a tertiary carbocation and a primary carbocation. Thus, 1-bromo-2-methylpropane is *not* obtained as a product

A MECHANISM FOR THE REACTION — Addition of HBr to 2-Methylpropene

This reaction takes place:



This reaction *does not* occur to any appreciable extent:



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of the reaction because its formation would require the formation of a primary carbocation. Such a reaction would have a much higher free energy of activation than that leading to a tertiary carbocation.

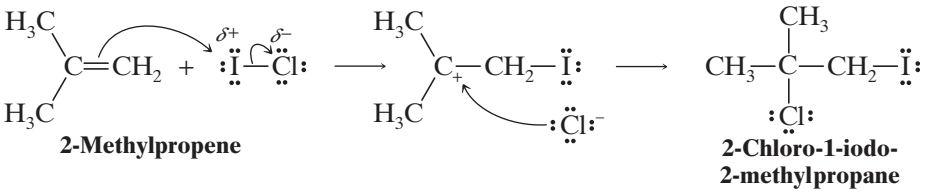
- Rearrangements invariably occur when the carbocation initially formed by addition of HX to an alkene can rearrange to a more stable one (see Section 7.8).

8.2B General Statement of Markovnikov's Rule

With this understanding of the mechanism for the ionic addition of hydrogen halides to alkenes, we can now generalize about how electrophiles add to alkenes.

- General statement of **Markovnikov's rule**: In the ionic addition of an unsymmetrical reagent to a double bond, the positive portion of the adding reagent attaches itself to a carbon atom of the double bond so as to yield the more stable carbocation as an intermediate.
- Addition of the electrophile determines the overall orientation of the addition, because it occurs first (before the addition of the nucleophilic portion of the adding reagent).

Notice that this formulation of Markovnikov's rule allows us to predict the outcome of the addition of a reagent such as ICl. Because of the greater electronegativity of chlorine, the positive portion of this molecule is iodine. The addition of ICl to 2-methylpropene takes place in the following way and produces 2-chloro-1-iodo-2-methylpropane:

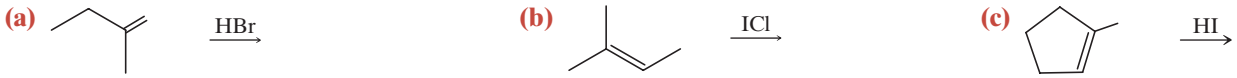


Practice Problem 8.1

Give the structure and name of the product that would be obtained from the ionic addition of IBr to propene.

Practice Problem 8.2

Outline mechanisms for the following addition reactions:



8.2C Regioselective Reactions

Chemists describe reactions like the Markovnikov additions of hydrogen halides to alkenes as being **regioselective**. *Regio* comes from the Latin word *regionem* meaning direction.

- When a reaction that can potentially yield two or more constitutional isomers actually produces only one (or a predominance of one), the reaction is said to be a **regioselective reaction**.

The addition of HX to an unsymmetrical alkene such as propene could conceivably yield two constitutional isomers, for example. As we have seen, however, the reaction yields only one, and therefore it is regioselective.

8.2D An Exception to Markovnikov's Rule

In Section 9.8 we shall study an exception to Markovnikov's rule. This exception concerns the addition of HBr to alkenes ***when the addition is carried out in the presence of peroxides*** (i.e., compounds with the general formula ROOR).

- When alkenes are treated with HBr in the presence of peroxides, an **anti-Markovnikov addition** occurs in the sense that the hydrogen atom becomes attached to the carbon atom with the fewer hydrogen atoms.

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With propene, for example, the addition takes place as follows:

$$CH_3CH{=}CH_2 + HBr \xrightarrow{ROOR} CH_3CH_2CH_2Br$$

In Section 9.9 we shall find that this addition occurs by *a radical mechanism*, and not by the ionic mechanism given at the beginning of Section 8.2.

- This anti-Markovnikov addition occurs ***only when* HBr *is used in the presence of peroxides*** and does not occur significantly with HF, HCl, and HI even when peroxides are present.

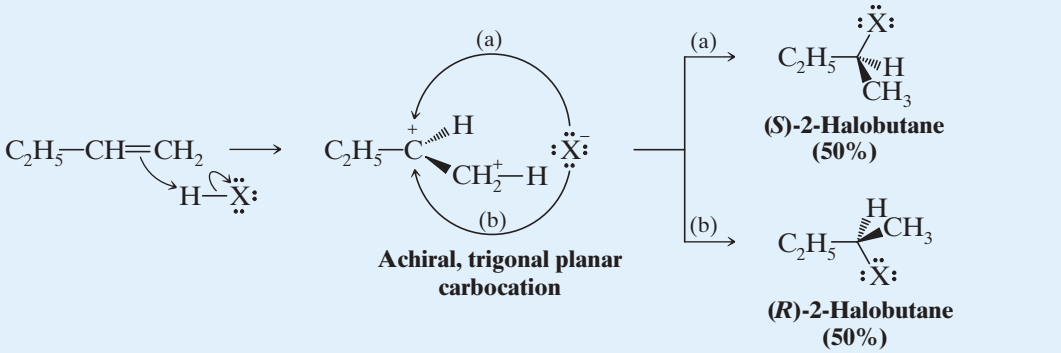
8.3 | STEREOCHEMISTRY OF THE IONIC ADDITION TO AN ALKENE

Consider the following addition of HX to 1-butene and notice that the reaction leads to the formation of a 2-halobutane that contains a chirality center:

$$CH_3CH_2CH{=}CH_2 + HX \longrightarrow CH_3CH_2\overset{*}{C}HCH_3 \quad (X \text{ on } C)$$

The product, therefore, can exist as a pair of enantiomers. The question now arises as to how these enantiomers are formed. Is one enantiomer formed in greater amount than the other? The answer is *no*; the carbocation that is formed in the first step of the addition (see the following scheme) is trigonal planar and is ***achiral*** (a model will show that it has a plane of symmetry). When the halide ion reacts with this achiral carbocation in the second step, ***reaction is equally likely at either face.*** The reactions leading to the two enantiomers occur at the same rate, and the enantiomers, therefore, are produced in equal amounts ***as a racemic mixture***.

THE STEREOCHEMISTRY OF THE REACTION... Ionic Addition to an Alkene



8.4 | ADDITION OF WATER TO ALKENES: ACID-CATALYZED HYDRATION

The acid-catalyzed addition of water to the double bond of an alkene (**hydration** of an alkene) is a method for the preparation of low-molecular-weight alcohols. This reaction has its greatest utility in large-scale industrial processes. The acids most commonly used to catalyze the hydration of alkenes are dilute aqueous solutions of sulfuric acid and phosphoric acid. These reactions, too, are usually regioselective, and the addition of water to the double bond follows Markovnikov's rule. In general, the reaction takes the form that follows:

$$C{=}C + HOH \xrightarrow{H_3O^+} -\overset{|}{C}-\overset{|}{C}- \quad (H \text{ and } OH)$$

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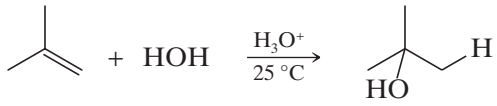
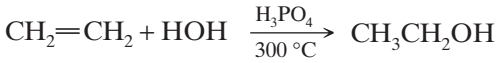
An example is the hydration of 2-methylpropene:



2-Methylpropene (isobutylene) **2-Methyl-2-propanol (*tert*-butyl alcohol)**

Because the reactions follow Markovnikov's rule, acid-catalyzed hydrations of alkenes do not yield primary alcohols except in the special case of the hydration of ethene:

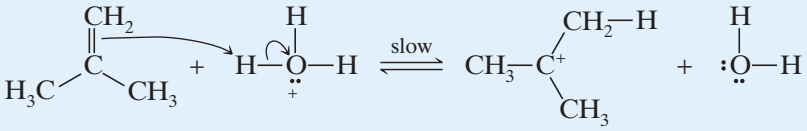


8.4A Mechanism

The mechanism for the hydration of an alkene is simply the reverse of the mechanism for the dehydration of an alcohol. We can illustrate this by giving the mechanism for the **hydration** of 2-methylpropene and by comparing it with the mechanism for the **dehydration** of 2-methyl-2-propanol given in Section 7.7A.

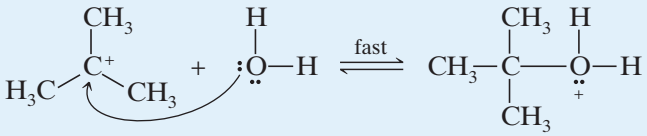
A MECHANISM FOR THE REACTION Acid-Catalyzed Hydration of an Alkene

Step 1



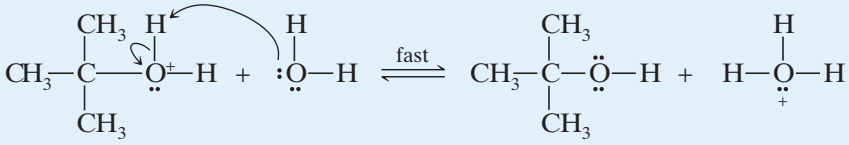
The alkene donates an electron pair to a proton to form the more stable 3° carbocation.

Step 2



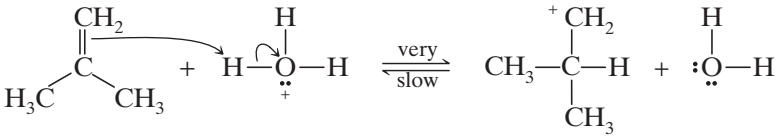
The carbocation reacts with a molecule of water to form a protonated alcohol.

Step 3



A transfer of a proton to a molecule of water leads to the product.

The rate-determining step in the *hydration* mechanism is step 1: the formation of the carbocation. It is this step, too, that accounts for the Markovnikov addition of water to the double bond. The reaction produces 2-methyl-2-propanol because step 1 leads to the formation of the more stable tertiary (3°) cation rather than the much less stable primary (1°) cation:



For all practical purposes this reaction does not take place because it produces a 1° carbocation.

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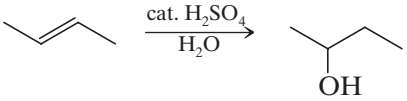
The reactions whereby *alkenes are hydrated or alcohols are dehydrated* are reactions in which the ultimate product is governed by the position of an equilibrium. Therefore, in the *dehydration of an alcohol* it is best to use a concentrated acid so that the concentration of water is low. (The water can be removed as it is formed, and it helps to use a high temperature.) In the *hydration of an alkene* it is best to use dilute acid so that the concentration of water is high. It also usually helps to use a lower temperature.

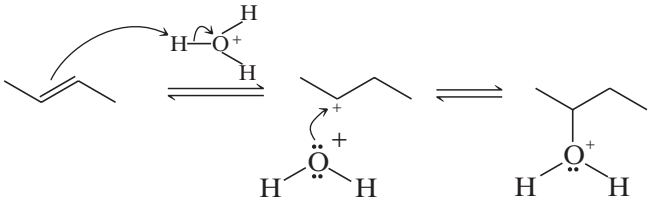
Solved Problem 8.1

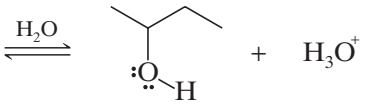
Write a mechanism that explains the following reaction.



Answer

We know that a hydronium ion, formed from sulfuric acid and water, can donate a proton to an alkene to form a carbocation. The carbocation can then accept an electon pair from a molecule of water to form a protonated alcohol. The protonated alcohol can donate a proton to water to become an alcohol.





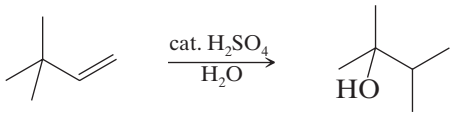
Practice Problem 8.3

In one industrial synthesis of ethanol, ethene is first dissolved in 95% sulfuric acid. In a second step water is added and the mixture is heated. Outline the reactions involved.

8.4B Rearrangements

- One complication associated with alkene hydrations is the occurrence of **rearrangements**.

Because the reaction involves the formation of a carbocation in the first step, the carbocation formed initially invariably rearranges to a more stable one (or possibly to an isoenergetic one) if such a rearrangement is possible. An illustration is the formation of 2,3-dimethyl-2-butanol as the major product when 3,3-dimethyl-1-butene is hydrated:



3,3-Dimethyl-1-butene **2,3-Dimethyl-2-butanol (major product)**

Practice Problem 8.4

Outline all steps in a mechanism showing how 2,3-dimethyl-2-butanol is formed in the acid-catalyzed hydration of 3,3-dimethyl-1-butene.

Practice Problem 8.5

The following order of reactivity is observed when the following alkenes are subjected to acid-catalyzed hydration:

$$(CH_3)_2C{=}CH_2 > CH_3CH{=}CH_2 > CH_2{=}CH_2$$

Explain this order of reactivity.

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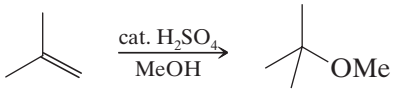
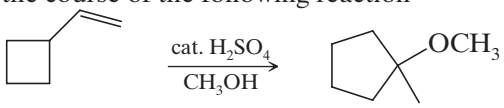
Practice Problem 8.6

Write a mechanism for the following reaction.



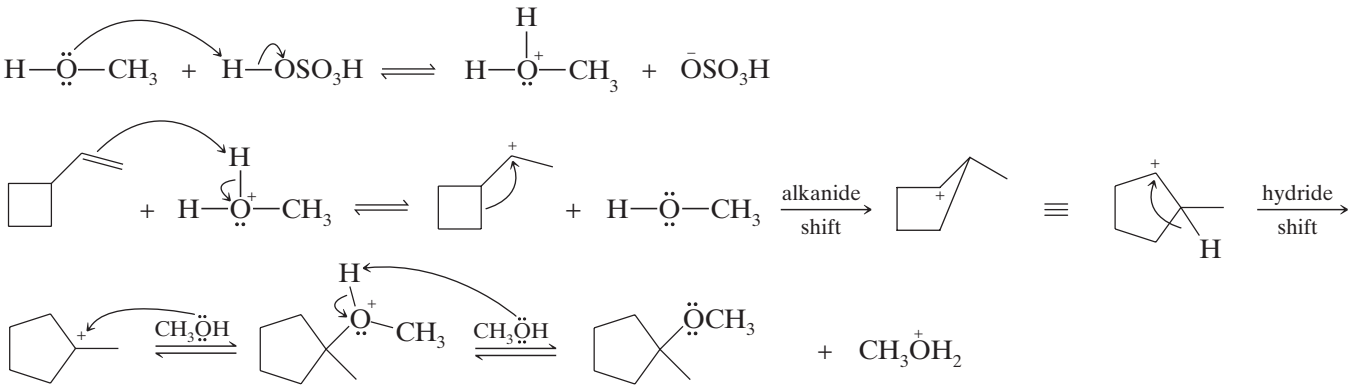
Solved Problem 8.2

Write a mechanism that will explain the course of the following reaction



Answer

As we have learned, in a strongly acidic medium such as methanol containing catalytic sulfuric acid, an alkene can accept a proton to become a carbocation. In the reaction above, the 2° carbocation formed initially can undergo an alkanide shift and a hydride shift as shown below to become a 3° carbocation, which can then react with the solvent (methanol) to form an ether.

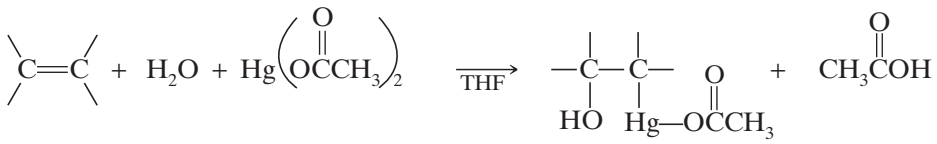


8.5 | ALCOHOLS FROM ALKENES THROUGH OXYMERCURATION–DEMERCURATION: MARKOVNIKOV ADDITION

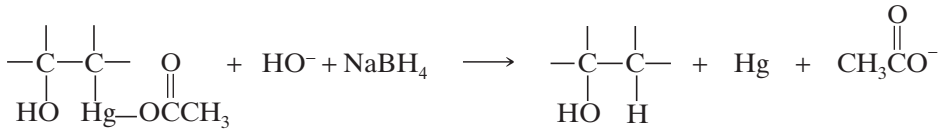
A useful laboratory procedure for synthesizing alcohols from alkenes that avoids rearrangement is a two-step method called **oxymercuration–demercuration**.

- Alkenes react with mercuric acetate in a mixture of tetrahydrofuran (THF) and water to produce (hydroxyalkyl) mercury compounds. These (hydroxyalkyl)mercury compounds can be reduced to alcohols with sodium borohydride.

Step 1: Oxymercuration



Step 2: Demercuration



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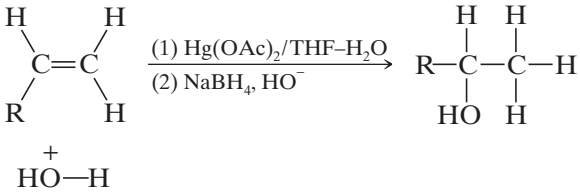
- In the first step, **oxymercuration**, water and mercuric acetate add to the double bond.
- In the second step, **demercuration**, sodium borohydride reduces the acetoxymercury group and replaces it with hydrogen. (The acetate group is often abbreviated —OAc.)

Both steps can be carried out in the same vessel, and both reactions take place very rapidly at room temperature or below. The first step—oxymercuration—usually goes to completion within a period of seconds to minutes. The second step—demercuration—normally requires less than an hour. The overall reaction gives alcohols in very high yields, usually greater than 90%.

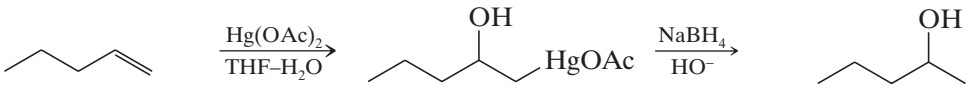
8.5A Regioselectivity of Oxymercuration–Demercuration

Oxymercuration–demercuration is also highly regioselective.

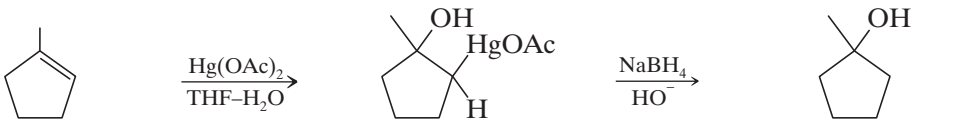
- In oxymercuration–demercuration, the net orientation of the addition of the elements of water, H— and —OH, ***is in accordance with Markovnikov's rule***. The H— becomes attached to the carbon atom of the double bond with the greater number of hydrogen atoms.



The following are specific examples:



1-Pentene **2-Pentanol (93%)**

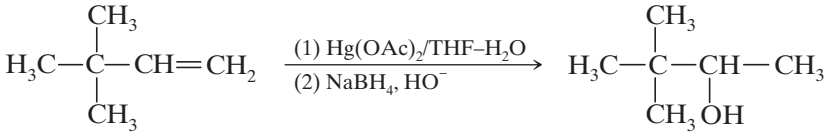


1-Methylcyclopentene **1-Methylcyclopentanol**

8.5B Rearrangements Seldom Occur in Oxymercuration–Demercuration

- Rearrangements of the carbon skeleton seldom occur in oxymercuration–demercuration.

The oxymercuration–demercuration of 3,3-dimethyl-1-butene is a striking example illustrating this feature. It is in direct contrast to the **hydration** of 3,3-dimethyl-1-butene we studied previously (Section 8.4B).



3,3-Dimethyl-1-butene **3,3-Dimethyl-2-butanol (94%)**

Analysis of the mixture of products by gas chromatography failed to reveal the presence of any 2,3-dimethyl-2-butanol. The acid-catalyzed hydration of 3,3-dimethyl-1-butene, by contrast, gives 2,3-dimethyl-2-butanol as the major product.

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8.5C Mechanism of Oxymercuration

A mechanism that accounts for the orientation of addition in the oxymercuration stage, and one that also explains the general lack of accompanying rearrangements, is shown below.

- Central to this mechanism is an electrophilic attack by the mercury species, $^{+}HgOAc$, at the less substituted carbon of the double bond (i.e., at the carbon atom that bears the greater number of hydrogen atoms), and the formation of a bridged intermediate.

We illustrate the mechanism using 3,3-dimethyl-1-butene as the example:

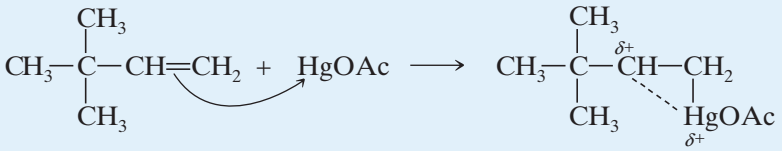
A MECHANISM FOR THE REACTION — Oxymercuration

Step 1

$$Hg(OAc)_2 \rightleftharpoons {}^{+}HgOAc + AcO^{-}$$

Mercuric acetate dissociates to form a $^{+}HgOAc$ cation and an acetate anion.

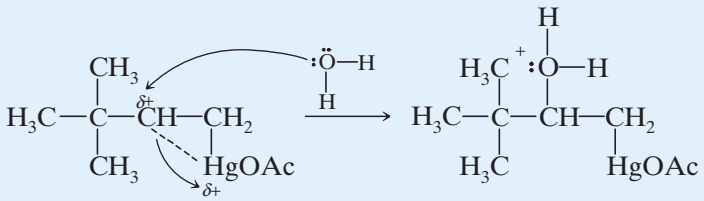
Step 2



3,3-Dimethyl-1-butene **Mercury-bridged carbocation**

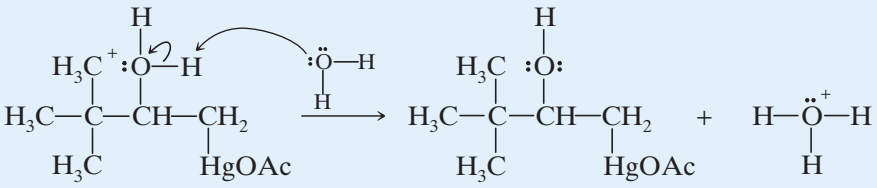
The alkene donates a pair of electrons to the electrophilic $^{+}HgOAc$ cation to form a mercury-bridged carbocation. In this carbocation, the positive charge is shared between the 2° (more substituted) carbon atom and the mercury atom. The charge on the carbon atom is large enough to account for the Markovnikov orientation of the addition, but not large enough for a rearrangement to occur.

Step 3



A water molecule attacks the carbon of the bridged mercurinium ion that is better able to bear the partial positive charge.

Step 4



(Hydroxyalkyl)mercury compound

An acid–base reaction transfers a proton to another water molecule (or to an acetate ion). This step produces the (hydroxyalkyl)mercury compound.

Calculations indicate that mercury-bridged carbocations (termed mercurinium ions) such as those formed in this reaction retain much of the positive charge on the mercury moiety. Only a small portion of the positive charge resides on the more substituted carbon atom. The charge is large enough to account for the observed Markovnikov addition, but it is too small to allow the usual rapid carbon skeleton rearrangements that take place with more fully developed carbocations.

Although attack by water on the bridged mercurinium ion leads to anti addition of the hydroxyl and mercury groups, the reaction that replaces mercury with hydrogen is not stereocontrolled (it likely involves radicals; see Chapter 9). This step scrambles the overall stereochemistry.

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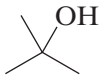
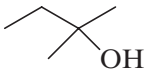
- The net result of oxymercuration–demercuration is a mixture of syn and anti addition of —H and —OH to the alkene.
- As already noted, oxymercuration–demercuration takes place with Markovnikov regiochemistry.

Practice Problem 8.7

Write the structure of the appropriate alkene and specify the reagents needed for synthesis of the following alcohols by oxymercuration–demercuration:

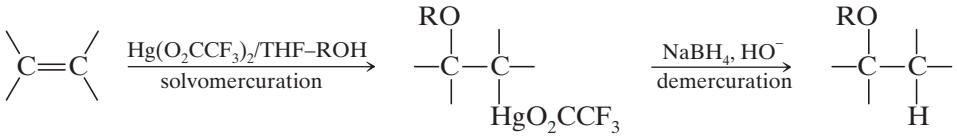
(a) 

(b) 

(c) 

When an alkene is treated with mercuric trifluoroacetate, $Hg(O_2CCF_3)_2$, in THF containing an alcohol, ROH, the product is an (alkoxyalkyl)mercury compound. Treating this product with $NaBH_4/HO^-$ results in the formation of an ether.

- When a solvent molecule acts as the nucleophile in the oxymercuration step the overall process is called *solvomercuration–demercuration*:



Alkene **(Alkoxyalkyl)mercuric trifluoroacetate** **Ether**

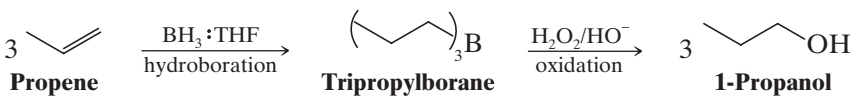
Practice Problem 8.8

(a) Outline a likely mechanism for the solvomercuration step of the ether synthesis just shown. **(b)** Show how you would use solvomercuration–demercuration to prepare *tert*-butyl methyl ether. **(c)** Why would one use $Hg(O_2CCF_3)_2$ instead of $Hg(OAc)_2$?

8.6 | ALCOHOLS FROM ALKENES THROUGH HYDROBORATION–OXIDATION: ANTI-MARKOVNIKOV SYN HYDRATION

- **Anti-Markovnikov hydration** of a double bond can be achieved through the use of diborane (B_2H_6) or a solution of borane in tetrahydrofuran (BH_3:THF).

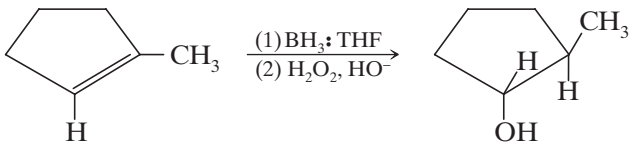
The addition of water is indirect in this process, and two reactions are involved. The first is the addition of a boron atom and hydrogen atom to the double bond, called **hydroboration**; the second is **oxidation** and hydrolysis of the alkylborane intermediate to an alcohol and boric acid. The anti-Markovnikov regiochemistry of the addition is illustrated by the hydroboration–oxidation of propene:



Propene **Tripropylborane** **1-Propanol**

- Hydroboration–oxidation takes place with **syn** stereochemistry, as well as anti-Markovnikov regiochemistry.

This can be seen in the following example with 1-methylcyclopentene:



In the following sections we shall consider details of the mechanism that lead to the anti-Markovnikov regiochemistry and syn stereochemistry of hydroboration–oxidation.

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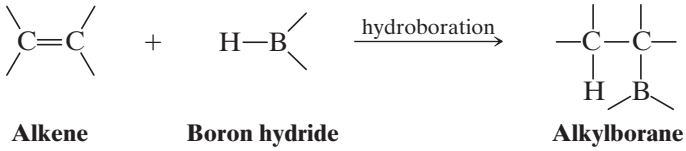
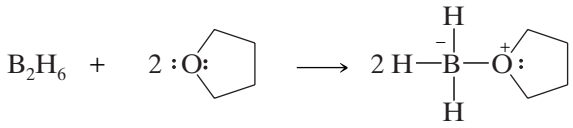
8.7 | HYDROBORATION: SYNTHESIS OF ALKYLBORANES

Hydroboration of an alkene is the starting point for a number of useful synthetic procedures, including the anti-Markovnikov syn **hydration** procedure we have just mentioned. Hydroboration was discovered by Herbert C. Brown (Purdue University), and it can be represented in its simplest terms as follows:



Alkene **Boron hydride** **Alkylborane**

Hydroboration can be accomplished with diborane (B_2H_6), which is a gaseous dimer of borane (BH_3), or more conveniently with a reagent prepared by dissolving diborane in THF. When diborane is introduced to THF, it reacts to form a Lewis acid–base complex of borane (the Lewis acid) and THF. The complex is represented as BH_3:THF.

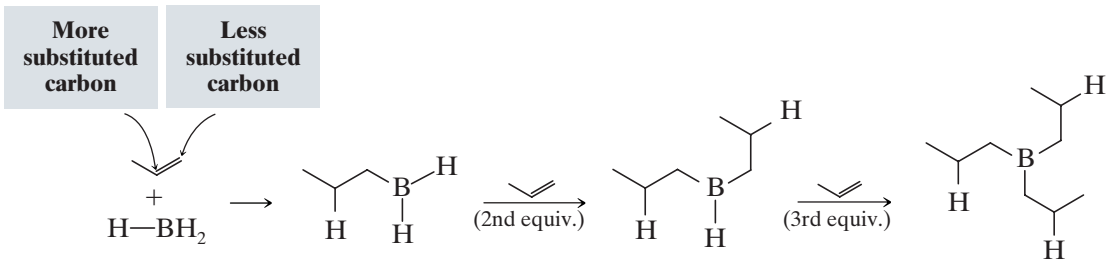


Diborane **THF (tetrahydrofuran)** **BH_3 :THF**

Solutions containing the BH_3:THF complex can be obtained commercially. Hydroboration reactions are usually carried out in ethers: either in diethyl ether, $(CH_3CH_2)_2O$, or in some higher molecular weight ether such as "diglyme" [$(CH_3OCH_2CH_2)_2O$, *di*ethylene *gly*col dimethyl ether]. Great care must be used in handling diborane and alkylboranes because they ignite spontaneously in air (with a green flame). The solution of BH_3:THF must be used in an inert atmosphere (e.g., argon or nitrogen) and with care.

8.7A Mechanism of Hydroboration

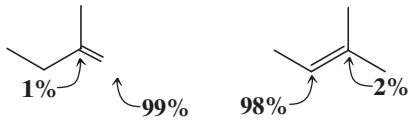
When a terminal alkene such as propene is treated with a solution containing BH_3:THF, the boron hydride adds successively to the double bonds of three molecules of the alkene to form a trialkylborane:



Tripropylborane

- In each addition step ***the boron atom becomes attached to the less substituted carbon atom of the double bond***, and a hydrogen atom is transferred from the boron atom to the other carbon atom of the double bond.
- Hydroboration is **regioselective** and it is **anti-Markovnikov** (the hydrogen atom becomes attached to the carbon atom with fewer hydrogen atoms).

Other examples that illustrate the tendency for the boron atom to become attached to the less substituted carbon atom are shown here. The percentages designate where the boron atom becomes attached.



These percentages, indicating where boron becomes attached in reactions using these starting materials, illustrate the tendency for boron to bond at the less substituted carbon of the double bond.

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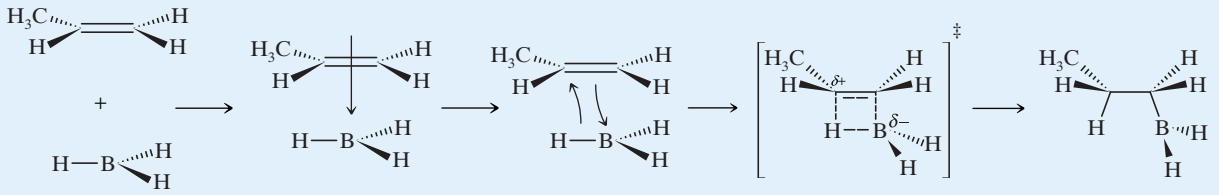
This observed attachment of boron to the less substituted carbon atom of the double bond seems to result in part from **steric factors**—the bulky boron-containing group can approach the less substituted carbon atom more easily.

In the mechanism proposed for hydroboration, addition of BH_3 to the double bond begins with a donation of π electrons from the double bond to the vacant p orbital of BH_3 (see the following mechanism). In the next step this complex becomes the addition product by passing through a four-atom transition state in which the boron atom is partially bonded to the less substituted carbon atom of the double bond and one hydrogen atom is partially bonded to the other carbon atom. As this transition state is approached, electrons shift in the direction of the boron atom and away from the more substituted carbon atom of the double bond. This makes the more substituted carbon atom develop a partial positive charge, *and because it bears an electron-releasing alkyl group, it is better able to accommodate this positive charge*. Thus, electronic factors also favor addition of boron at the least substituted carbon.

- Overall, both *electronic* and *steric factors* account for the anti-Markovnikov orientation of the addition.

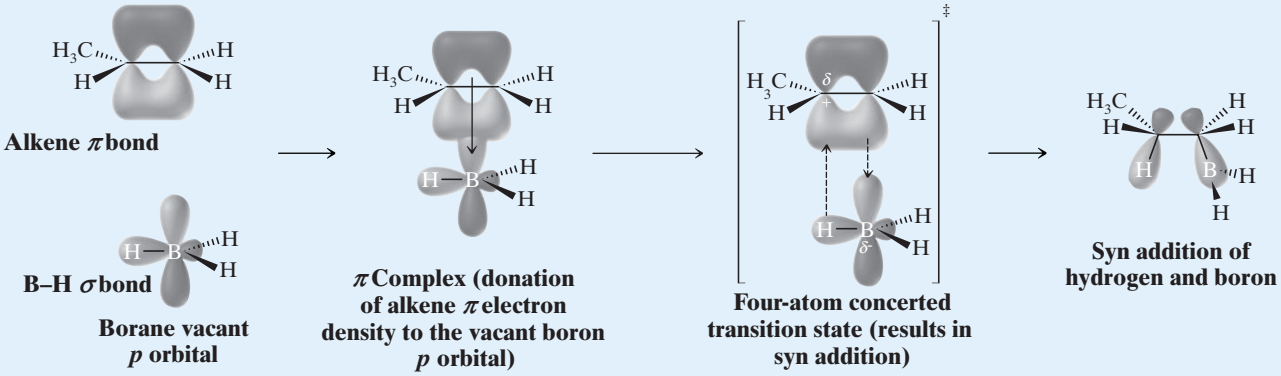
A MECHANISM FOR THE REACTION — Hydroboration

Hydroboration



Addition takes place through the initial formation of a π complex, which changes into a cyclic four-atom transition state with the boron adding to the less hindered carbon atom. The dashed bonds in the transition state represent bonds that are partially formed or partially broken. The transition state results in syn addition of the hydrogen and boron group, leading to an alkylborane. The other B–H bonds of the alkylborane can undergo similar additions, leading finally to a trialkylborane.

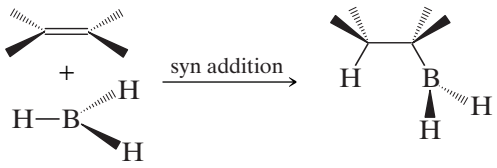
An orbital view of hydroboration



8.7B Stereochemistry of Hydroboration

- The transition state for hydroboration requires that the boron atom and the hydrogen atom add to the same face of the double bond:

Stereochemistry of Hydroboration



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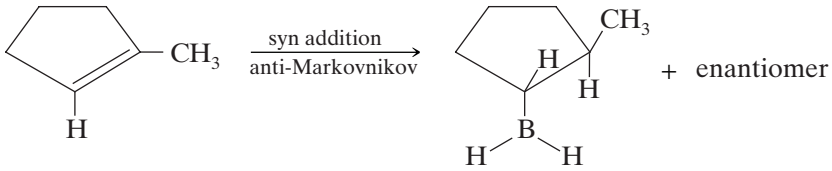
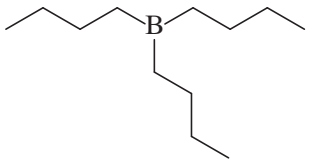
We can see the results of a syn addition in our example involving the hydroboration of 1-methylcyclopentene. Formation of the enantiomer, which is equally likely, results when the boron hydride adds to the top face of the 1-methylcyclopentene ring:



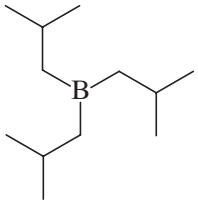
Practice Problem 8.9

Specify the alkene needed for synthesis of each of the following alkylboranes by hydroboration:

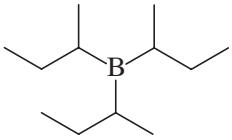
(a)



(b)



(c)



(d) Show the stereochemistry involved in the hydroboration of 1-methylcyclohexene.

Practice Problem 8.10

Treating a hindered alkene such as 2-methyl-2-butene with BH_3:THF leads to the formation of a dialkylborane instead of a trialkylborane. When 2 mol of 2-methyl-2-butene is added to 1 mol of BH_3, the product formed is bis(3-methyl-2-butyl)borane, nicknamed "disiamylborane." Write its structure. Bis(3-methyl-2-butyl)borane is a useful reagent in certain syntheses that require a sterically hindered borane. (The name "disiamyl" comes from "*dis*econdary-*i*so-*amyl*," a completely unsystematic and unacceptable name. The name "amyl" is an old common name for a five-carbon alkyl group.)

8.8 | OXIDATION AND HYDROLYSIS OF ALKYLBORANES

The alkylboranes produced in the hydroboration step are usually not isolated. They are oxidized and hydrolyzed to alcohols in the same reaction vessel by the addition of hydrogen peroxide in an aqueous base:

$$R_3B \xrightarrow[\text{Oxidation and hydrolysis}]{H_2O_2,\ \text{aq. NaOH, 25 °C}} 3R\text{—}OH + B(ONa)_3$$

- **The oxidation and hydrolysis steps take place with retention of configuration** at the carbon initially bearing boron and ultimately bearing the hydroxyl group.

We shall see how this occurs by considering the mechanisms of oxidation and hydrolysis.

Alkylborane oxidation begins with addition of a hydroperoxide anion (HOO^-) to the trivalent boron atom. An unstable intermediate is formed that has a formal negative charge on the boron. Migration of an alkyl group with a pair of electrons from the boron to the adjacent oxygen leads to neutralization of the charge on boron and displacement of a hydroxide anion. The alkyl migration takes place with retention of configuration at the migrating carbon. Repetition of the hydroperoxide anion addition and migration steps occurs twice more until all of the alkyl groups have become attached to oxygen atoms, resulting in a trialkyl borate ester, $B(OR)_3$. The borate ester then undergoes basic hydrolysis to produce three molecules of the alcohol and an inorganic borate anion.

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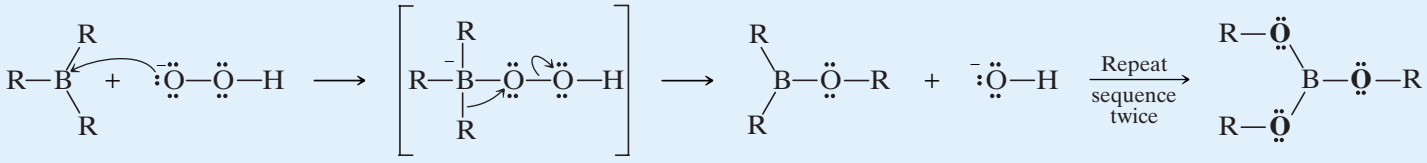
A MECHANISM FOR THE REACTION — Oxidation of Trialkylboranes

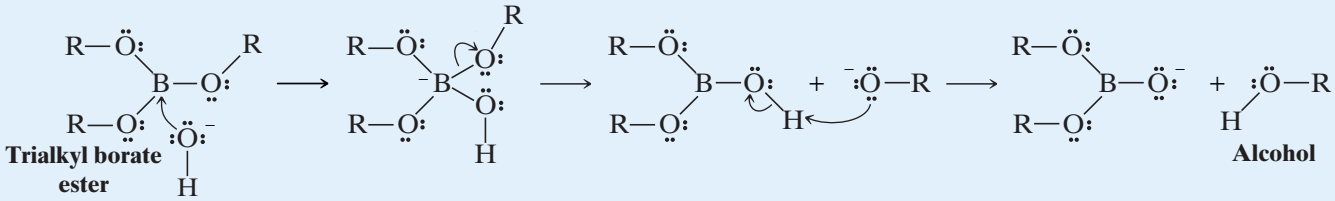


Trialkyl-borane **Hydroperoxide ion** **Unstable intermediate** **Borate ester**

The boron atom accepts an electron pair from the hydroperoxide ion to form an unstable intermediate.

An alkyl group migrates from boron to the adjacent oxygen atom as a hydroxide ion departs. The configuration at the migrating carbon remains unchanged.

Hydrolysis of the Borate Ester



Trialkyl borate ester **Alcohol**

Hydroxide anion attacks the boron atom of the borate ester.

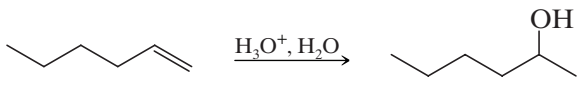
An alkoxide anion departs from the borate anion, reducing the formal change on boron to zero.

Proton transfer completes the formation of one alcohol molecule. The sequence repeats until all three alkoxy groups are released as alcohols and inorganic borate remains.

8.8A Regiochemistry and Stereochemistry of Alkylborane Oxidation and Hydrolysis

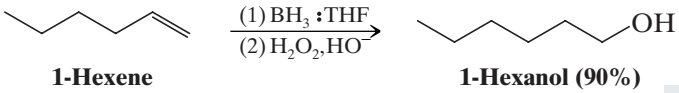
- Hydroboration–oxidation reactions are **regioselective**; the net result of hydroboration–oxidation is **anti-Markovnikov** addition of water to an alkene.
- As a consequence, hydroboration–oxidation gives us a method for the preparation of alcohols that cannot normally be obtained through the acid-catalyzed hydration of alkenes or by oxymercuration–demercuration.

For example, the acid-catalyzed hydration (or oxymercuration–demercuration) of 1-hexene yields 2-hexanol, the Markovnikov addition product.

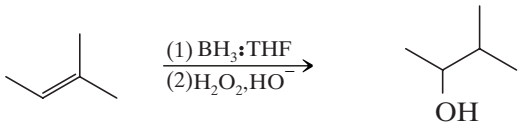


1-Hexene **2-Hexanol** **Markovnikov addition**

In contrast, hydroboration–oxidation of 1-hexene yields 1-hexanol, the anti-Markovnikov product.



1-Hexene **1-Hexanol (90%)** **Anti-Markovnikov addition**



2-Methyl-2-butene **3-Methyl-2-butanol**

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- Hydroboration–oxidation reactions are **stereospecific**; the net addition of —H and —OH is **syn**, and if chirality centers are formed, their configuration depends on the stereochemistry of the starting alkene.

Because the oxidation step in the hydroboration–oxidation synthesis of alcohols takes place with retention of configuration, **the hydroxyl group replaces the boron atom where it stands in the alkylboron compound**. The net result of the two steps (hydroboration and oxidation) is the syn addition of —H and —OH. We can review the anti-Markovnikov and syn aspects of hydroboration–oxidation by considering the hydration of 1-methylcyclopentene, as shown in Fig. 8.3.

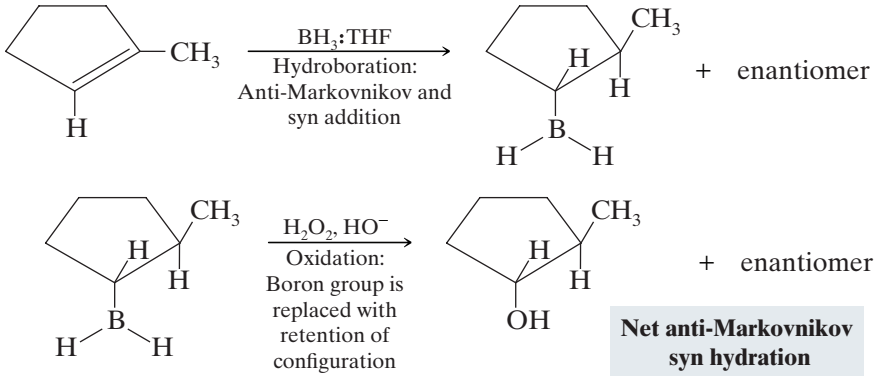
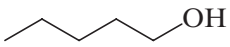
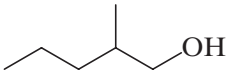


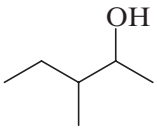
Figure 8.3 The hydroboration–oxidation of 1-methylcyclopentene. The first reaction is a syn addition of borane. In this illustration we have shown the boron and hydrogen entering from the bottom side of 1-methylcyclopentene. The reaction also takes place from the top side at an equal rate to produce the enantiomer. In the second reaction the boron atom is replaced by a hydroxyl group with retention of configuration. The product is *trans*-2-methylcyclopentanol, and the overall result is the syn addition of —H and —OH.

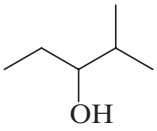
Practice Problem 8.11

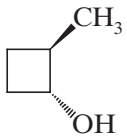
Specify the appropriate alkene and reagents for synthesis of each of the following alcohols by hydroboration–oxidation.

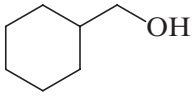
(a) 

(b) 

(c) 

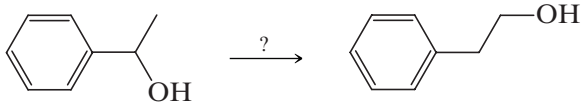
(d) 

(e) 

(f) 

Solved Problem 8.3

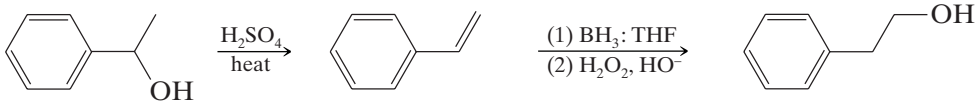
Outline a method for carrying out the following conversion.



1-Phenylethanol **2-Phenylethanol**

Answer

Working backward we realize we could synthesize 2-phenylethanol by hydroboration–oxidation of phenylethene (styrene), and that we could make phenylethene by dehydrating 1-phenylethanol.



Phenylethene

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8.9 | SUMMARY OF ALKENE HYDRATION METHODS

The three methods we have studied for alcohol synthesis by addition reactions to alkenes have different regiochemical and stereochemical characteristics.

1. **Acid-catalyzed hydration of alkenes** takes place with Markovnikov regiochemistry but may lead to a mixture of constitutional isomers if the carbocation intermediate in the reaction undergoes rearrangement to a more stable carbocation.
2. **Oxymercuration–demercuration** occurs with Markovnikov regiochemistry and results in hydration of alkenes without complication from carbocation rearrangement. It is often the preferred choice over acid-catalyzed hydration for Markovnikov addition. The overall stereochemistry of addition in acid-catalyzed hydration and oxymercuration–demercuration is not controlled—they both result in a mixture of cis and trans addition products.
3. **Hydroboration–oxidation** results in **anti-Markovnikov** and syn hydration of an alkene.

The complementary regiochemical and stereochemical aspects of these methods provide useful alternatives when we desire to synthesize a specific alcohol by hydration of an alkene. We summarize them here in Table 8.1.

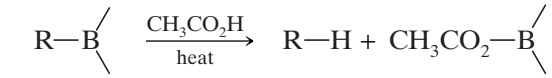
Table 8.1 Summary of Methods for Converting an Alkene to an Alcohol

Reaction	Conditions	Regiochemistry	Stereochemistry[a]	Occurrence of Rearrangements
Acid-catalyzed hydration	cat. HA, H_2O	Markovnikov addition	Not controlled	Frequent
Oxymercuration–demercuration	(1) $Hg(OAc)_2$, THF—H_2O (2) $NaBH_4$, HO^-	Markovnikov addition	Not controlled	Seldom
Hydroboration–oxidation	(1) BH_3:THF (2) H_2O_2, HO^-	Anti-Markovnikov addition	Stereospecific: syn addition of H— and —OH	Seldom

[a]All of these methods produce racemic mixtures in the absence of a chiral influence.

8.10 | PROTONOLYSIS OF ALKYLBORANES

Heating an alkylborane with acetic acid causes cleavage of the carbon–boron bond and replacement with hydrogen:



Alkylborane **Alkane**

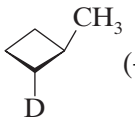
- Protonolysis of an alkylborane takes place with retention of configuration; hydrogen replaces boron **where it stands** in the alkylborane.
- The overall stereochemistry of hydroboration–protonolysis, therefore, is **syn** (like that of the oxidation of alkylboranes).

Hydroboration followed by protonolysis of the resulting alkylborane can be used as an alternative method for hydrogenation of alkenes, although catalytic hydrogenation (Section 7.12) is the more common procedure. Reaction of alkylboranes with deuterated or tritiated acetic acid also provides a very useful way to introduce these isotopes into a compound in a specific way.

Practice Problem 8.12

Starting with any needed alkene (or cycloalkene) and assuming you have deuterioacetic acid (CH_3CO_2D) available, outline syntheses of the following deuterium-labeled compounds.

(a) $(CH_3)_2CHCH_2CH_2D$ **(b)** $(CH_3)_2CHCHDCH_3$ **(c)**



(+ enantiomer)

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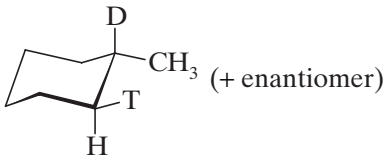
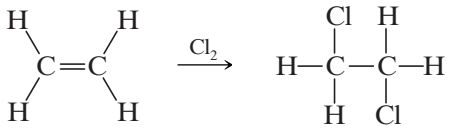
(d) Assuming you also have available BD_3:THF and CH_3CO_2T, can you suggest a synthesis of the following?



(+ enantiomer)

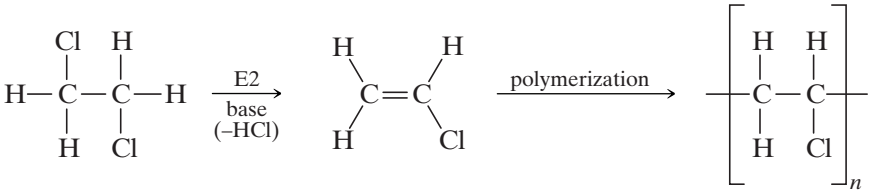
8.11 | ELECTROPHILIC ADDITION OF BROMINE AND CHLORINE TO ALKENES

Alkenes react rapidly with bromine and chlorine in nonnucleophilic solvents to form **vicinal dihalides**. An example is the addition of chlorine to ethene.



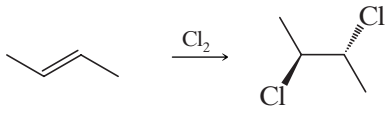
Ethene **1,2-Dichloroethane**

This addition is a useful industrial process because 1,2-dichloroethane can be used as a solvent and can be used to make vinyl chloride, the starting material for poly(vinyl chloride).

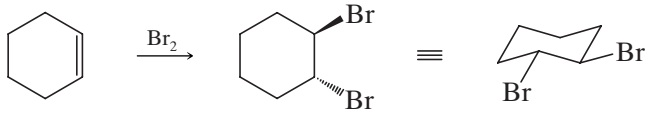


1,2-Dichloroethane **Vinyl chloride** **Poly(vinyl chloride)**

Other examples of the addition of halogens to a double bond are the following:



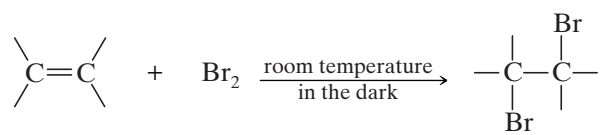
***trans*-2-Butene** ***meso*-1,2-Dichlorobutane**



Cyclohexene ***trans*-1,2-Dibromocyclohexane (racemic)**

These two examples show an aspect of these additions that we shall address later when we examine a mechanism for the reaction: **the addition of halogens is an anti addition to the double bond**.

When bromine is used for this reaction, it can serve as a test for the presence of carbon–carbon multiple bonds. If we add bromine to an alkene (or alkyne, see Section 8.16), the red-brown color of the bromine disappears almost instantly as long as the alkene (or alkyne) is present in excess:



An alkene (colorless) **Bromine (red-brown)** ***vic*-Dibromide (a colorless compound)**

Rapid decolorization of Br_2 is a positive test for alkenes and alkynes.

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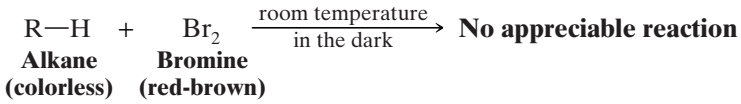
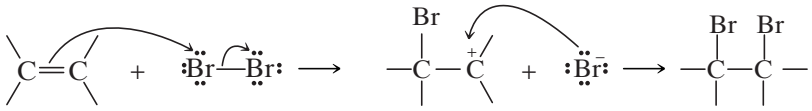
This behavior contrasts markedly with that of **alkanes**. Alkanes do not react appreciably with bromine or chlorine at room temperature and in the absence of light. When alkanes *do* react under those conditions, however, it is by substitution rather than addition and by a mechanism involving radicals that we shall discuss in Chapter 9:



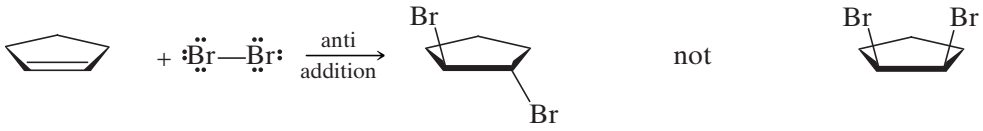
8.11A Mechanism of Halogen Addition

A possible mechanism for the addition of a bromine or chlorine to an alkene is one that involves the formation of a carbocation.



Although this mechanism is similar to ones we have studied earlier, such as the addition of H—X to an alkene, it does not explain an important fact. As we have just seen (in Section 8.11) the addition of bromine or chlorine to an alkene is an **anti addition**.

The addition of bromine to cyclopentene, for example, produces *trans*-1,2-dibromocyclopentane, not *cis*-1,2-dibromocyclopentane.



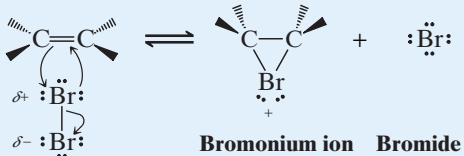
***trans*-1,2-Dibromocyclopentane (as a racemic mixture)** ***cis*-1,2-Dibromocyclohexane (a meso compound)**

A mechanism that explains anti addition is one in which a bromine molecule transfers a bromine atom to the alkene to form a cyclic **bromonium ion** and a bromide ion, as shown in step 1 of "A Mechanism for the Reaction" that follows. The cyclic bromonium ion causes net anti addition, as follows.

In step 2, a bromide ion attacks the back side of either carbon 1 or carbon 2 of the bromonium ion (an S_N2 process) to open the ring and produce the *trans*-1,2-dibromide. Attack occurs from the side **opposite the bromine of the bromonium ion** because attack from this direction is unhindered. Attack at the other carbon of the cyclic bromonium ion produces the enantiomer.

A MECHANISM FOR THE REACTION — Addition of Bromine to an Alkene

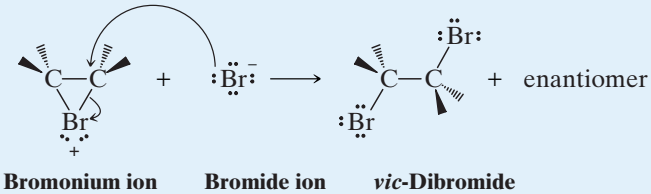
Step 1



Bromonium ion **Bromide ion**

As a bromine molecule approaches an alkene, the electron density of the alkene π bond repels electron density in the closer bromine, polarizing the bromine molecule and making the closer bromine atom electrophilic. The alkene donates a pair of electrons to the closer bromine, causing displacement of the distant bromine atom. As this occurs, the newly bonded bromine atom, due to its size and polarizability, donates an electron pair to the carbon that would otherwise be a carbocation, thereby stabilizing the positive charge by delocalization. The result is a bridged bromonium ion intermediate.

Step 2



Bromonium ion **Bromide ion** ***vic*-Dibromide**

A bromide anion attacks at the back side of one carbon (or the other) of the bromonium ion in an S_N2 reaction, causing the ring to open and resulting in the formation of a *vic*-dibromide.

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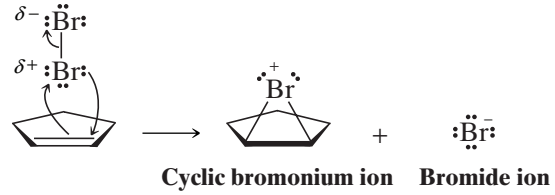
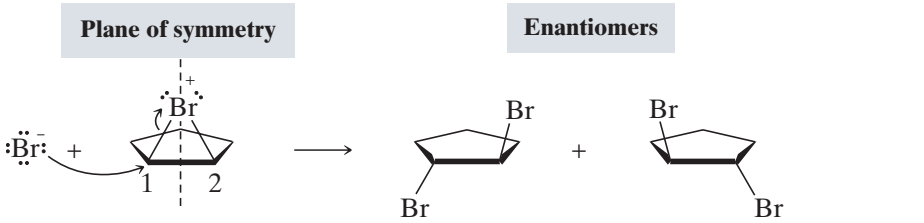
This process is shown for the addition of bromine to cyclopentene below.



Cyclic bromonium ion **Bromide ion**



Cyclic bromonium ion ***trans*-1,2-Dibromocyclopentane (as a racemic mixture)**

Attack at either carbon of the cyclopentene bromonium ion is equally likely because the cyclic bromonium ion is symmetric. It has a vertical plane of symmetry passing through the bromine atom and halfway between carbons 1 and 2. The *trans*-dibromide, therefore, is formed as a racemic mixture.

The mechanisms for addition of Cl_2 and I_2 to alkenes are similar to that for Br_2, involving formation and ring opening of their respective **halonium ions**.

As with bridged mercurinium ions, the bromonium ion does not necessarily have symmetrical charge distribution at its two carbon atoms. If one carbon of the bromonium ion is more highly substituted than the other, and therefore able to stabilize positive charge better, it may bear a greater fraction of positive charge than the other carbon (i.e., the positively charged bromine draws electron density from the two carbon atoms of the ring, but not equally if they are of different substitution). Consequently, the more positively charged carbon may be attacked by the reaction nucleophile more often than the other carbon. However, in reactions with symmetrical reagents (e.g., Br_2, Cl_2, and I_2) there is no observed difference. We shall discuss this point further in Section 8.13, where we will study a reaction where we can discern regioselectivity of attack on a halonium ion by the nucleophile.

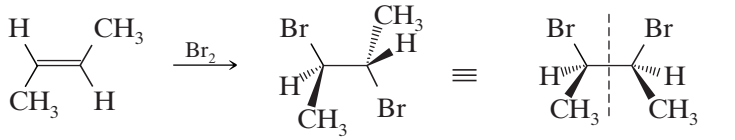
8.12 | STEREOSPECIFIC REACTIONS

The anti addition of a halogen to an alkene provides us with an example of what is called a **stereospecific reaction**.

- A **stereospecific reaction** is one where a particular stereoisomer of the starting material yields a specific stereoisomeric form of the product.

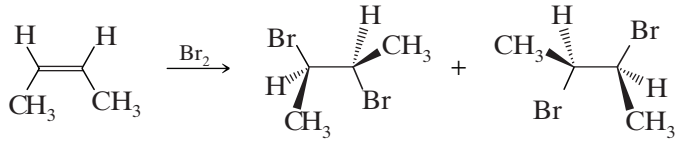
Consider the reactions of *cis*- and *trans*-2-butene with bromine shown below. When *trans*-2-butene adds bromine, the product is the meso compound, (2*R*,3*S*)-2,3-dibromobutane. When *cis*-2-butene adds bromine, the product is a *racemic mixture* of (2*R*,3*R*)-2,3-dibromobutane and (2*S*,3*S*)-2,3-dibromobutane:

Reaction 1



***trans*-2-Butene** **(2*R*,3*S*)-2,3-Dibromobutane (a meso compound)**

Reaction 2



***cis*-2-Butene** **(2*R*,3*R*)** **(2*S*,3*S*)**
(a pair of enantiomers)

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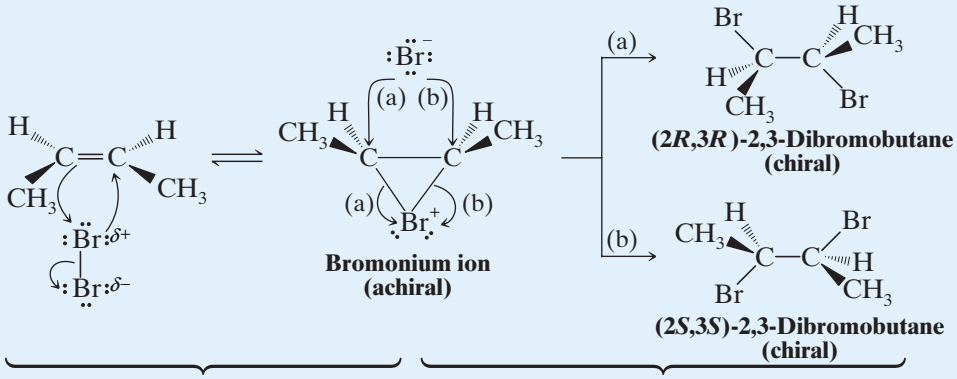
The reactants *cis*-2-butene and *trans*-2-butene are stereoisomers; they are *diastereomers*. The product of reaction 1, (2*R*,3*S*)-2,3-dibromobutane, is a meso compound, and it is a stereoisomer of both of the products of reaction 2 (the enantiomeric 2,3-dibromobutanes). Thus, by definition, both reactions are stereospecific. One stereoisomeric form of the reactant (e.g., *trans*-2-butene) gives one product (the meso compound), whereas the other stereoisomeric form of the reactant (*cis*-2-butene) gives a stereoisomerically different product (the enantiomers).

We can better understand the results of these two reactions if we examine their mechanisms. The first mechanism in the following box shows how *cis*-2-butene adds bromine to yield intermediate bromonium ions that are achiral. (The bromonium ion has a plane of symmetry.) These bromonium ions can then react with bromide ions by either path (a) or path (b). Reaction by path (a) yields one 2,3-dibromobutane enantiomer; reaction by path (b) yields the other enantiomer. The reaction occurs at the same rate by either path; therefore, the two enantiomers are produced in equal amounts (as a racemic form).

The second mechanism in the box shows how *trans*-2-butene reacts at the bottom face to yield an intermediate bromonium ion that is chiral. (Reaction at the other face would produce the enantiomeric bromonium ion.) Reaction of this chiral bromonium ion (or its enantiomer) with a bromide ion either by path (a) or by path (b) yields the same achiral product, *meso*-2,3-dibromobutane.

THE STEREOCHEMISTRY OF THE REACTION... Addition of Bromine to *cis*- and *trans*-2-Butene

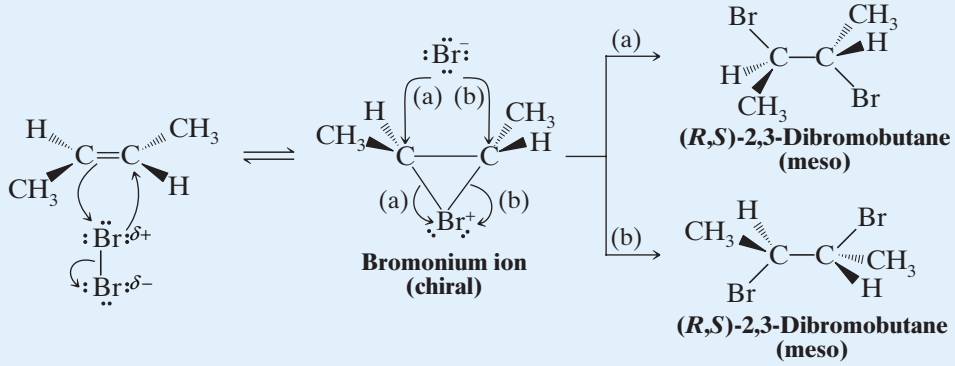
cis-2-Butene reacts with bromine to yield the enantiomeric 2,3-dibromobutanes by the following mechanism:



***cis*-2-Butene reacts with bromine to yield an achiral bromonium ion and a bromide ion. [Reaction at the other face of the alkene (top) would yield the same bromonium ion.]**

The bromonium ion reacts with the bromide ions at equal rates by paths (a) and (b) to yield the two enantiomers in equal amounts (i.e., as the racemic form).

trans-2-Butene reacts with bromine to yield *meso*-2,3-dibromobutane.



***trans*-2-Butene reacts with bromine to yield chiral bromonium ions and bromide ions. [Reaction at the other face (top) would yield the enantiomer of the bromonium ion as shown here.]**

When the bromonium ions react by either path (a) or path (b), they yield the *same* achiral meso compound. (Reaction of the enantiomer of the intermediatebromonium ion would produce the same result.)

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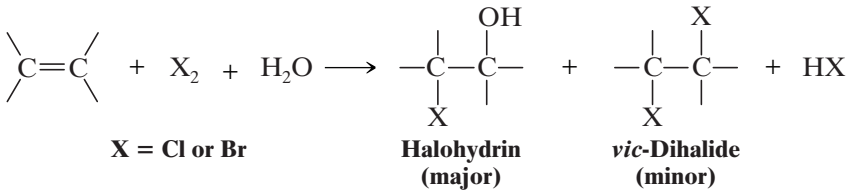
8.13 | HALOHYDRIN FORMATION

- When the halogenation of an alkene is carried out in aqueous solution, rather than in a non-nucleophilic solvent, the major product is a **halohydrin** (also called a halo alcohol) instead of a *vic*-dihalide.

Molecules of water react with the halonium ion intermediate as the predominant nucleophile because they are in high concentration (as the solvent). The result is formation of a halohydrin as the major product. If the halogen is bromine, it is called a **bromohydrin**, and if chlorine, a **chlorohydrin**.

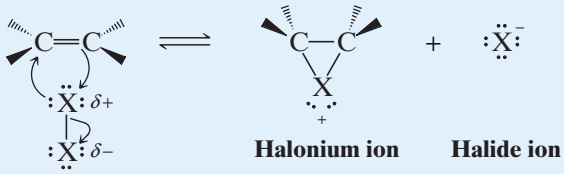


X = Cl or Br | **Halohydrin (major)** | ***vic*-Dihalide (minor)**

Halohydrin formation can be described by the following mechanism.

A MECHANISM FOR THE REACTION — Halohydrin Formation from an Alkene

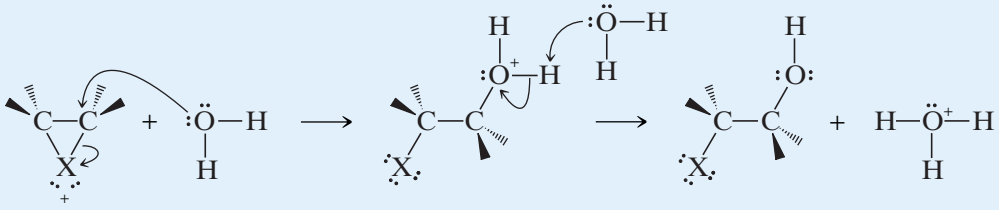
Step 1



Halonium ion | **Halide ion**

This step is the same as for halogen addition to an alkene (see Section 8.11A).

Steps 2 and 3



Halonium ion | **Protonated halohydrin** | **Halohydrin**

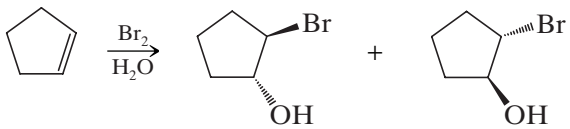
Here, however, a water molecule acts as the nucleophile and attacks a carbon of the ring, causing the formation of a protonated halohydrin.

The protonated halohydrin loses a proton (it is transferred to a molecule of water). This step produces the halohydrin and hydronium ion.

The first step is the same as that for halogen addition. In the second step, however, the two mechanisms differ. In halohydrin formation, water acts as the nucleophile and attacks one carbon atom of the halonium ion. The three-membered ring opens, and a protonated halohydrin is produced. Loss of a proton then leads to the formation of the halohydrin itself.

Practice Problem 8.13

Write a mechanism to explain the following reaction.



(as a racemic mixture)

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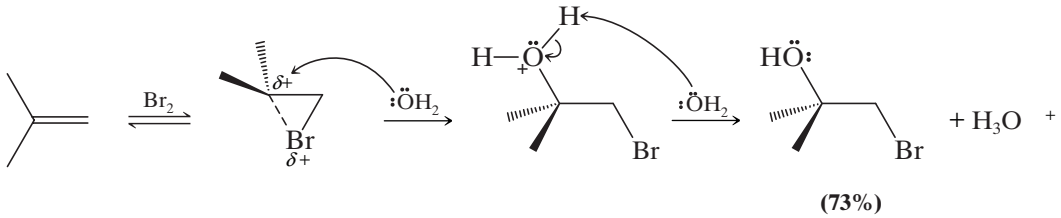
- If the alkene is unsymmetrical, the halogen ends up on the carbon atom with the greater number of hydrogen atoms.

Bonding in the intermediate bromonium ion is *unsymmetrical*. The more highly substituted carbon atom bears the greater positive charge because it resembles the more stable carbocation. Consequently, water attacks this carbon atom preferentially. The greater positive charge on the tertiary carbon permits a pathway with a lower free energy of activation even though attack at the primary carbon atom is less hindered:

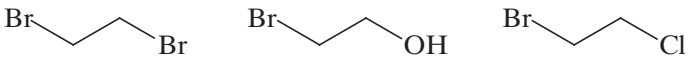
This bromonium ion is bridged asymmetrically because the 3° carbon can accommodate more positive charge than the 1° carbon.



(73%)

Practice Problem 8.14

When ethene gas is passed into an aqueous solution containing bromine and sodium chloride, the products of the reaction are the following:



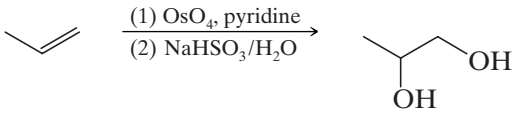
Write mechanisms showing how each product is formed.

8.14 | OXIDATION OF ALKENES: SYN 1,2-DIHYDROXYLATION

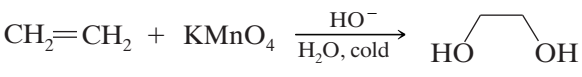
Alkenes undergo a number of reactions in which the carbon–carbon double bond is oxidized.

- **1,2-Dihydroxylation** is an important oxidative addition reaction of alkenes.

Osmium tetroxide is widely used to synthesize **1,2-diols** (the products of 1,2-**dihydroxylation**, sometimes also called **glycols**). Potassium permanganate can also be used, although because it is a stronger oxidizing agent it is prone to cleave the diol through further oxidation (Section 8.15).



Propene **1,2-Propanediol (propylene glycol)**



Ethene **1,2-Ethanediol (ethylene glycol)**

8.14A Mechanism for Syn Dihydroxylation of Alkenes

- The mechanism for the formation of a 1,2-diol by osmium tetroxide involves a cyclic intermediate that results in **syn addition** of the oxygen atoms.

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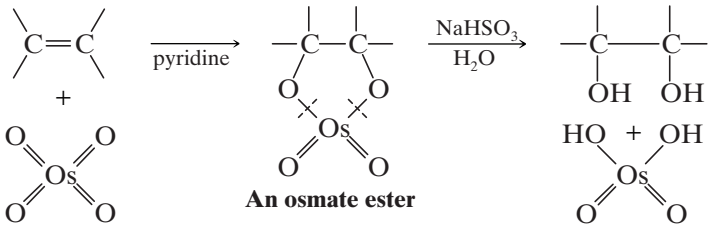
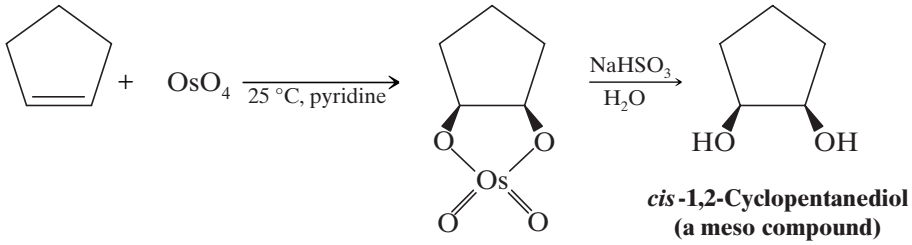
After formation of the cyclic intermediate with osmium, cleavage at the oxygen–metal bonds takes place without altering the stereochemistry of the two new C—O bonds.

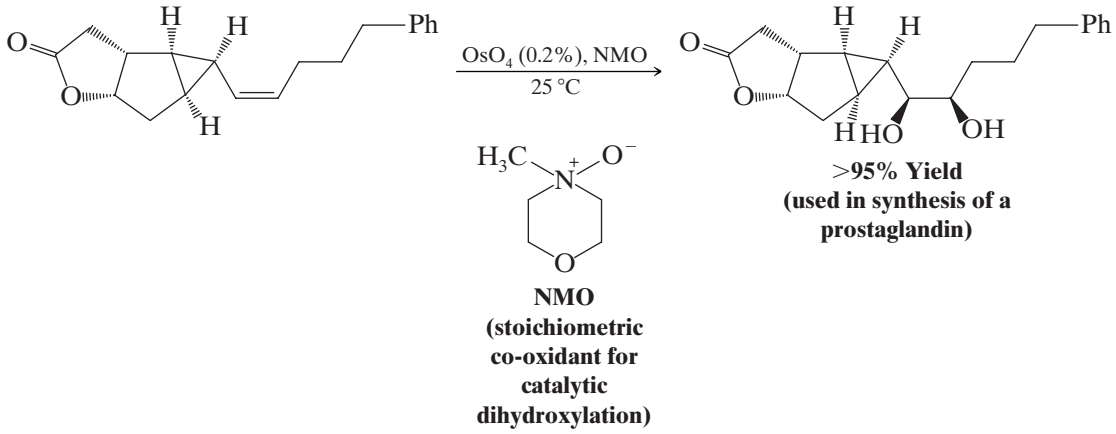


The syn stereochemistry of this dihydroxylation can readily be observed by the reaction of cyclopentene with osmium tetroxide. The product is *cis*-1,2-cyclopentanediol.



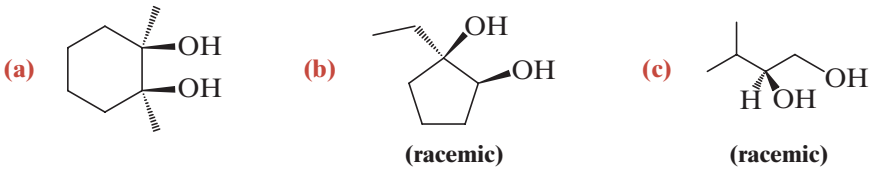
Osmium tetroxide is highly toxic, volatile, and very expensive. For these reasons, methods have been developed that permit OsO_4 to be used *catalytically* in conjunction with a co-oxidant.* A very small molar percentage of OsO_4 is placed in the reaction mixture to do the dihydroxylation step, while a stoichiometric amount of co-oxidant reoxidizes the OsO_4 as it is used in each cycle, allowing oxidation of the alkene to continue until all has been converted to the diol. *N*-Methylmorpholine *N*-oxide (NMO) is one of the most commonly used co-oxidants with catalytic OsO_4. The method was discovered at Upjohn Corporation in the context of reactions for synthesis of a prostaglandin†.

Catalytic OsO_4 1,2-Dihydroxylation



Practice Problem 8.15

Specify the alkene and reagents needed to synthesize each of the following diols.



*See Nelson, D. W., et al., *J. Am. Chem. Soc.* **1997**, *119*, 1840–1858; and Corey, E. J., et al., *J. Am. Chem. Soc.* **1996**, *118*, 319–329.
†Van Rheenan, V., Kelley, R. C., and Cha, D. Y., *Tetrahedron Lett.* **1976**, *25*, 1973.

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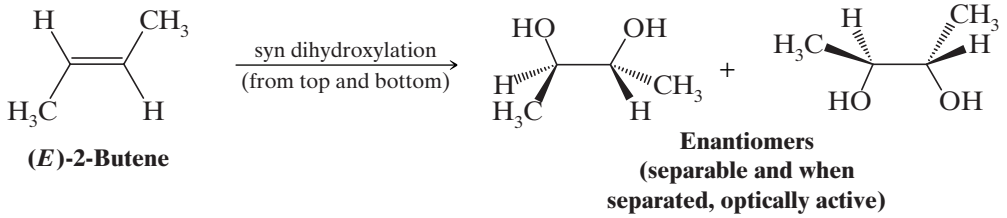
Solved Problem 8.4

Explain the following facts: Treating (*Z*)-2-butene with OsO_4 in pyridine and then $NaHSO_3$ in water gives a diol that is optically inactive and cannot be resolved. Treating (*E*)-2-butene with the same reagents gives a diol that is optically inactive but can be resolved into enantiomers.

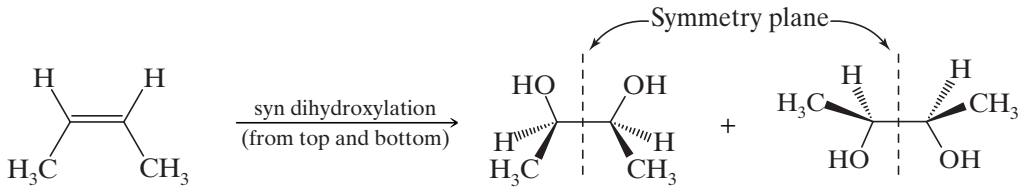
Answer

Syn dihydroxylation of (*E*)-2-butene gives a pair of enantiomers, while syn dihydroxylation of (*Z*)-2-butene gives a single product that is a meso compound.



(*E*)-2-Butene

Enantiomers (separable and when separated, optically active)



(*Z*)-2-Butene

Identical (a meso compound)

8.15 | OXIDATIVE CLEAVAGE OF ALKENES

Alkenes can be **oxidatively cleaved** using potassium permanganate or ozone (as well as by other reagents). Potassium permanganate ($KMnO_4$) is used when strong oxidation is needed. Ozone (O_3) is used when mild oxidation is desired. [Alkynes and aromatic rings are also oxidized by $KMnO_4$ and O_3 (Sections 8.18 and 14.13D).]

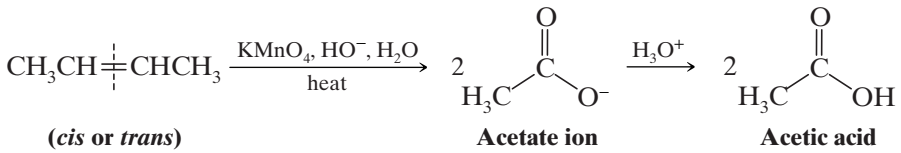
8.15A Cleavage with Hot Basic Potassium Permanganate

- Treatment with hot basic potassium permanganate oxidatively cleaves the double bond of an alkene.

Cleavage is believed to occur via a cyclic intermediate similar to the one formed with osmium tetroxide and intermediate formation of a 1,2-diol.

- Alkenes with monosubstituted carbon atoms are oxidatively cleaved to salts of carboxylic acids.
- Disubstituted alkene carbons are oxidatively cleaved to ketones.
- Unsubstituted alkene carbons are oxidized to carbon dioxide.

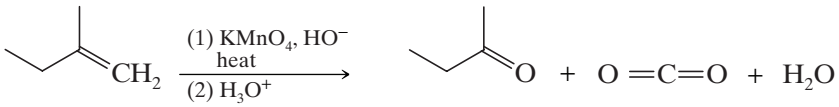
The following examples illustrate the results of potassium permanganate cleavage of alkenes with different substitution patterns. In the case where the product is a carboxylate salt, an acidification step is required to obtain the carboxylic acid.



(*cis* or *trans*)

Acetate ion

Acetic acid



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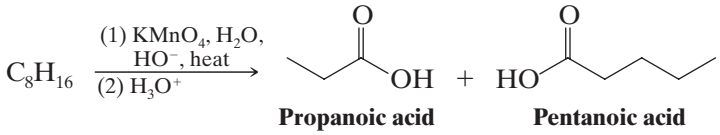
One of the uses of potassium permanganate, other than for oxidative cleavage, is as a **chemical test for unsaturation** in an unknown compound.

- If an alkene is present (or an alkyne, Section 8.18), the purple color of a potassium permanganate solution is discharged and a brown precipitate of manganese dioxide (MnO_2) forms as the oxidation takes place.

The oxidative cleavage of alkenes has also been used to establish the location of the double bond in an alkene chain or ring. The reasoning process requires us to think backward much as we do with retrosynthetic analysis. Here we are required to work backward from the products to the reactant that might have led to those products. We can see how this might be done with the following example.

Solved Problem 8.5

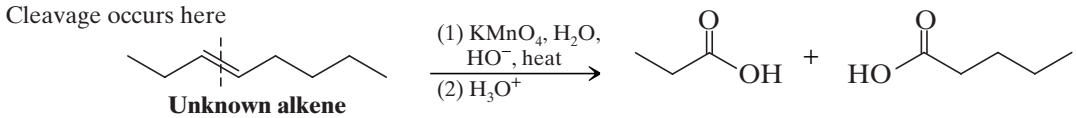
An unknown alkene with the formula C_8H_{16} was found, on oxidation with hot basic permanganate, to yield a three-carbon carboxylic acid (propanoic acid) and a five-carbon carboxylic acid (pentanoic acid). What was the structure of this alkene?



Propanoic acid **Pentanoic acid**

Answer

The carbonyl groups in the products are the key to seeing where the oxidative cleavage occurred. Therefore, oxidative cleavage must have occurred as follows, and the unknown alkene must have been *cis*- or *trans*-3-octene, which is consistent with the molecular formula given.

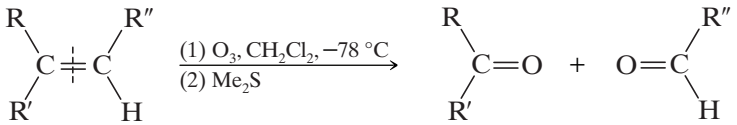


Unknown alkene (either *cis*- or *trans*-3-octene)

8.15B Cleavage with Ozone

- The most useful method for cleaving alkenes is to use ozone (O_3).

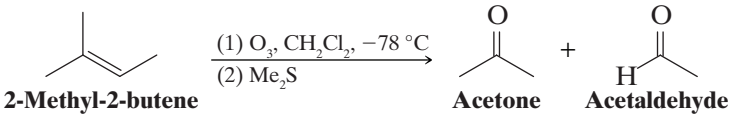
Ozonolysis consists of bubbling ozone into a very cold (–78°C) solution of the alkene in CH_2Cl_2, followed by treatment of the solution with dimethyl sulfide (or zinc and acetic acid). The overall result is as follows:



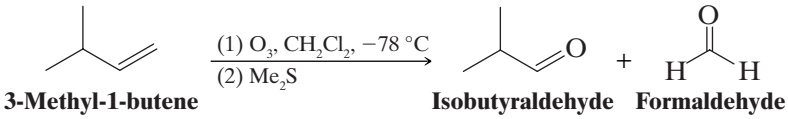
The reaction is useful as a synthetic tool, as well as a method for determining the location of a double bond in an alkene by reasoning backward from the structures of the products.

- The overall process (above) results in alkene cleavage at the double bond, with each carbon of the double bond becoming doubly bonded to an oxygen atom.

The following examples illustrate the results for each type of alkene carbon.



2-Methyl-2-butene **Acetone** **Acetaldehyde**



3-Methyl-1-butene **Isobutyraldehyde** **Formaldehyde**

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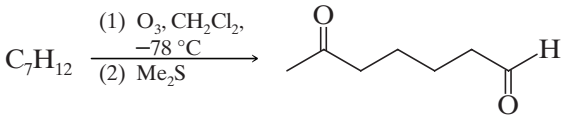
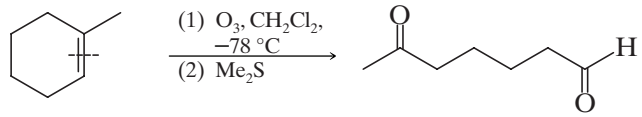
Solved Problem 8.6

Give the structure of an unknown alkene with the formula C_7H_{12} that undergoes ozonolysis to yield, after acidification, *only the following product*:



Answer

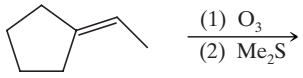
Since there is only a single product containing the same number of carbon atoms as the reactant, the only reasonable explanation is that the reactant has a double bond contained in a ring. Ozonolysis of the double bond opens the ring:

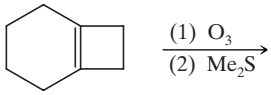


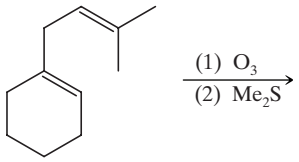
Unknown alkene (1-methylcyclohexene)

Practice Problem 8.16

Predict the products of the following ozonolysis reactions.

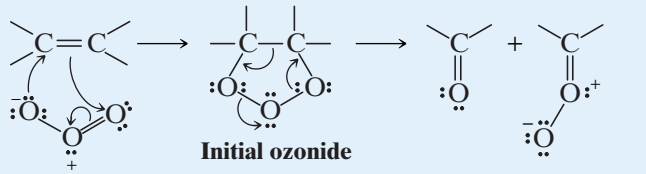
(a) 

(b) 

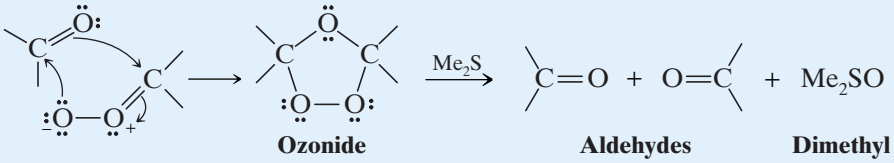
(c) 

The mechanism of ozone addition to alkenes begins with formation of unstable compounds called *initial ozonides* (sometimes called molozonides). The process occurs vigorously and leads to spontaneous (and sometimes noisy) rearrangement to compounds known as **ozonides.** The rearrangement is believed to occur with dissociation of the initial ozonide into reactive fragments that recombine to yield the ozonide. Ozonides are very unstable compounds, and low-molecular-weight ozonides often explode violently.

A MECHANISM FOR THE REACTION — Ozonolysis of an Alkene



Ozone adds to the alkene to form an initial ozonide. **Initial ozonide** **The initial ozonide fragments.**



The fragments recombine to form the ozonide. **Ozonide** **Aldehydes and/or ketones** **Dimethyl sulfoxide**

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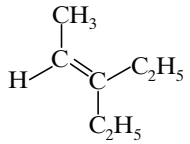
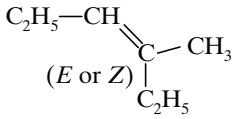
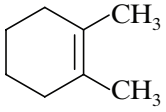
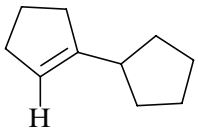
Solved Problem 8.7

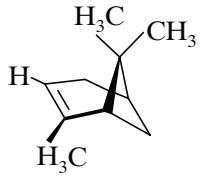
Give the reactions for the ozonolysis of the following reactants:

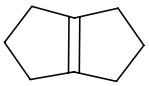
(a) 

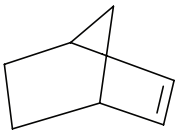
(b) 

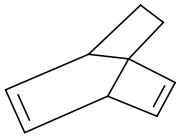
(c) 

(d) 

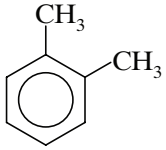
(e) 

(f) 

(g) 

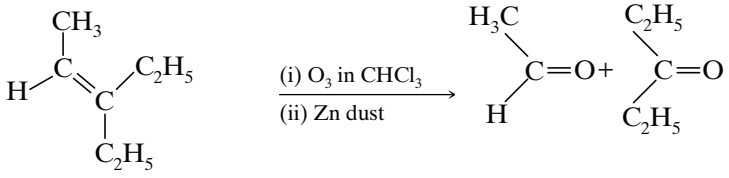
(h) 

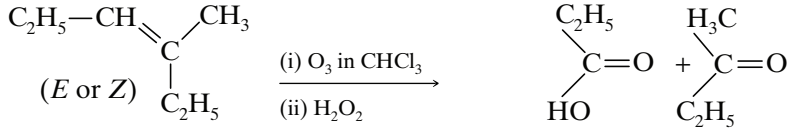
(i) $CH_3—CH=C=CH—CH_3$

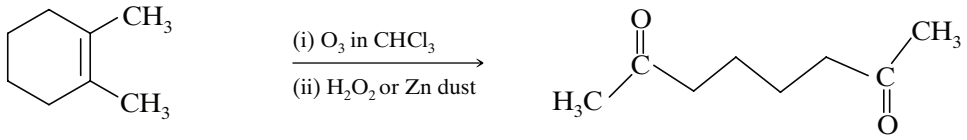
(j) 
(*o*-Xylene)

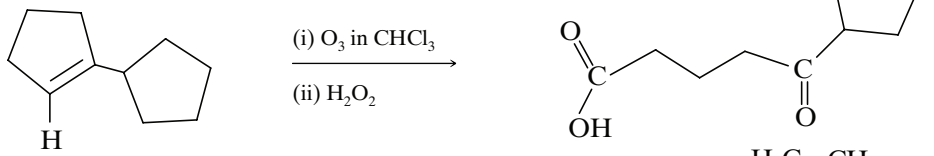
Answer

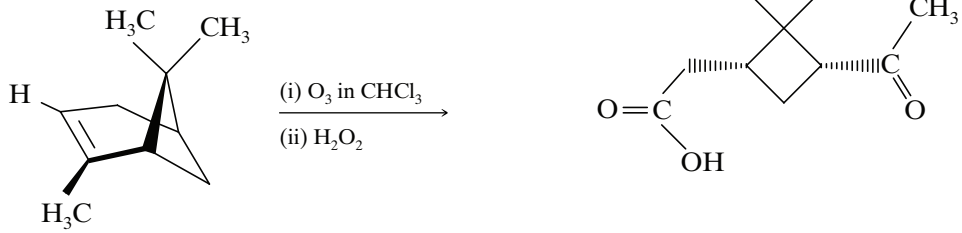
The reactions for the ozonolysis of the reactants are as follows:

(a) 

(b) 

(c) 

(d) 

(e) 

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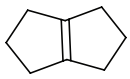
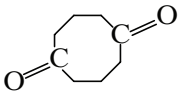
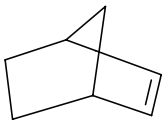
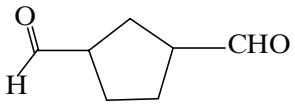
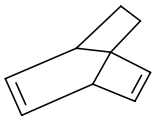
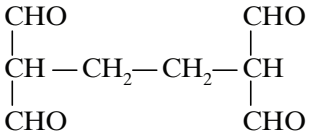
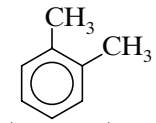
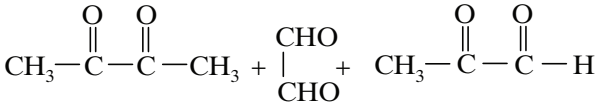
(f)  $\xrightarrow[\text{(ii) } H_2O_2 \text{ or Zn dust}]{\text{(i) } O_3 \text{ in } CHCl_3}$ 

(g)  $\xrightarrow[\text{(ii) Zn dust}]{\text{(i) } O_3 \text{ in } CHCl_3}$ 

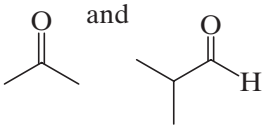
(h)  $\xrightarrow[\text{(ii) Zn dust}]{\text{(i) } O_3 \text{ in } CHCl_3}$ 

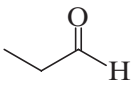
(i) $CH_3{-}CH{=}C{=}CH{-}CH_3 \xrightarrow[\text{(ii) Zn dust}]{\text{(i) } O_3 \text{ in } CHCl_3} 2CH_3{-}CHO + CO_2$

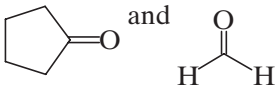
(j) 
(*o*-Xylene)
$\xrightarrow[\text{(ii) Zn dust}]{\text{(i) } O_3 \text{ in } CHCl_3}$ 

Practice Problem 8.17

Write the structures of the alkenes that would yield the following carbonyl compounds when treated with ozone and then with dimethyl sulfide.

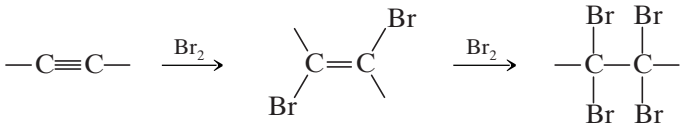
(a) 

(b)  (2 mol is produced from 1 mol of alkene)

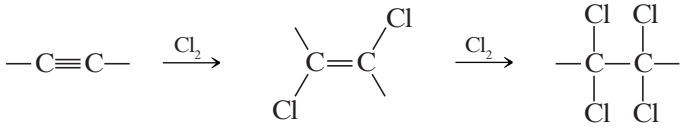
(c) 

8.16 | ELECTROPHILIC ADDITION OF BROMINE AND CHLORINE TO ALKYNES

- Alkynes show the same kind of addition reactions with chlorine and bromine that alkenes do.
- With alkynes **the addition may occur once or twice**, depending on the number of molar equivalents of halogen we employ:



Dibromoalkene **Tetrabromoalkane**



Dichloroalkene **Tetrachloroalkane**

It is usually possible to prepare a dihaloalkene by simply adding one molar equivalent of the halogen:

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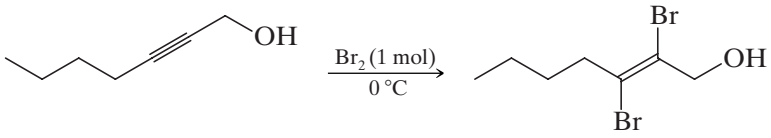
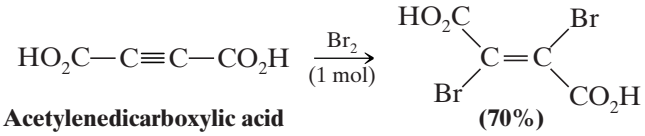


- Addition of one molar equivalent of chlorine or bromine to an alkyne generally results in anti addition and yields a *trans*-dihaloalkene.

Addition of bromine to acetylenedicarboxylic acid, for example, gives the trans isomer in 70% yield:



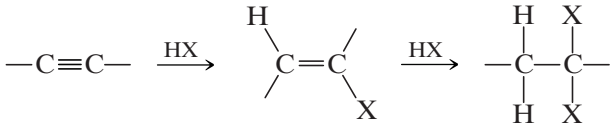
Acetylenedicarboxylic acid **(70%)**

Practice Problem 8.18

Alkenes are more reactive than alkynes toward addition of electrophilic reagents (i.e., Br_2, Cl_2, or HCl). Yet when alkynes are treated with one molar equivalent of these same electrophilic reagents, it is easy to stop the addition at the "alkene stage." This appears to be a paradox and yet it is not. Explain.

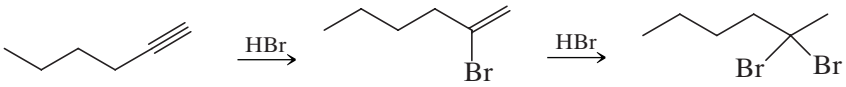
8.17 | ADDITION OF HYDROGEN HALIDES TO ALKYNES

- Alkynes react with one molar equivalent of hydrogen chloride or hydrogen bromide to form haloalkenes, and with two molar equivalents to form geminal dihalides.
- Both additions are **regioselective** and follow **Markovnikov's rule**:



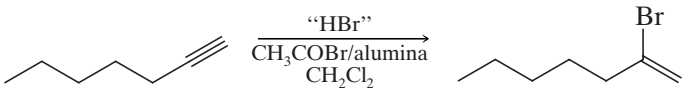
Haloalkene ***gem*-Dihalide**

The hydrogen atom of the hydrogen halide becomes attached to the carbon atom that has the greater number of hydrogen atoms. 1-Hexyne, for example, reacts slowly with one molar equivalent of hydrogen bromide to yield 2-bromo-1-hexene and with two molar equivalents to yield 2,2-dibromohexane:



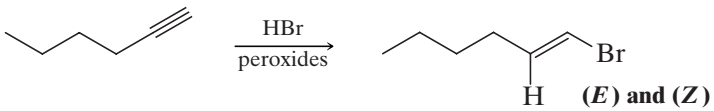
2-Bromo-1-hexene **2,2-Dibromohexane**

The addition of HBr to an alkyne can be facilitated by using acetyl bromide (CH_3COBr) and alumina instead of aqueous HBr. Acetyl bromide acts as an HBr precursor by reacting with the alumina to generate HBr. For example, 1-heptyne can be converted to 2-bromo-1-heptene in good yield using this method:



(82%)

Anti-Markovnikov addition of hydrogen bromide to alkynes occurs when peroxides are present in the reaction mixture. These reactions take place through a free-radical mechanism (Section 9.9):



(*E*) and (*Z*)

(74%)

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8.18 | OXIDATIVE CLEAVAGE OF ALKYNES

Treating alkynes with **ozone** followed by acetic acid, or with basic potassium permanganate followed by acid, leads to cleavage at the carbon–carbon triple bond. The products are carboxylic acids:

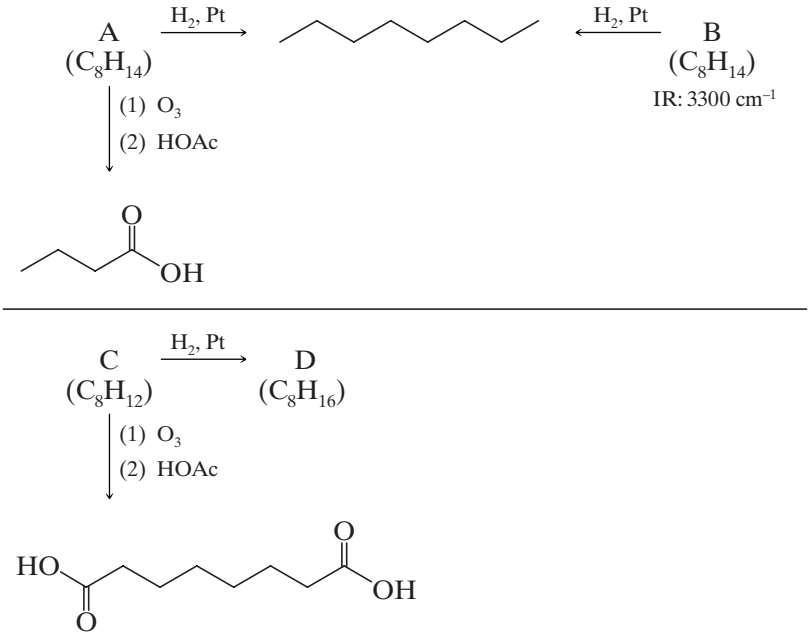
$$R{-}C{\equiv}C{-}R' \xrightarrow[(2)\ HOAc]{(1)\ O_3} RCO_2H + R'CO_2H$$

or

$$R{-}C{\equiv}C{-}R' \xrightarrow[(2)\ H_3O^+]{(1)\ KMnO_4,\ HO^-} RCO_2H + R'CO_2H$$

Practice Problem 8.19

A, **B**, and **C** are alkynes. Elucidate their structures and that of **D** using the following reaction roadmap.



8.19 | HOW TO PLAN A SYNTHESIS: SOME APPROACHES AND EXAMPLES

In planning a synthesis we often have to consider four interrelated aspects:

1. construction of the carbon skeleton,
2. functional group interconversions,
3. control of regiochemistry, and
4. control of stereochemistry.

You have had some experience with certain aspects of synthetic strategies in earlier sections.

- In Section 7.15B you learned about *retrosynthetic analysis* and how this kind of thinking could be applied to the construction of carbon skeletons of alkanes and cycloalkanes.
- In Section 6.14 you learned the meaning of a *functional group interconversion* and how nucleophilic substitution reactions could be used for this purpose.

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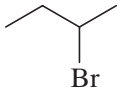
In other sections, perhaps without realizing it, you have begun adding to your basic store of methods for construction of carbon skeletons and for making functional group interconversions. This is the time to begin keeping a card file for all the reactions that you have learned, noting especially their applications to synthesis. This file will become your **Tool Kit for Organic Synthesis**. Now is also the time to look at some new examples and to see how we integrate all four aspects of synthesis into our planning.

8.19A Retrosynthetic Analysis

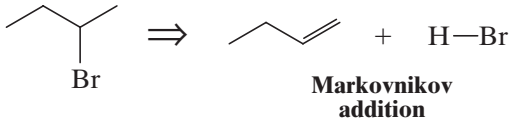
Consider a problem in which we are asked to outline a synthesis of 2-bromobutane from compounds of two carbon atoms or fewer. This synthesis, as we shall see, involves construction of the carbon skeleton, functional group interconversion, and control of regiochemistry.

HOW TO Apply Retrosynthetic Analysis to 2-Bromobutane

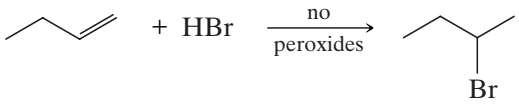


We begin by thinking backward. The final target, 2-bromobutane, can be made in one step from 1-butene by addition of hydrogen bromide. The regiochemistry of this functional group interconversion must be Markovnikov addition:

Retrosynthetic Analysis



Synthesis



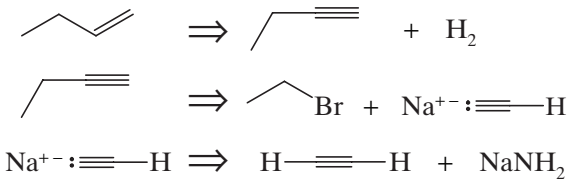
Remember: The open arrow is a symbol used to show a retrosynthetic process that relates the target molecule to its precursors:

$$\text{Target molecule} \Longrightarrow \text{precursors}$$

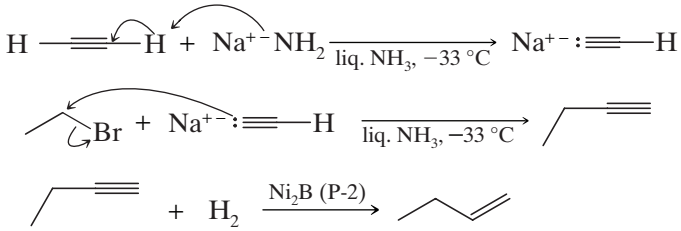
Continuing to work backward one hypothetical reaction at a time, we realize that a synthetic precursor of 1-butene is 1-butyne. Addition of 1 mol of hydrogen to 1-butyne would lead to 1-butene. With 1-butyne as our new target, and bearing in mind that we are told that we have to construct the carbon skeleton from compounds with two carbons or fewer, we realize that 1-butyne can be formed in one step from ethyl bromide and acetylene by an alkynide anion alkylation.

- The **key to retrosynthetic analysis** is to think of how to synthesize each target molecule in one reaction from an immediate precursor, considering first the ultimate target molecule and working backward.

Retrosynthetic Analysis



Synthesis



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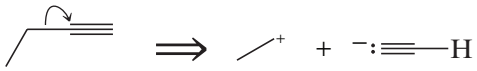
8.19B Disconnections, Synthons, and Synthetic Equivalents

- One approach to retrosynthetic analysis is to consider a retrosynthetic step as a "disconnection" of one of the bonds (Section 7.15).*

For example, an important step in the synthesis that we have just given is the one in which a new carbon–carbon bond is formed. Retrosynthetically, it can be shown in the following way:



The hypothetical fragments of this disconnection are an ethyl cation and an ethynide anion.

- In general, we call the fragments of a hypothetical retrosynthetic disconnection **synthons**.

Seeing the synthons above may help us to reason that we could, in theory, synthesize a molecule of 1-butyne by combining an ethyl cation with an ethynide anion. We know, however, that bottles of carbocations and carbanions are not to be found on our laboratory shelves and that even as a reaction intermediate, it is not reasonable to consider an ethyl carbocation. What we need are the **synthetic equivalents** of these synthons. The synthetic equivalent of an ethynide ion is sodium ethynide, because sodium ethynide contains an ethynide ion (and a sodium cation). The synthetic equivalent of an ethyl cation is ethyl bromide. To understand how this is true, we reason as follows: if ethyl bromide were to react by an S_N1 reaction, it would produce an ethyl cation and a bromide ion. However, we know that, being a primary halide, ethyl bromide is unlikely to react by an S_N1 reaction. Ethyl bromide, however, will react readily with a strong nucleophile such as sodium ethynide by an S_N2 reaction, and when it reacts, the product that is obtained is the same as the product that would have been obtained from the reaction of an ethyl cation with sodium ethynide. Thus, ethyl bromide, in this reaction, functions as the synthetic equivalent of an ethyl cation.

2-Bromobutane could also be synthesized from compounds of two carbons or fewer by a route in which (*E*)- or (*Z*)-2-butene is an intermediate. You may wish to work out the details of that synthesis for yourself.

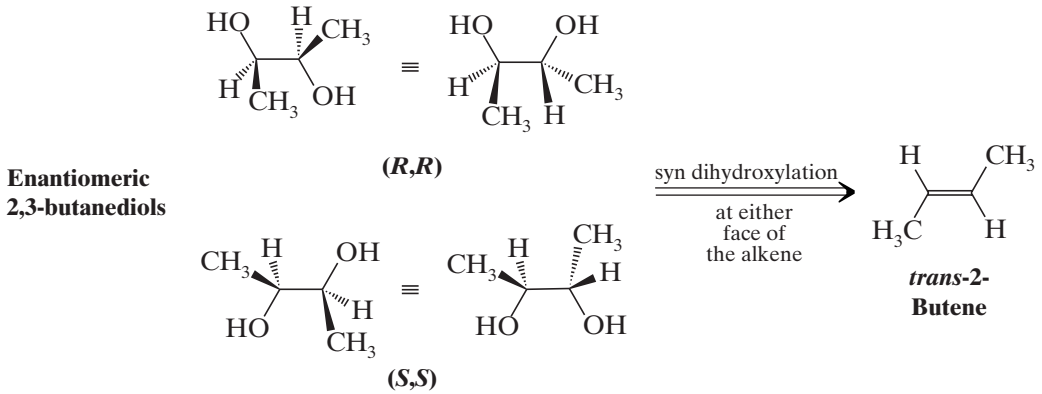
8.19C Stereochemical Considerations

Consider another example, a synthesis that requires stereochemical control: the synthesis of the enantiomeric 2,3-butanediols, (2*R*,3*R*)-2,3-butanediol and (2*S*,3*S*)-2,3-butanediol, from compounds of two carbon atoms or fewer, and in a way that does not produce the meso stereoisomer.

HOW TO Apply Stereochemical Considerations in Planning a Synthesis of 2,3-Butanediol Enantiomers

Here we see that a possible final step to the enantiomers is syn dihydroxylation of *trans*-2-butene. This reaction is stereospecific and produces the desired enantiomeric 2,3-butanediols as a racemic form. Here we have made the key choice **not** to use *cis*-2-butene. Had we chosen *cis*-2-butene, our product would have been the meso 2,3-butanediol stereoisomer.

Retrosynthetic Analysis



*For an excellent detailed treatment of this approach you may want to read the following: Warren, S., and Wyatt, P., *Organic Synthesis, The Disconnection Approach,* 2nd Ed. Wiley: New York, 2009; and Warren, S., and Wyatt, P., *Workbook for Organic Synthesis, The Disconnection Approach,* 2nd Ed. Wiley: New York, 2009.

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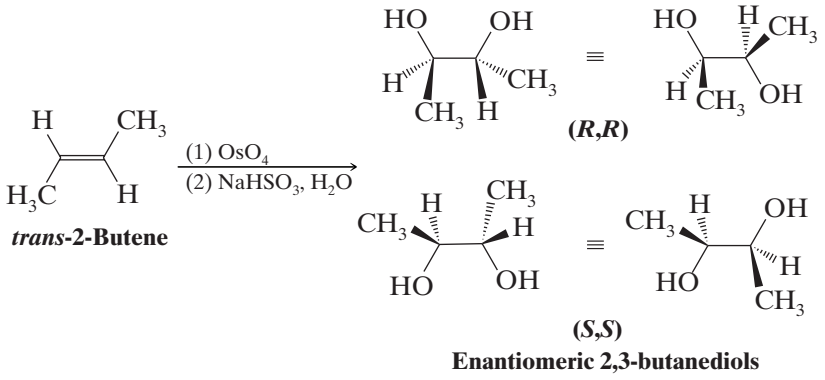
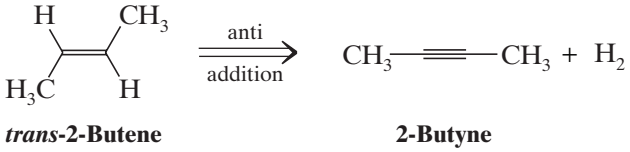
Synthesis

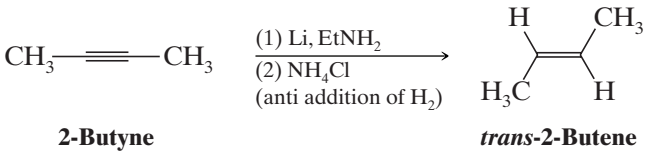


Synthesis of *trans*-2-butene can be accomplished by treating 2-butyne with lithium in liquid ammonia. The anti addition of hydrogen by this reaction gives us the trans product that we need.

Retrosynthetic Analysis



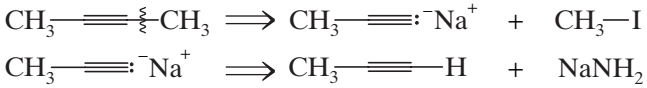
Synthesis



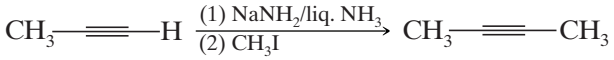
- The reaction above is an example of a **stereoselective reaction**. A **stereoselective reaction** is one in which the reactant is not necessarily chiral (as in the case of an alkyne) but in which the reaction produces predominantly or exclusively one stereoisomeric form of the product (or a certain subset of stereoisomers from among all those that are possible).
- Note the difference between stereoselective and stereospecific. A stereospecific reaction is one that produces predominantly or exclusively one stereoisomer of the product when a specific stereoisomeric form of the reactant is used. (All stereospecific reactions are stereoselective, but the reverse is not necessarily true.)

We can synthesize 2-butyne from propyne by first converting it to sodium propynide and then alkylating sodium propynide with methyl iodide:

Retrosynthetic Analysis

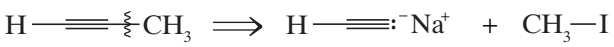


Synthesis



And to get propyne, we synthesize it from ethyne:

Retrosynthetic Analysis



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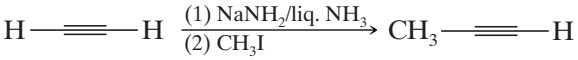
Synthesis

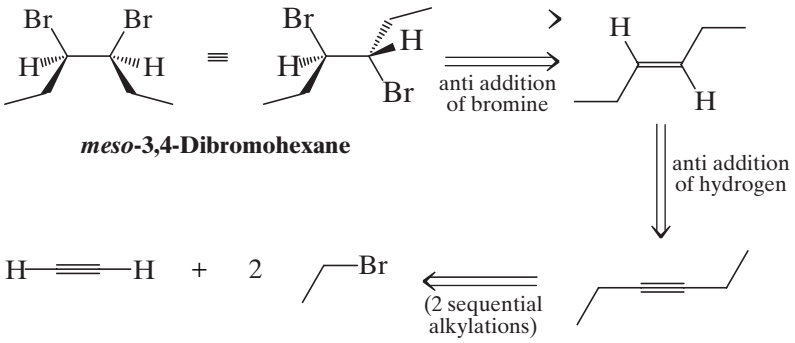


Solved Problem 8.8

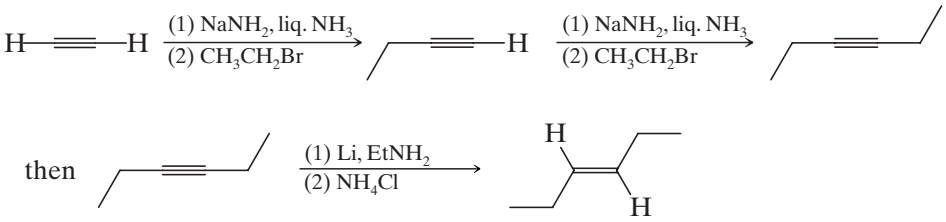
Starting with compounds of two carbon atoms or fewer, outline a stereospecific synthesis of *meso*-3,4-dibromohexane.

Answer

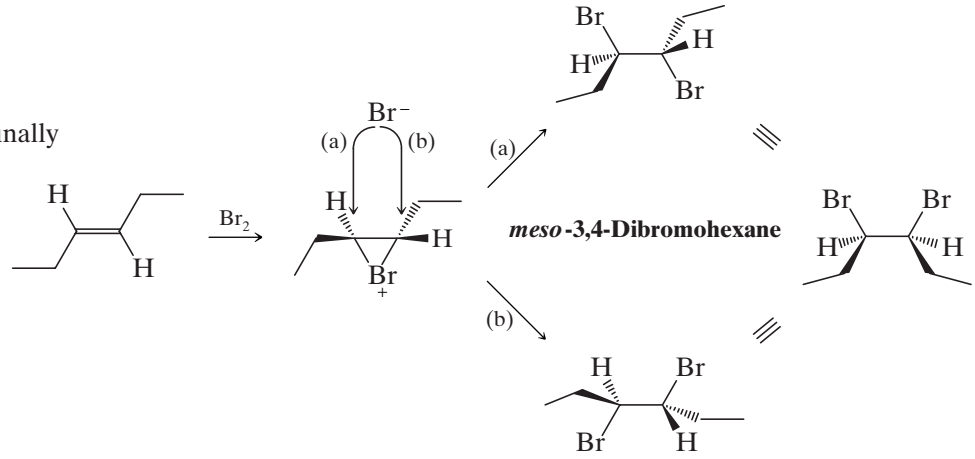
Retrosynthetic Analysis



The synthesis could be written as follows:



and finally



Practice Problem 8.20

How would you modify the procedure given in Solved Problem 8.8 so as to synthesize a racemic form of (3*R*,4*R*)- and (3*S*,4*S*)-3,4-dibromohexane?

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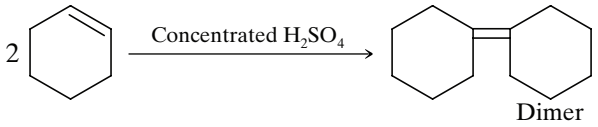
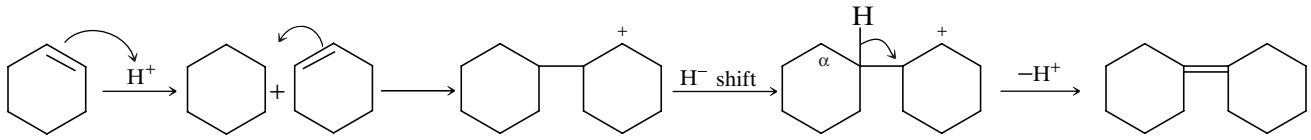
8.20 | DIMERIZATION OF ALKENE

When a cyclohexene reacts with concentrated H_2SO_4, its dimerization takes place as follows.



The mechanism of the above reaction may be given as follows:



The examples for the dimerization of alkene are as follows:

1. $CH_3-\underset{}{\overset{CH_3}{C}}=CH_2 \xrightarrow[(ii)\ H_2SO_4]{(i)\ \Delta\ (60\ ^\circ C)} CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH=\underset{}{\overset{CH_3}{C}}-CH_3 + CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH_2-\underset{}{\overset{CH_3}{C}}=CH_2$

Major

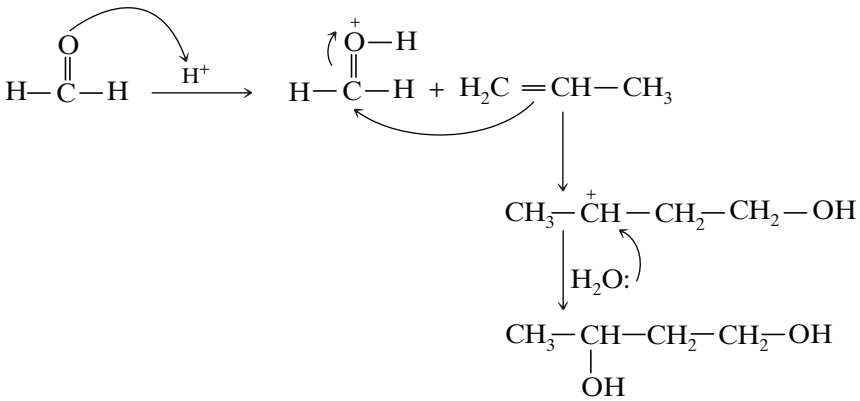
2. $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>C=CH_2 + H_2C=CH_2 \xrightarrow[\Delta]{H^+} \begin{matrix}CH_3\\CH_3\end{matrix}\!\!>C=C<\!\!\begin{matrix}CH_3\\CH_3\end{matrix}$

8.21 | PRINS REACTION

Prins reaction involves the acid-catalyzed addition of aldehyde to alkene. For example,

$$H-\overset{O}{\overset{\|}{C}}-H + CH_3-CH=CH_2 \xrightarrow[H_2O]{H^+} CH_3-\underset{OH}{CH}-CH_2-CH_2-OH$$

The mechanism of the above reaction is as follows:



Some examples of Prins reaction are given below:

1. $Ph-CH=CH_2 \xrightarrow[(ii)\ H^+]{(i)\ H-\overset{O}{\overset{\|}{C}}-H} Ph-\underset{OH}{CH}-CH_2-\underset{OH}{CH_2}$

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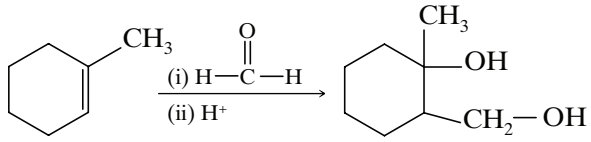
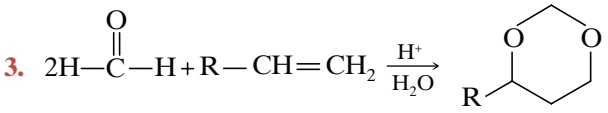
2. 

3. 

Solved Problem 8.9

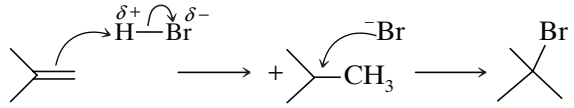
Consider the reaction of an alkene with HBr:

(a) Write the mechanism of the reaction.

(b) Why do the π-bond electrons attack the hydrogen end of HBr?

(c) Briefly explain why the addition of HBr gives the product as shown instead of a primary alkyl halide.

Answer

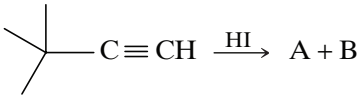
(a) 

(b) The hydrogen was attacked because it is less electronegative than bromine and bears the $\delta+$ charge in the HBr bond (vacant antibonding of H–Br).

(c) Looking at the mechanism, we can see that the formation of the carbocation is the first step. The formation of a more stable carbocation has a lower energy of activation (E_{act}). A tertiary carbocation is much more stable than the isomeric primary carbocation, so the E_{act} for the formation of the tertiary carbocation is lower than that of the primary carbocation.

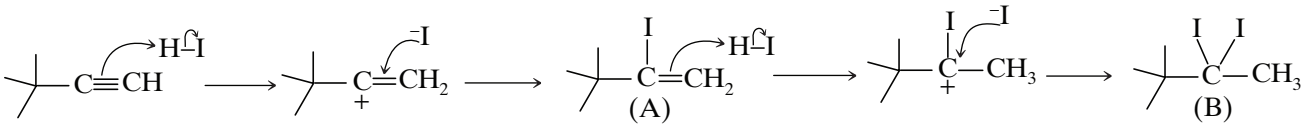
Solved Problem 8.10

Give the structures of products A and B and write the mechanism for the formation of each.



Answer

The structures of A and B and the mechanism of their formation are:



Solved Problem 8.11

Should an alkyne react with HBr in the same manner as an alkene? Briefly explain why or why not.

Answer

We predict that an alkyne will react in the same manner as an alkene in the presence of HBr because the only difference in these two is that an alkyne has two C–C π bonds instead of just one in alkene. This shows that similar functional groups have similar reactions and reactivity.

Solved Problem 8.12

Consider the reaction of a non-conjugated diene with aqueous sulfuric acid:

(a) Give the major product for the reaction and provide a detailed mechanism for the reaction.

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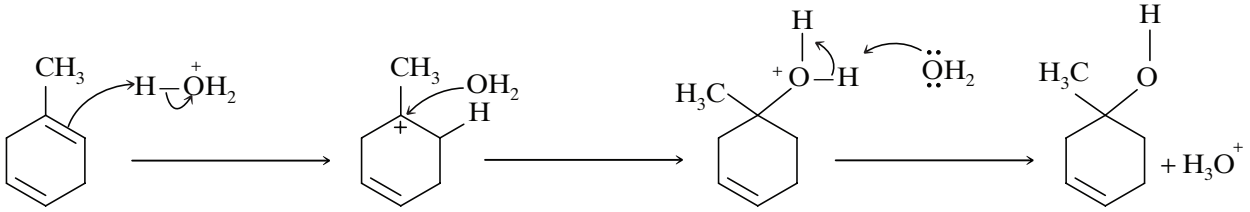
(b) Give the products if a second equivalent of H_2O is added.

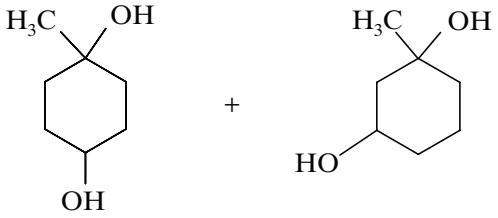
(c) What happens if no acid catalyst is added?

Answer

(a)



(b)



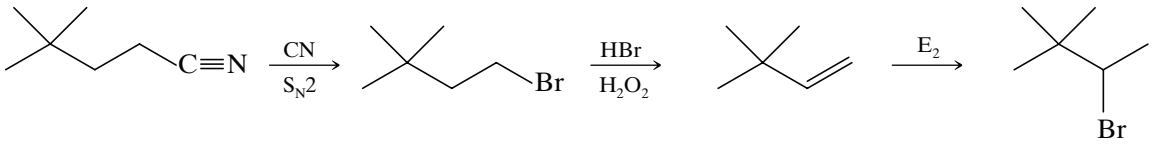
(c) Water by itself is a poor electrophile, since the magnitude of $\delta+$ charge on the hydrogen atom is not large enough for the reaction to proceed. Protonation of the oxygen in water makes this oxygen atom more electron poor, thus amplifying the magnitude of $\delta+$ charge on hydrogen. The resulting hydronium ion is sufficiently electrophilic to undergo the energetically expensive reaction with the alkene π-bond to form a carbocation. In the absence of acid catalyst, the reaction will not proceed at a the required rate.

Solved Problem 8.13

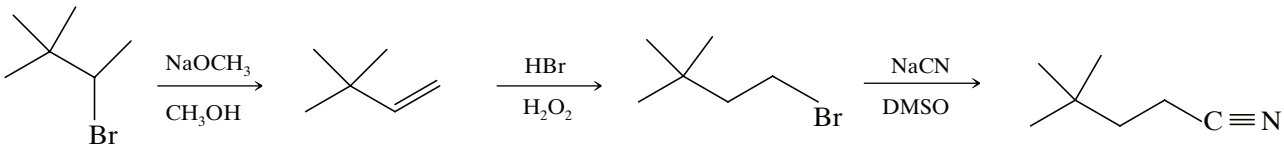
Show how the following transformations may be carried out? Include your retrosynthetic reasoning.

Answer

Retrosynthesis:

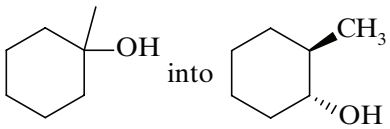


Forward direction:



Solved Problem 8.14

Consider the following reaction:



(a) Write the mechanism for this reaction.

(b) Draw the transition state for the rate determining step of this reaction.

(c) Briefly explain the choice for the rate determining step.

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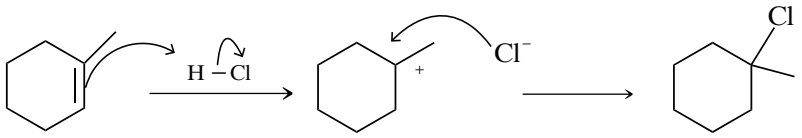
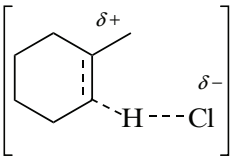
(d) Write reaction that is clearly faster than the reaction shown above.
(e) Briefly explain why this reaction is faster.

Answer

(a)

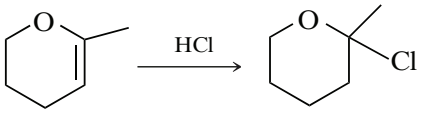


(b)

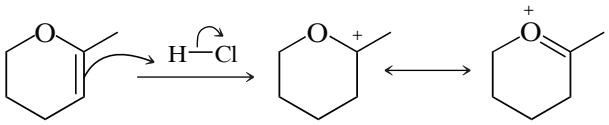


(c) The rate determining step (rds) in the mechanism is the step with the largest (most positive) energy of activation (E_{act}). In this reaction, the first step is the rds because a carbocation is being formed; which is an energetically expensive process. The second step is much faster because it involves only bond formation.

(d)



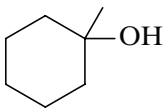
(e) The rate of the reaction is controlled by the transition state for the rds. Stabilizing this transition state will lower the E_{act} and thus accelerate the reaction. In this example, replacing the methylene group (CH_2) with an oxygen atom adds resonance stabilization to the carbocation intermediate.



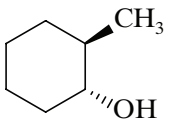
This stabilization results in a faster reaction.

Solved Problem 8.15

Convert the following:

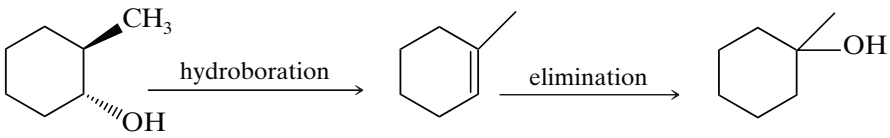


into

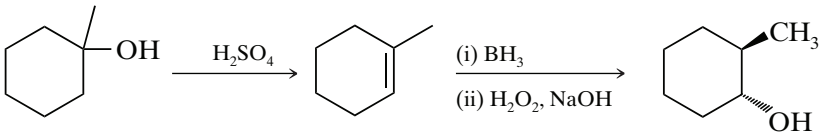


Answer

Retrosynthesis:

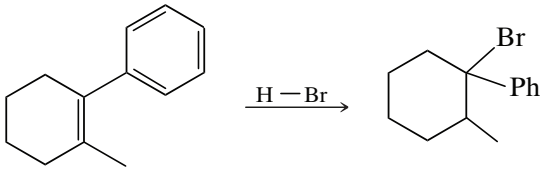


Forward direction:



Solved Problem 8.16

Consider the following reaction:



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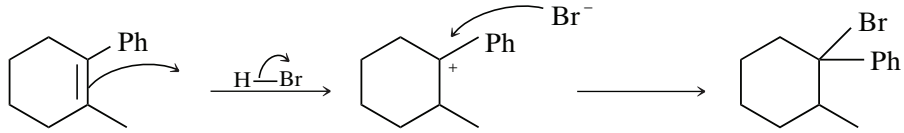
(a) Write a detailed curved arrow mechanism that shows how the major product is formed.

(b) Briefly explain why this isomer, instead of others, is formed.

Answer

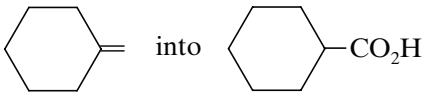
(a) The curved arrow mechanism is given as follows:



(b) Addition of HBr to the alkene π bond proceeds through the most stable carbocation. In this case, the carbocation is tertiary and benzylic (which results in significant resonance stabilization). The other alkene-derived carbocation would also be tertiary, but would not enjoy resonance stabilization. Electrophilic attack on the benzene ring could lead to a tertiary carbocation with resonance. This would disrupt aromaticity, and is therefore energetically expensive. (Benzene aromaticity is 36 kcal/mol of stabilization).

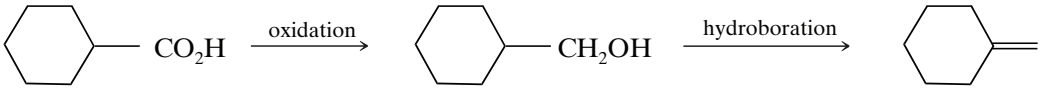
Solved Problem 8.17

Convert the following:

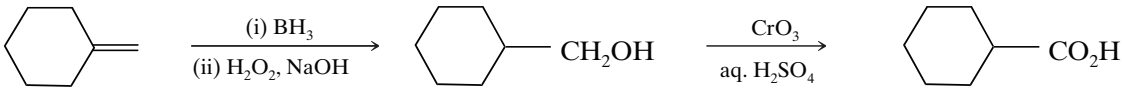


Answer

Retrosynthesis:

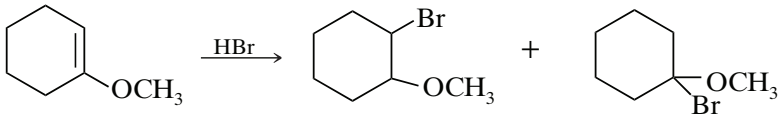


Forward direction:



Solved Problem 8.18

Consider the following reaction:



(a) Provide a complete curved arrow mechanism that shows how the major product is formed.

(b) Briefly explain the choice of the major product.

Answer

(a) The curved arrow mechanism is given as follows:

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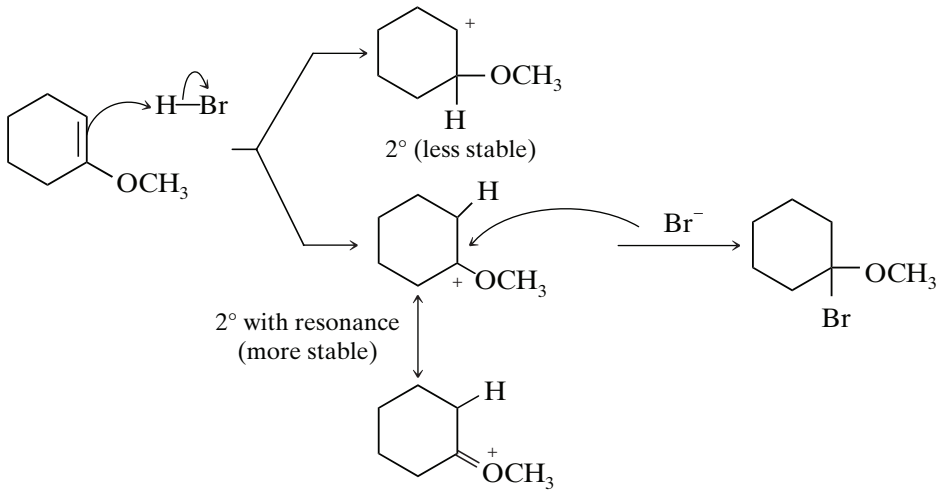
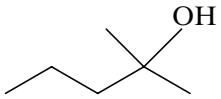
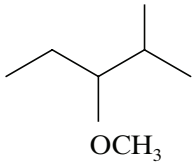


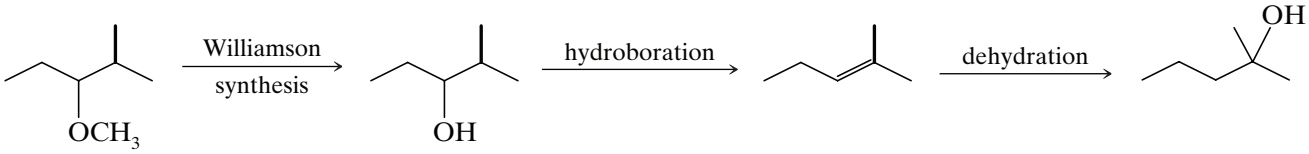
(b) In any mechanism in the step that produces a reactive intermediate such as a carbocation, carbanion or radical, the more stable reactive intermediate is formed more readily (because of low energy of activation). In this case, both carbocations are secondary; but the one with resonance is more stable, and so is formed more readily. Reaction of this carbocation with bromide ion then gives the α-bromoether product.

Solved Problem 8.19

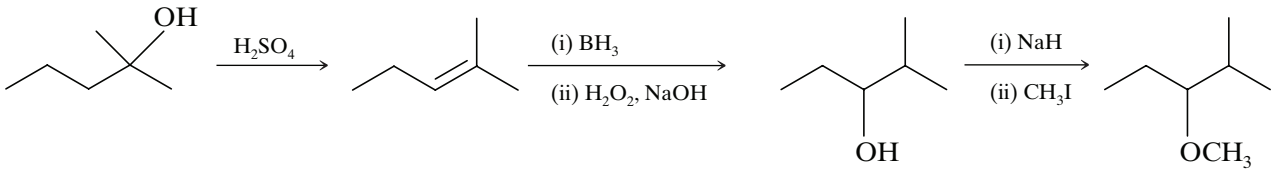
Convert the following:  into 

Answer

Retrosynthesis:

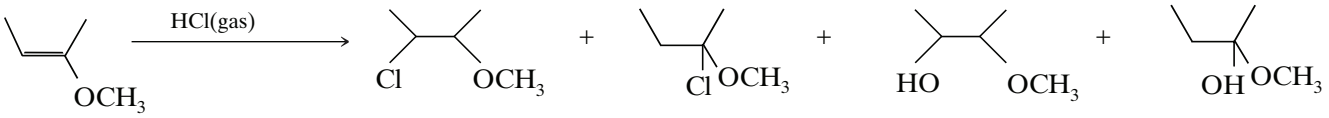


Forward direction:



Solved Problem 8.20

Consider the following reaction:



(A) **(B)** **(C)** **(D)**

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(a) Identify the major product of this reaction.

(b) Write a detailed mechanism showing how the major product is formed.

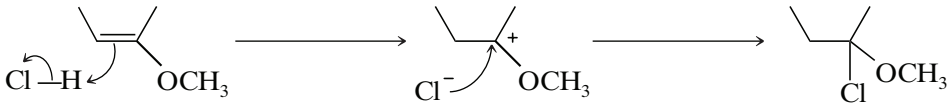
(c) Clearly explain your choice of major product.

(d) Write a reaction that is similar to the one shown above, but obviously occurs at a faster rate. Support your reasoning.

Answer

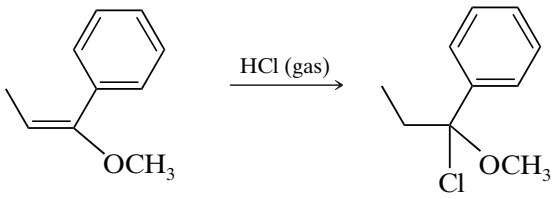
(a) The major product of this reaction is B.

(b)

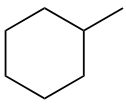
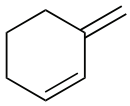


(c) Attack of the π bond on HCl will proceed to give the most stable carbocation. A secondary carbocation with resonance is more stable than a secondary carbocation without resonance. This fact controls the position of the chloride in the final product (regioselectivity). Products (C) and (D) cannot be formed because no water (neither HCl gas nor aqueous HCl) is present to be captured by the carbocation intermediate.

(d) The rate determining step of this reaction is the formation of the carbocation. The more stable the carbocation, the faster is the reaction. Thus, addition to afford a secondary carbocation with more resonance (provided by the benzene ring) will occur more readily. For example,

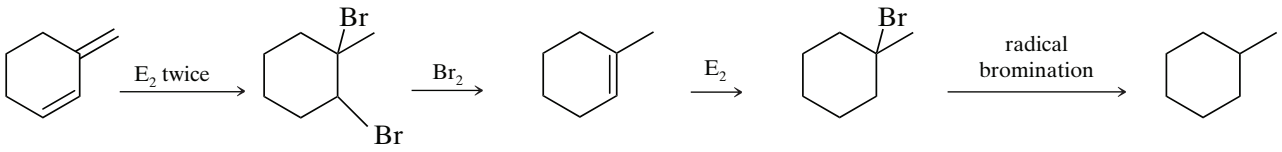


Solved Problem 8.21

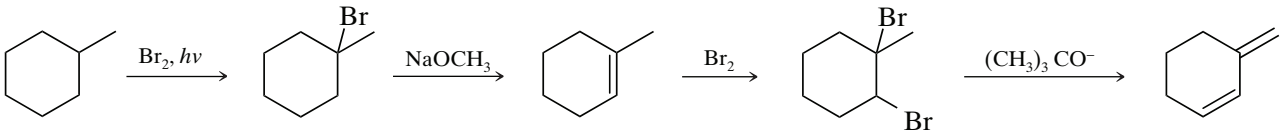
Convert the following:  into 

Answer

Retrosynthesis:



Forward direction:



In the last step, use of a sterically hindered base such as $(CH_3)_3CO^-$ helps ensure that the less substituted alkene is formed.

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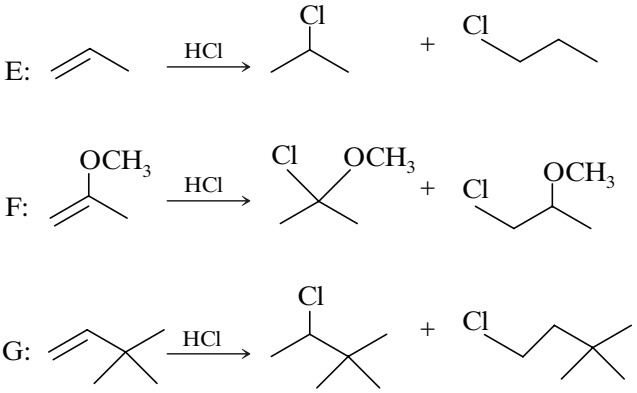
Solved Problem 8.22

Consider reactions (E)–(G):



(a) Which reaction is the fastest? Briefly explain.

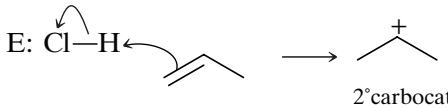
(b) What is the major product of the fastest reaction? Briefly explain.

(c) Write a detailed curved arrow mechanism that shows how the major product is formed. Write "rds" above the arrow in the rate determining step of the mechanism.

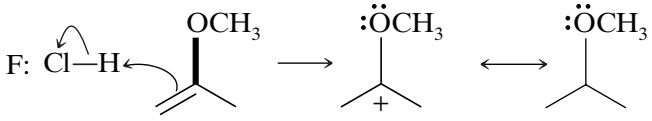
(d) Provide an explanation for the choice of the rate determining step.

Answer

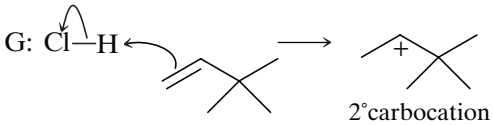
(a) The relative rates of these reactions are controlled by their rate determining step (carbocation formation). The most stable carbocation is formed more quickly because its formation has a low E_{act}.



2°carbocation

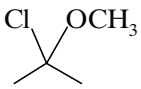


2°carbocation with resonance

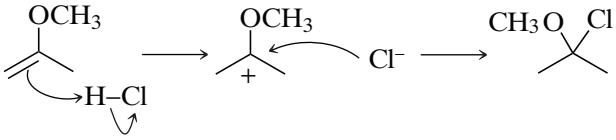


2°carbocation

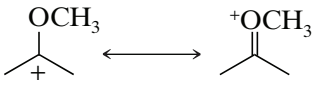
All the carbocations are secondary, but only the carbocation formed in reaction (F) has the extra stability afforded by resonance. Therefore, the fastest reaction is (F).

(b) 

This product results when the carbocation intermediate captures chloride ion, the formation of which is shown in answer (c):

(c) 

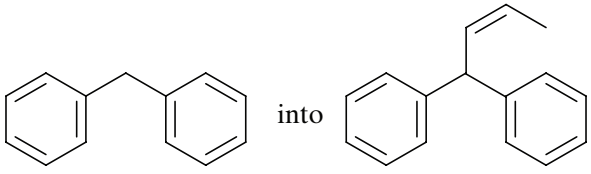
(d) When a reaction proceeds via a mechanism that has more than one step, the overall reaction rate is dominated by the rate determining (i.e., the slowest) step. In this reaction the slowest step is the first step in which the energetically expensive process of carbocation formation occurs. The more stable the carbocation that is formed, the faster is the rate of this step. Of all the carbocations that would have to be formed to produce the products shown above, the most stable one (shown below) is secondary with resonance



Since this carbocation is the most stable, it will be formed most readily, and thus in a large amount. As this is the most prevalent carbocation, it forms most of the product.

Solved Problem 8.23

Convert the following:



There may be more than one solution to each synthesis.

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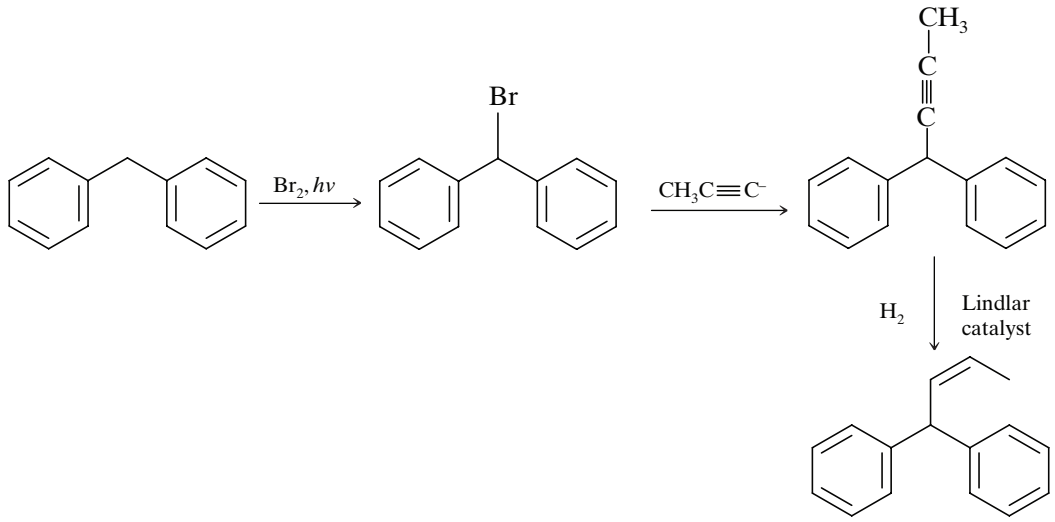
Answer

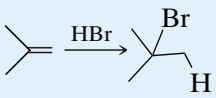
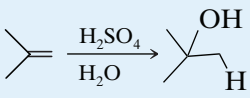
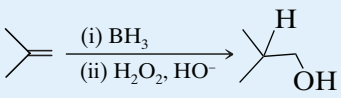
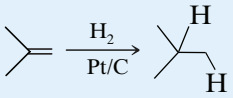


Solved Problem 8.24

For each reactant given below, categorize its reaction with a C=C π bond as "electrophilic addition" or "other." Write the reaction of each reactant with isobutylene, and any other reagents commonly used or required with that reactant.

Reactant	Reaction Type	Reaction with Isobutylene
HBr (gas)		
H_3O^+		
BH_3		
H_2		
O_3		
OsO_4		
HBr/H_2O_2		
Br_2		
$Hg(OAc)_2$		

Answer

Reactant	Reaction Type	Reaction with Isobutylene
HBr (gas)	Electrophillic addition	
H_3O^+	Electrophillic addition	
BH_3	Electrophillic addition	
H_2	Other	

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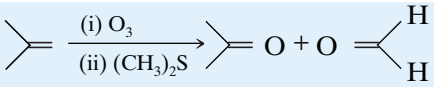
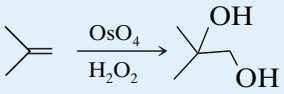
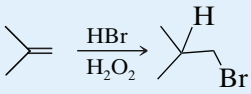
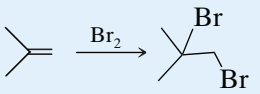
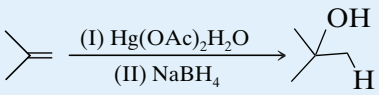
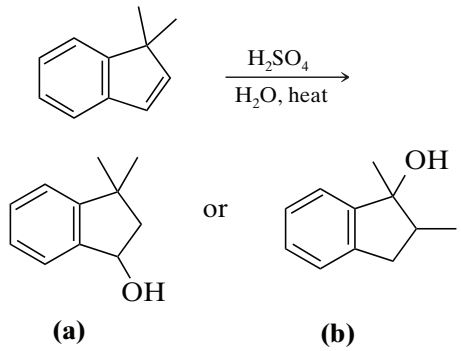
O_3	Other	
OsO4	Other	
HBr/H_2O_2	Free radical addition	
Br_2	Electrophillic addition	
$Hg(OAc)_2$	Electrophillic addition	

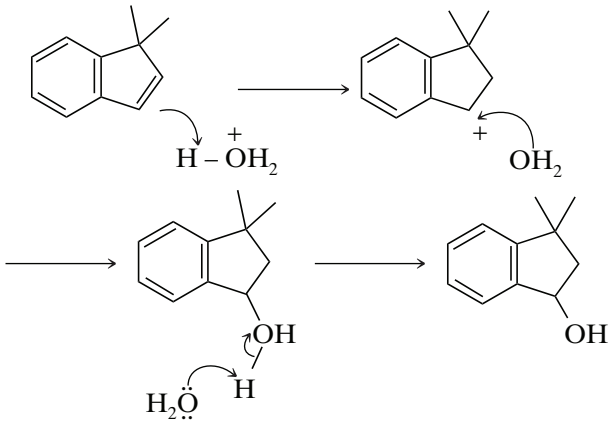
Solved Problem 8.25

Draw a complete curved arrow mechanism that shows how the major product is formed in the reaction given below. Briefly explain the choice of the major product.



Answer

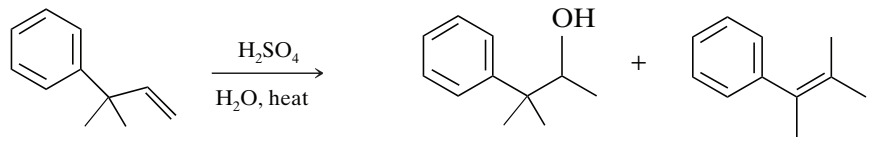
The major product formed is **(a)**. The curved arrow mechanism is given as follows:



Electrophilic addition to a π bond proceeds to give the most stable carbocation intermediate. Attack of the alkene on hydronium ion can yield two secondary carbocations, one of which has resonance stabilization. Formation of the secondary carbocation that has resonance leads to the secondary alcohol product shown above. Formation of the tertiary alcohol product would have to involve the less stable secondary carbocation, and hence is not favoured.

Solved Problem 8.26

Write a detailed mechanism for the following reactions. Be sure that your mechanisms account for all of the given products.

(a) 

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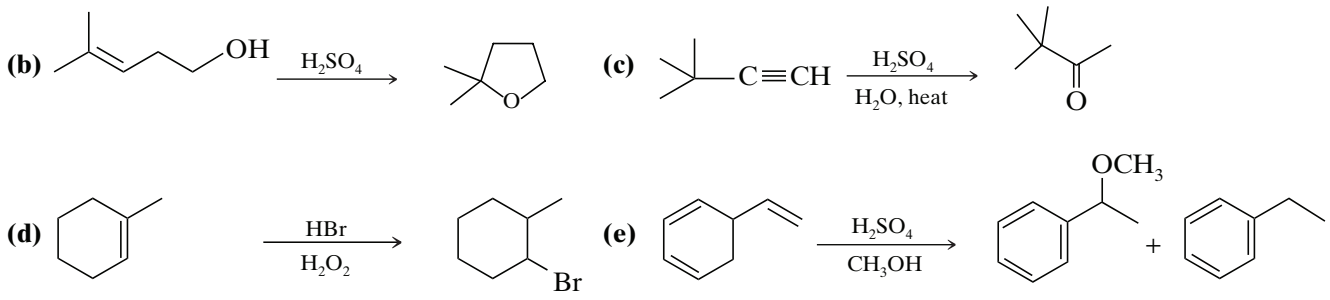
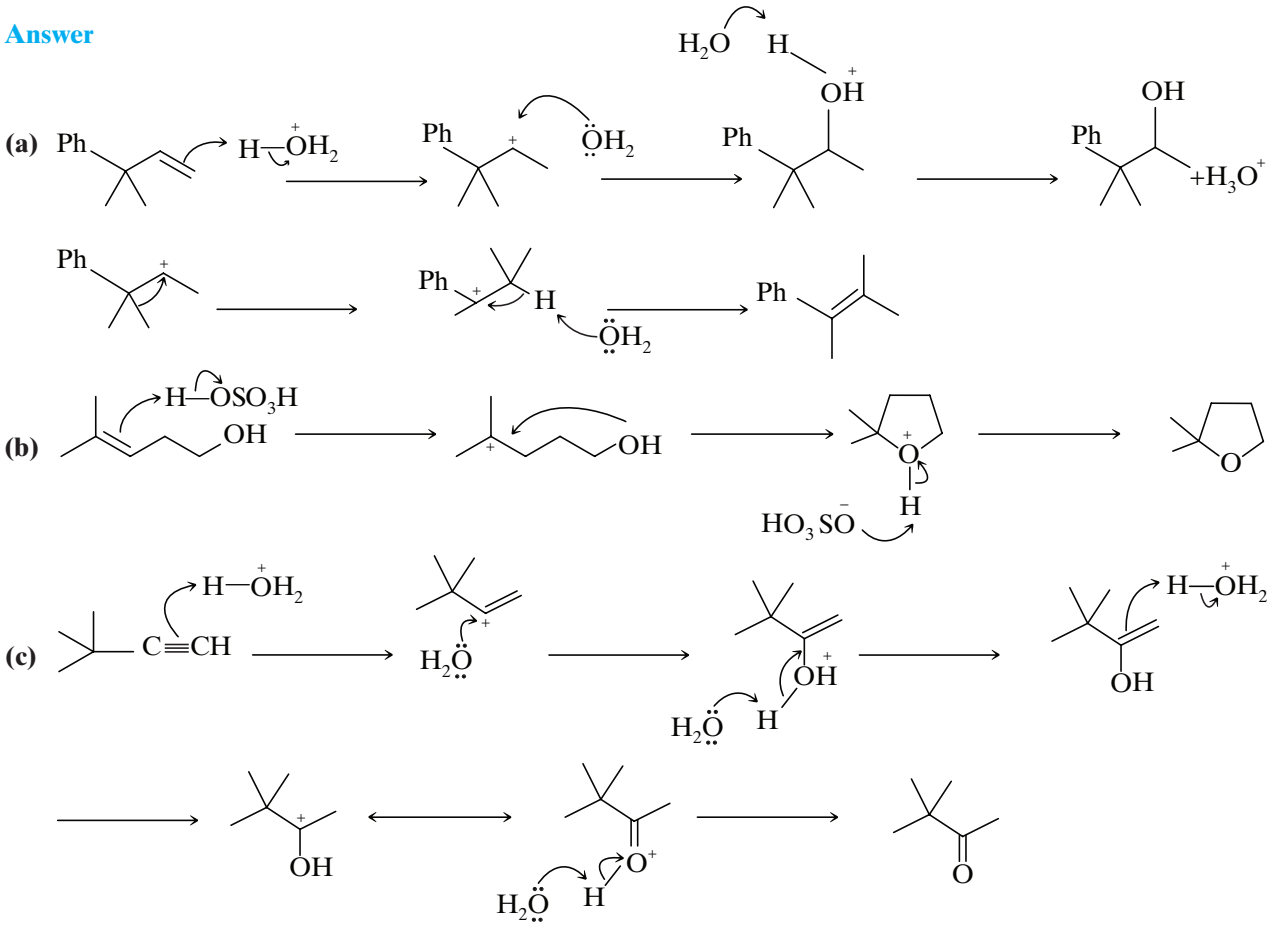
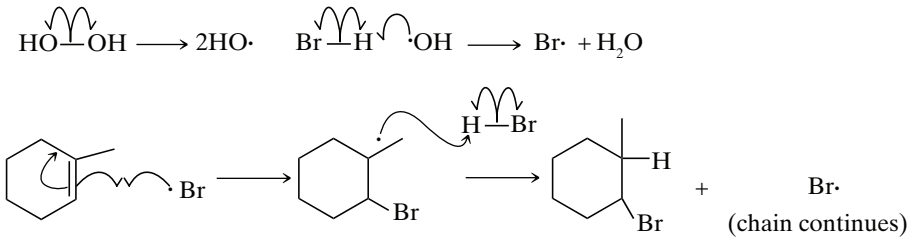


Answer



(d) The presence of molecular oxygen (O_2) or peroxides (such as H_2O_2) often, but not always, indicates that the reaction mechanism involves radicals.



(e) Protonation of an alkene forms a carbocation with an open octet, whereas protonation of methanol does not form an open octet. Therefore, we predict methanol to be a stronger base than alkene. The mechanism starts with the reaction of a stronger base with sulfuric acid.

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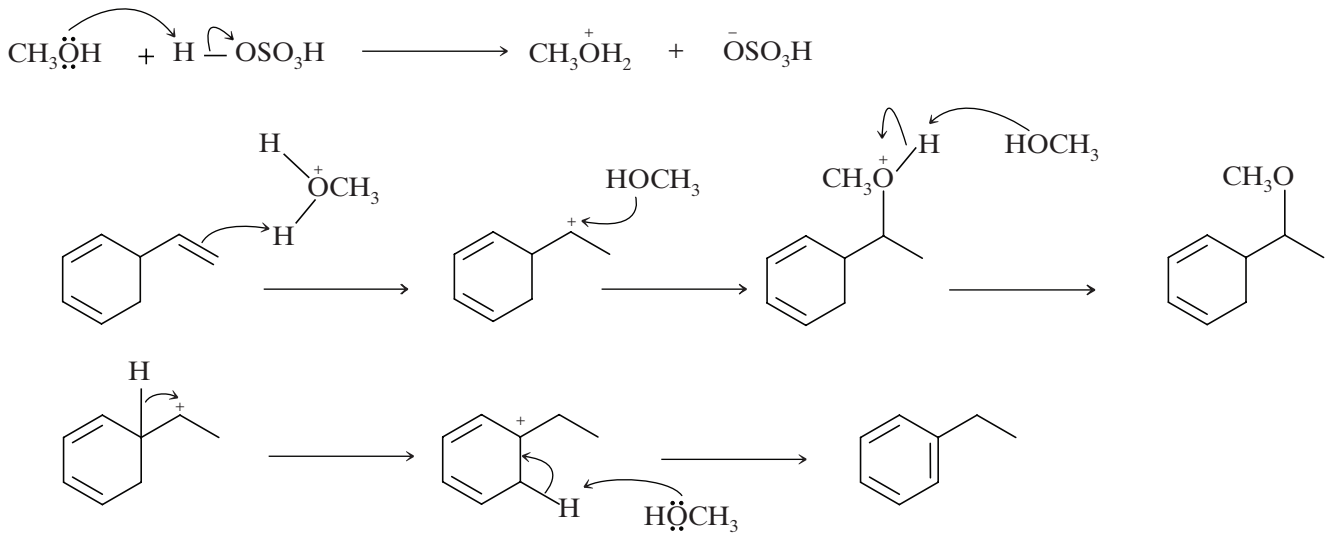


Solved Problem 8.27

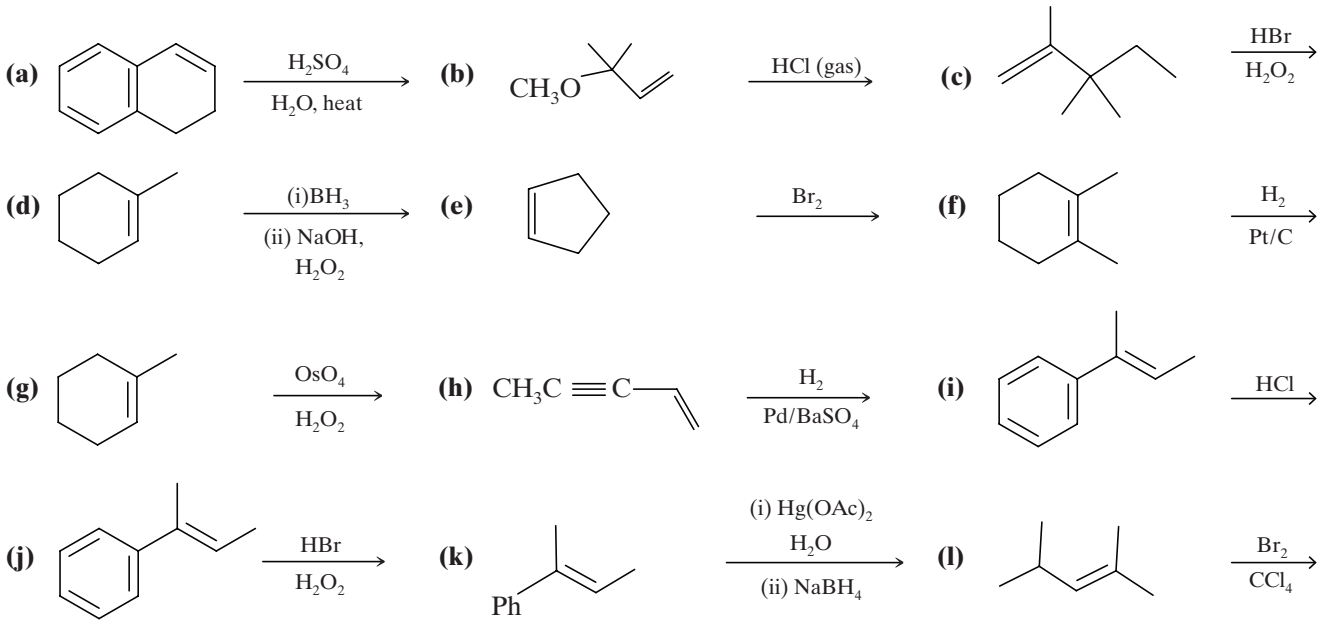
Briefly explain why BH_3 and $Hg(OAc)_2$ are electrophiles.

Answer

BH_3: Borane is electrophilic because boron has only six valence electrons (an open octet).
$Hg(OAc)_2$: Mercuric acetate ionizes to form ^+HgOAc and acetate ion $^-(OAc)$. The ^+HgOAc cation is electrophilic (because it bears a full positive charge) and so is $Hg(OAC)_2$.

Solved Problem 8.28

Provide the organic product(s) for the following reactions. If more than one products are possible, indicate which product (if any) is the major one. If no reaction occurs, write "NR". Pay careful attention to the stereochemistry of the reactants and products.



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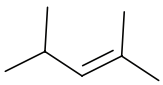
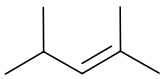
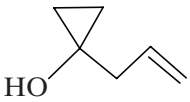
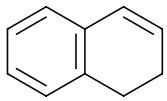
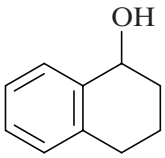
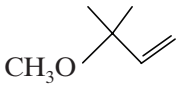
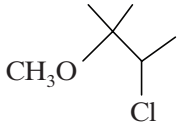
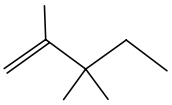
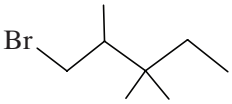
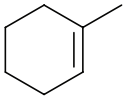
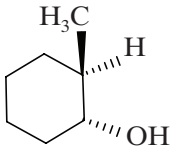
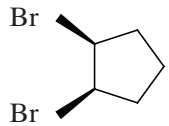
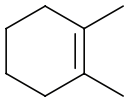
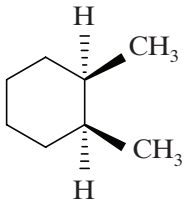
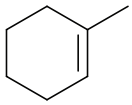
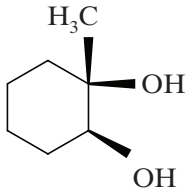
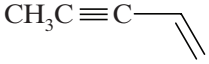
(m)  (i) $Hg(OAc)_2$, H_2O; (ii) $NaBH_4$ **(n)**  (i) O_3; (ii) $(CH_3)_2S$ **(o)**  (i) O_3; (ii) H_2O_2

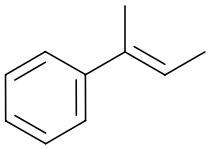
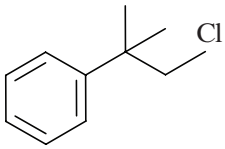
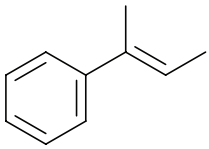
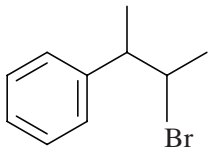
Answer

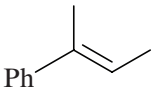
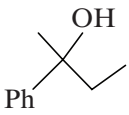
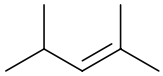
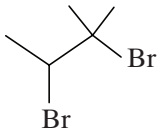
(a)  H_2SO_4, H_2O, heat  **(b)**  HCl (gas) 

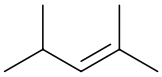
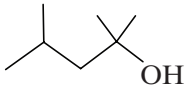
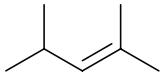
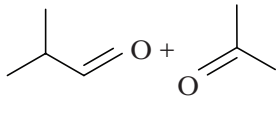
(c)  HBr, H_2O_2  **(d)**  (i) BH_3; (ii) NaOH, H_2O_2 

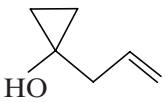
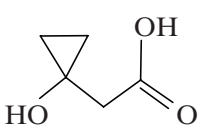
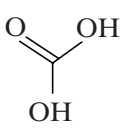
(e)  Br_2  **(f)**  H_2, Pt/C 

(g)  OsO_4, H_2O_2  **(h)**  H_2, $Pd/BaSO_4$, quinoline 

(i)  HCl  **(j)**  HBr, H_2O_2 

(k)  (i) $Hg(OAc)_2$, H_2O; (ii) $NaBH_4$  **(l)**  Br_2, CCl_4 

(m)  (i) $Hg(OAc)_2$, H_2O; (ii) $NaBH_4$  **(n)**  (i) O_3; (ii) $(CH_3)_2S$ 

(o)  (i) O_3; (ii) H_2O_2  + 

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Solved Problem 8.29

List two significant similarities between alkenes and alkynes. Clearly illustrate each similarity with a figure or reaction.

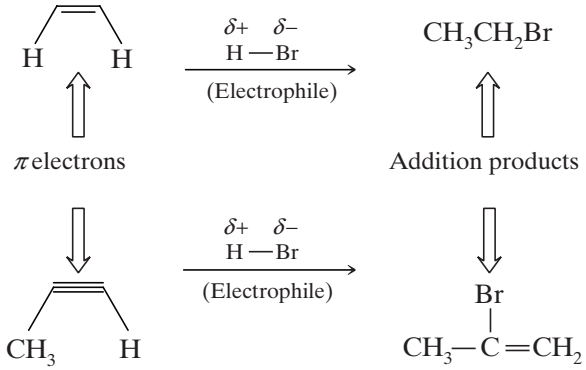
Answer

There are many possible answers to this question, as long as the answer gives a significant similarity. Some of the possibilities are as follows:

1. The alkene and alkyne molecules are both nucleophilic because they both have π electrons to share with an electrophile.
2. Alkenes and alkynes both undergo addition reactions.

The answer "alkenes and alkynes are similar because both begin with the letter *a*" is not sufficiently significant.

Both similarities can be illustrated by the same pair of reactions.



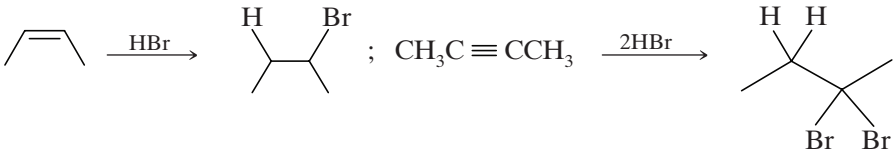
Solved Problem 8.30

List two significant differences between alkenes and alkynes. Clearly illustrate each difference with a figure or reaction.

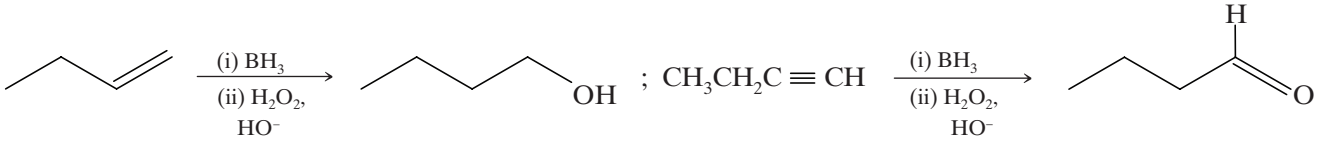
Answer

There are many possible answers to this question, as long as the answer gives a significant difference. Some possibilities are as follows:

1. An alkene molecule can react with 1 mole of HBr whereas an alkyne can react with 2 mol.

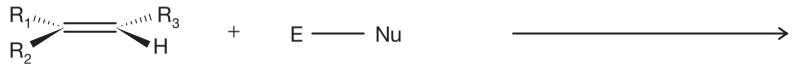


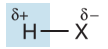
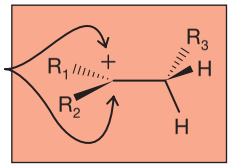
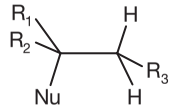
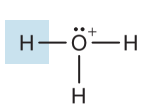
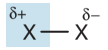
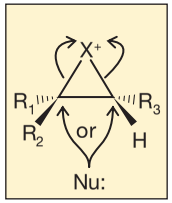
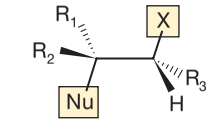
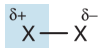
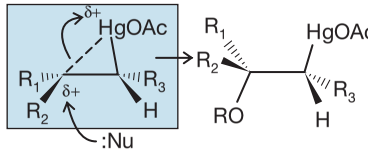
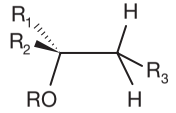
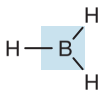
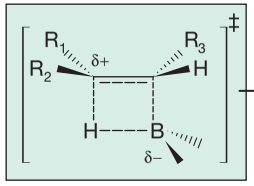
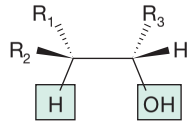
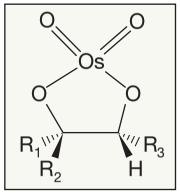
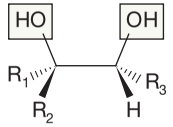
2. Hydroboration of a terminal alkene gives a primary alcohol whereas hydroboration of a terminal alkyne gives an aldehyde.



The answer "alkenes and alkynes are different because there is a *y* in alkynes but not in alkenes" is not sufficiently significant.

Summary of Alkene Addition Reactions



	Reaction Conditions	Electrophile	Nucleophile	Key Intermediates or Transition State	Regiochemistry	Stereochemistry of Addition	Product*
Hydrohalogenation	H—X				Markovnikov	Not controlled	 Nu = X or OH
Hydration (acid cat.)	Cat. HA, H_2O				Markovnikov	Not controlled	
Halogenation	X_2 (nonnucleophilic solvent)				Not applicable	Anti	 Nu = X or OR
Halohydrin Formation	X_2, ROH; R = H or C (nucleophilic solvent)				Markovnikov	Anti	
Oxymercuration–Demercuration	(1) $Hg(OAc)_2$, HOR: THF (R = H or C) (2) $NaBH_4$, HO^-				Markovnikov	Not controlled	
Hydroboration–Oxidation	(1) BH_3: THF (2) H_2O_2, HO^-				Net anti-Markovnikov	Syn	
1,2-Dihydroxylation	(1) OsO_4 (2) aq $NaHSO_3$					Syn	

*The generic alkene chosen has a substitution pattern that allows both regiochemistry and stereochemistry of the products to be discerned.

*The products are formed as a mixture of enantiomers in each case.

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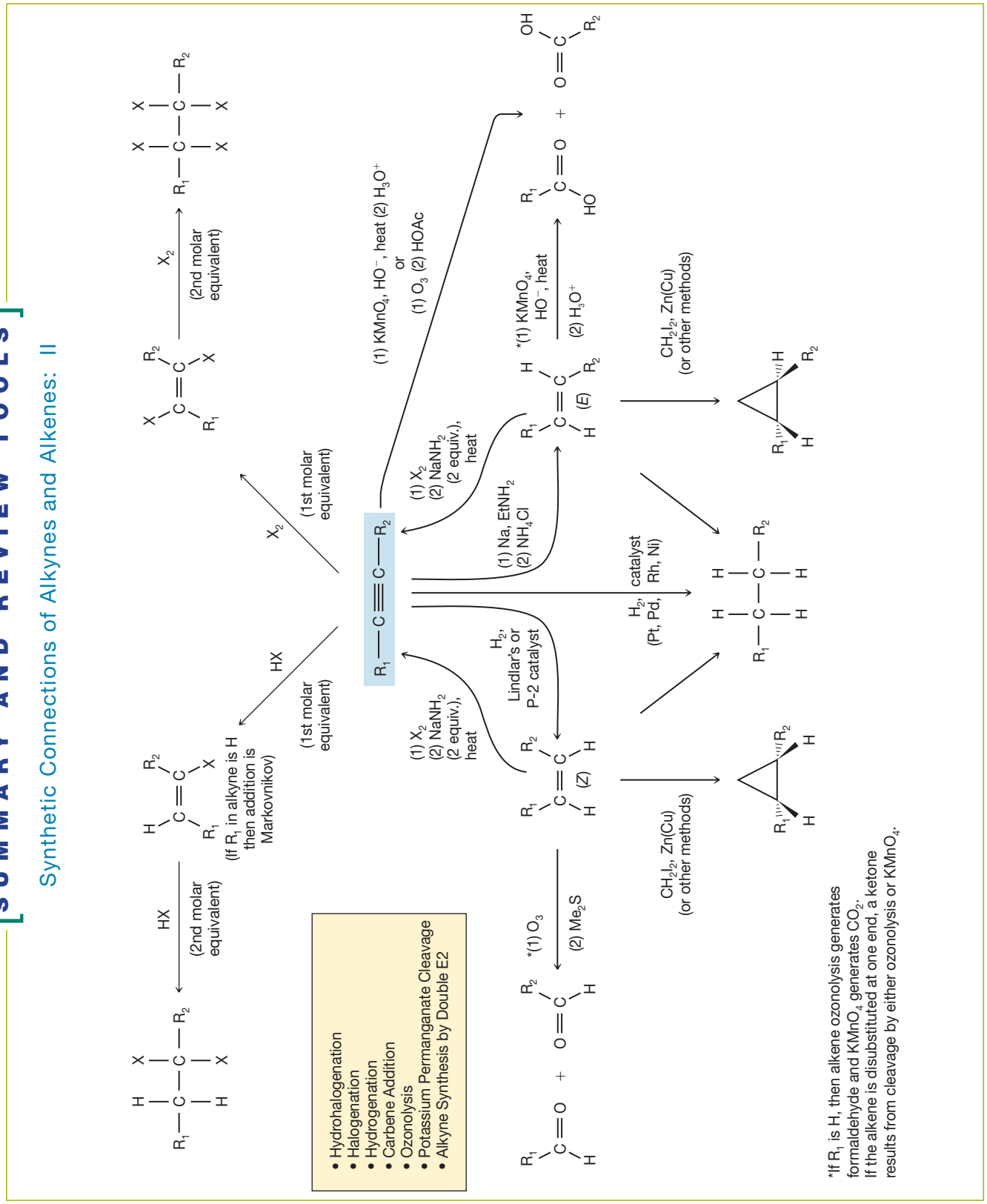
[SUMMARY AND REVIEW TOOLS]

Synthetic Connections of Alkynes and Alkenes: II



*If R_1 is H, then alkene ozonolysis generates formaldehyde and $KMnO_4$ generates CO_2.
If the alkene is disubstituted at one end, a ketone results from cleavage by either ozonolysis or $KMnO_4$.

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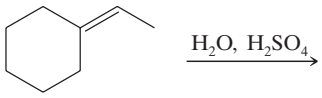
REVIEW PROBLEMS

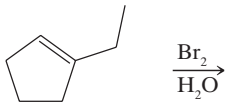
Alkenes and Alkynes Reaction Toolkit

8.21 Write structural formulas for the products that form when 1-butene reacts with each of the following reagents:
- **(a)** HI
- **(b)** H_2, Pt
- **(c)** Dilute H_2SO_4, warm
- **(d)** Cold concentrated H_2SO_4
- **(e)** Cold concentrated H_2SO_4, then H_2O and heat
- **(f)** HBr
- **(g)** Br_2 in CCl_4
- **(h)** Br_2 in H_2O
- **(i)** HCl
- **(j)** O_3, then Me_2S
- **(k)** OsO_4, then $NaHSO_3/H_2O$
- **(l)** $KMnO_4$, HO^-, heat, then H_3O^+
- **(m)** $Hg(OAc)_2$ in THF and H_2O, then $NaBH_4$, HO^-
- **(n)** BH_3:THF, then H_2O_2, HO^-

8.22 Repeat Exercise 8.21 using 1-methylcyclopentene instead of 1-butene.

8.23 Write structures for the major organic products from the following reactions. Show stereoisomers where applicable.

(a)


(b)


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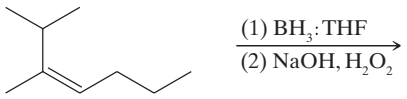
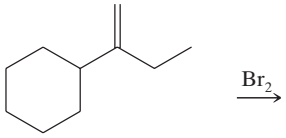


(d)


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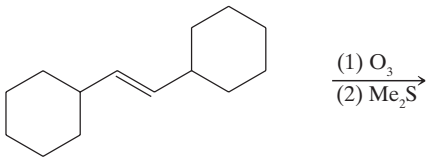
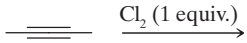


8.24 Give the structure of the products that you would expect from the reaction of 1-butyne with:
- **(a)** One molar equivalent of Br_2
- **(b)** One molar equivalent of HBr
- **(c)** Two molar equivalents of HBr
- **(d)** H_2 (in excess)/Pt
- **(e)** H_2, Ni_2B (P-2)
- **(f)** $NaNH_2$ in liquid NH_3, then CH_3I
- **(g)** $NaNH_2$ in liquid NH_3, then $(CH_3)_3CBr$

8.25 Give the structure of the products you would expect from the reaction (if any) of 2-butyne with:
- **(a)** One molar equivalent of HBr
- **(b)** Two molar equivalents of HBr
- **(c)** One molar equivalent of Br_2
- **(d)** Two molar equivalents of Br_2
- **(e)** H_2, Ni_2B (P-2)
- **(f)** One molar equivalent of HCl
- **(g)** Li/liquid NH_3
- **(h)** H_2 (in excess), Pt
- **(i)** Two molar equivalents of H_2, Pt
- **(j)** Hot $KMnO_4$, HO^-, then H_3O^+
- **(k)** O_3, then HOAc
- **(l)** $NaNH_2$, liquid NH_3

8.26 Write structures for the major organic products from the following reactions. Show stereoisomers where applicable.

(a)


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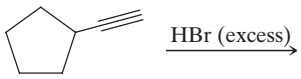
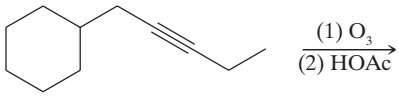
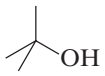


(c)

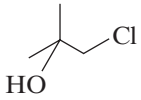

(d)


8.27 Show how 1-butyne could be synthesized from each of the following:
- **(a)** 1-Butene
- **(b)** 1-Chlorobutane
- **(c)** 1-Chloro-1-butene
- **(d)** 1,1-Dichlorobutane
- **(e)** Ethyne and ethyl bromide

8.28 Starting with 2-methylpropene (isobutylene) and using any other needed reagents, outline a synthesis of each of the following:

(a)


(b)


(c)


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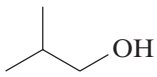
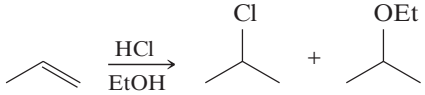


Mechanisms

8.29 Write a three-dimensional formula for the product formed when 1-methylcyclohexene is treated with each of the following reagents. In each case, designate the location of deuterium or tritium atoms.
- **(a)** (1) BH_3:THF, (2) CH_3CO_2T
- **(b)** (1) BD_3:THF, (2) CH_3CO_2D
- **(c)** (1) BD_3:THF, (2) NaOH, H_2O_2, H_2O

8.30 Write a mechanism that accounts for the formation of ethyl isopropyl ether in the following reaction.



8.31 When, in separate reactions, 2-methylpropene, propene, and ethene are allowed to react with HI under the same

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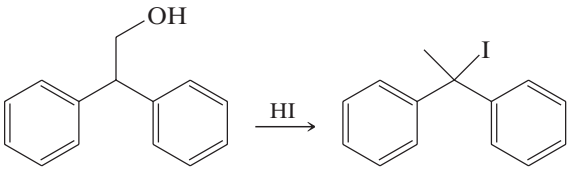
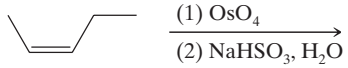
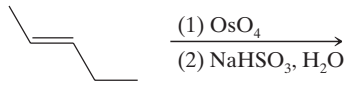
conditions (i.e., identical concentration and temperature), 2-methylpropene is found to react fastest and ethene slowest. Provide an explanation for these relative rates.

8.32 Propose a mechanism that accounts for the following reaction.



8.33 Write stereochemical formulas for all of the products that you would expect from each of the following reactions. (You may find models helpful.)

(a) 

(b) 

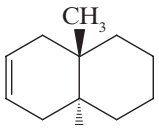
(c) 

(d) 

8.34 Give (*R*, *S*) designations for each different compound given as an answer to Problem 8.33.

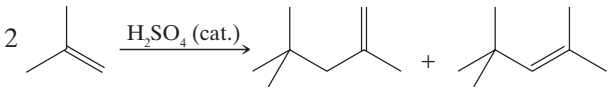
8.35 The double bond of tetrachloroethene is undetectable in the bromine test for unsaturation. Give a plausible explanation for this behavior.

8.36 The reaction of bromine with cyclohexene involves anti addition, which generates, initially, the diaxial conformation of the addition product that then undergoes a ring flip to the diequatorial conformation of *trans*-1,2-dibromocyclohexane. However, when the unsaturated bicyclic compound **I** is the alkene, instead of cyclohexene, the addition product is exclusively in a stable diaxial conformation. Account for this. (You may find it helpful to build handheld molecular models.)



I

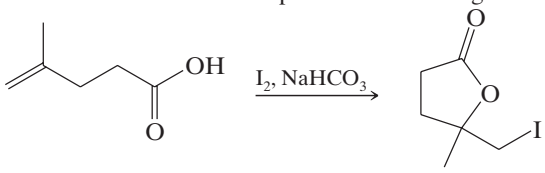
8.37 Propose a mechanism that explains formation of the products from the following reaction, including the distribution of the products as major and minor.



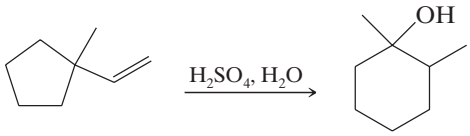
Major **Minor**

8.38 Internal alkynes can be isomerized to terminal alkynes on treatment with $NaNH_2$. The process is much less successful when NaOH is used. Why is there this difference?

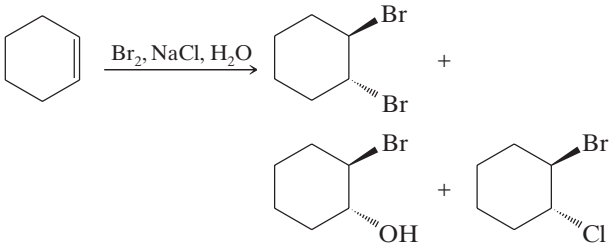
8.39 Write a mechanism that explains the following reaction.



8.40 Write a mechanism for the following reaction.



8.41 Write a mechanism that explains formation of the products shown in the following reaction.



Structure Elucidation

8.42 Myrcene, a fragrant compound found in bayberry wax, has the formula $C_{10}H_{16}$ and is known not to contain any triple bonds.

(a) What is the index of hydrogen deficiency of myrcene? When treated with excess hydrogen and a platinum catalyst, myrcene is converted to a compound **(A)** with the formula $C_{10}H_{22}$.

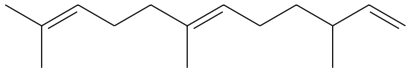
(b) How many rings does myrcene contain?

(c) How many double bonds? Compound **A** can be identified as 2,6-dimethyloctane. Ozonolysis of myrcene followed by treatment with dimethyl sulfide yields 2 mol of formaldehyde (HCHO), 1 mol of acetone (CH_3COCH_3), and a third compound **(B)** with the formula $C_5H_6O_3$.

(d) What is the structure of compound **B**?

(e) What is the structure of myrcene?

8.43 Farnesene (below) is a compound found in the waxy coating of apples. (**a**) Give the structure and IUPAC name of the product formed when farnesene is allowed to react with excess hydrogen in the presence of a platinum catalyst. (**b**) How many stereoisomers of the product are possible?



Farnesene

8.44 Write structural formulas for the products that would be formed when geranial, a component of lemongrass oil, is treated with ozone and then with dimethyl sulfide (Me_2S).

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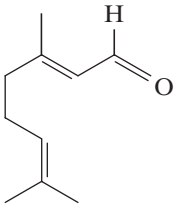
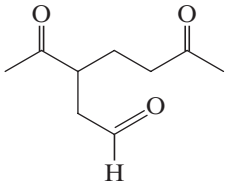


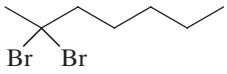
Geranial

8.45 Limonene is a compound found in orange oil and lemon oil. When limonene is treated with excess hydrogen and a platinum catalyst, the product of the reaction is 1-isopropyl-4-methylcyclohexane. When limonene is treated with ozone and then with dimethyl sulfide (Me_2S), the products of the reaction are formaldehyde (HCHO) and the following compound. Write a structural formula for limonene.

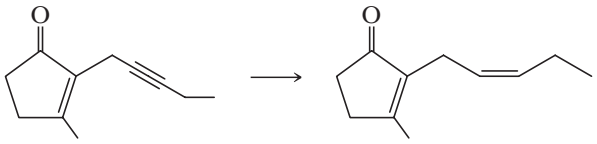


General Problems

8.46 Synthesize the following compound starting with ethyne and 1-bromopentane as your only organic reagents (except for solvents) and using any needed inorganic compounds.



8.47 Shown below is the final step in a synthesis of an important perfume constituent, *cis*-jasmone. Which reagents would you choose to carry out this last step?



***cis*-Jasmone**

8.48 Ricinoleic acid, a compound that can be isolated from castor oil, has the structure $CH_3(CH_2)_5CHOHCH_2CH{=}CH(CH_2)_7CO_2H$.

(a) How many stereoisomers of this structure are possible?

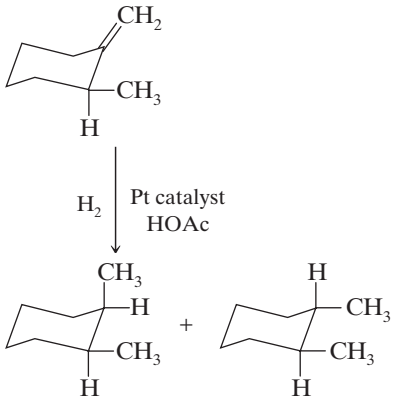
(b) Write these structures.

8.49 There are two dicarboxylic acids with the general formula $HO_2CCH{=}CHCO_2H$. One dicarboxylic acid is called maleic acid; the other is called fumaric acid. When treated with OsO_4, followed by $NaHSO_3/H_2O$, maleic acid yields *meso*-tartaric acid and fumaric acid yields (±)-tartaric acid. Show how this information allows one to write stereochemical formulas for maleic acid and fumaric acid.

8.50 Use your answers to the preceding problem to predict the stereochemical outcome of the addition of bromine to maleic acid and to fumaric acid. (a) Which dicarboxylic acid would add bromine to yield a meso compound? (b) Which would yield a racemic form?

8.51 Alkyl halides add to alkenes in the presence of $AlCl_3$; yields are the highest when tertiary halides are used. Predict the outcome of the reaction of *tert*-pentyl chloride (1-chloro-2,2-dimethylpropane) with propene and specify the mechanistic steps.

8.52 Explain the stereochemical results observed in this catalytic hydrogenation. (You may find it helpful to build hand-held molecular models.)



I (70%) **II (30%)**

8.53 A naturally occurring antibiotic called mycomycin has the structure shown here. Mycomycin is optically active. Explain this by writing structures for the enantiomeric forms of mycomycin.

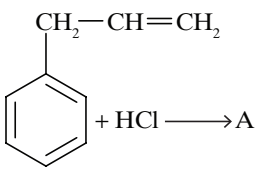
$HC{\equiv}C{-}C{\equiv}C{-}CH{=}C{=}CH{-}(CH{=}CH)_2CH_2CO_2H$

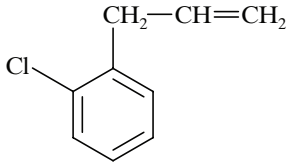
Mycomycin

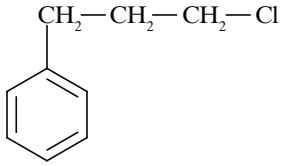
ADDITIONAL OBJECTIVE QUESTIONS

Single Correct Choice Type

1. What is A in the following reaction?



(a) 

(b) 

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(c) $CH_2-CH(Cl)-CH_3$ **(d)** $CH(Cl)-CH_2-CH_3$

2. Ozonolysis of an unknown compound gave $CH_2=O$, CH_3CHO and CH_3COCHO. What is the possible structures for the unknown compound?

(a) **(b)** **(c)** **(d)**

3. The product(s) obtained via oxymercuration ($HgSO_4$ + H_2SO_4) of 1-butyne would be

(a) $CH_3-CH_2-\overset{\overset{O}{\|}}{C}-CH_3$

(b) $CH_3-CH_2-CH_2-CHO$

(c) $CH_3-CH_2-CHO + HCHO$

(d) $CH_3-CH_2-COOH + HCOOH$

4. Find the product(s):

$\xrightarrow[CCl_4]{HBr}$ Kinetically controlled + Thermodynamically controlled products

(a) K.C. = ; T.C. =

(b) Both =

(c) Both =

(d) K.C. = ; T.C. =

5. Propyne and propene can be distinguished by

(a) conc. H_2SO_4 **(b)** Br_2 in CCl_4

(c) dil. $KMnO_4$ **(d)** $AgNO_3$ in NH_3

6. Hydrogenation of the following compound in the presence of poisoned palladium catalyst gives

(a) an optically active compound.

(b) an optically inactive compound.

(c) a racemic mixture.

(d) a diastereomeric mixture.

7. Give the major product(s) of the reaction shown:

$\xrightarrow[\text{Electrophilic addition}]{I-Cl}$

(a) + Enantiomer

(b)

(c) + Enantiomer

(d)

8. The reaction of propene with HOCl proceeds via the addition of

(a) H^+ in first step. **(b)** Cl^+ in first step.

(c) OH^- in first step. **(d)** Cl^- and OH^- in single step.

9. Choose the correct order of reactivity (most reactive on the left) for the following alkenes with HI:

(a) $H_2C=CH_2 > H_2C=CH-CH_3 > H_2C=C(CH_3)_2$

(b) $H_2C=CH_2 > H_2C=C(CH_3)_2 > H_2C=CH-CH_3$

(c) $H_2C=CH-CH_3 > H_2C=CH_2 > H_2C=C(CH_3)_2$

(d) $H_2C=C(CH_3)_2 > H_2C=CH-CH_3 > H_2C=CH_2$

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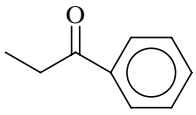
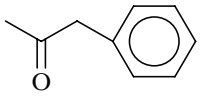
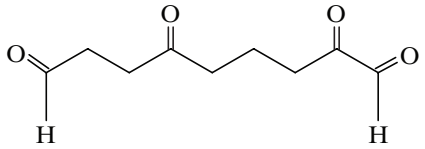
10. For the following reaction, the product P is

$$C_6H_5—C\equiv C—CH_3 \xrightarrow[H_2SO_4]{HgSO_4} P$$

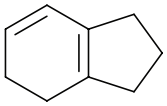
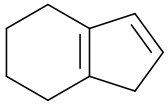
(a)  **(b)** 

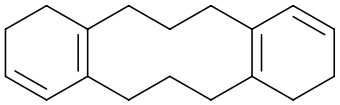
(c) $C_6H_5—\underset{\displaystyle OH}{\underset{|}{C}}=CHCH_3$ **(d)** $C_6H_5—CH=\underset{\displaystyle OH}{\underset{|}{C}}—CH_3$

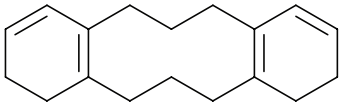
11. An unknown compound was treated with ozone followed by $(CH_3)_2S$ and the following product was obtained.



Which of the following compounds might have been the unknown?

(i)  (ii) 

(iii) 

(iv) 

(a) (i) **(b)** (ii) **(c)** (i) or (iii)
(d) (ii) or (iv) **(e)** (iii)

12. 2-Hexyne can be converted into *trans*-2-hexene by the action of

(a) H_2–Pd-$BaSO_4$ **(b)** Li in liq. NH_3
(c) H_2–PtO_2 **(d)** $NaBH_4$

13. $CH_3—CH=CH_2 + NOCl \longrightarrow P$

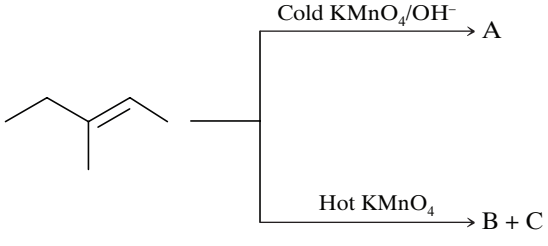
Identify the adduct P.

(a) $CH_3—\underset{\displaystyle Cl}{\underset{|}{CH}}—\underset{\displaystyle NO}{\underset{|}{CH_2}}$ **(b)** $CH_3—\underset{\displaystyle N=O}{\underset{|}{CH}}—\underset{\displaystyle Cl}{\underset{|}{CH_2}}$

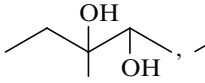
(c) $CH_3—CH_2—\underset{\displaystyle Cl}{\underset{|}{\overset{\displaystyle NO}{\overset{|}{CH}}}}$ **(d)** $\underset{\displaystyle NO}{\underset{|}{CH_2}}—CH_2—\underset{\displaystyle Cl}{\underset{|}{CH_2}}$

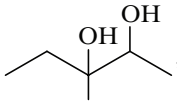
14. The Hydroboration-Oxidation reaction produces a ___ addition.

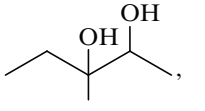
(a) Markovnikov **(b)** Anti-Markovnikov
(c) Syn addition **(d)** (b) and (c)

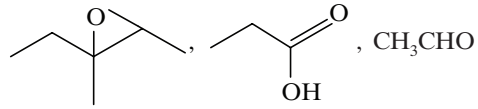
15. 

A, B and C are respectively are

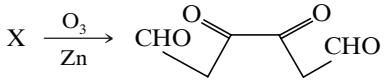
(a)  $+ CH_3—CH_2COOH$

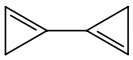
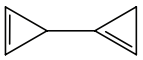
(b)  $CH_3—CH_2—CH_2—CHO + CH_3COOH$

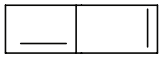
(c)  $+ CH_3—COOH$

(d)  CH_3CHO

16. Find out the X (reactant) of the given reaction:



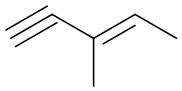
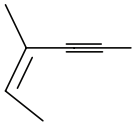
(a)  **(b)** 

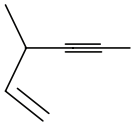
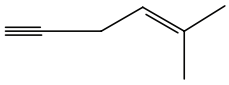
(c)  **(d)** All of these

17. Which one of the following compounds does not form an ozonide?

(a) Ethene **(b)** Propyne **(c)** Propene **(d)** Propane

18. Which of the following produces a chiral molecule after treatment with Lindlar's catalyst?

(a)  **(b)** 

(c)  **(d)** 

19. Ethylene reacts with Baeyer's reagent to give

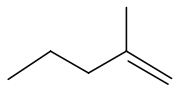
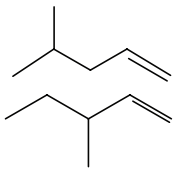
(a) ethane. **(b)** ethyl alcohol.
(c) ethylene glycol. **(d)** none of these.

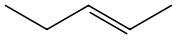
20. The value of *x* is

$$\textit{Cis}\text{-2-butene} \xrightarrow[CCl_4]{Br_2} (x) \text{ products.}$$

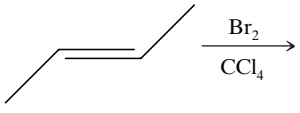
(a) 0 **(b)** 1 **(c)** 2 **(d)** 3

21. In which of the following alkenes will a hydrogen shift occur upon addition of HCl?

(a)  **(b)** 

(c)  **(d)**

22. In which of the following reaction, formation of racemic mixture occurs?

(a) 

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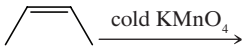
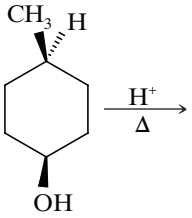
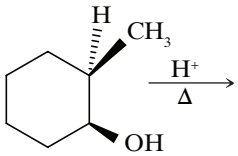
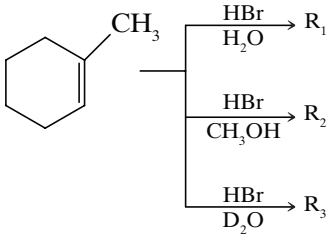
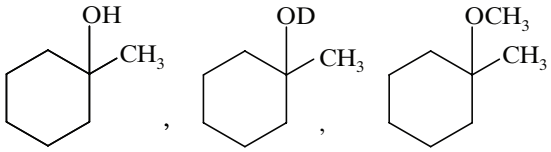
(b) 

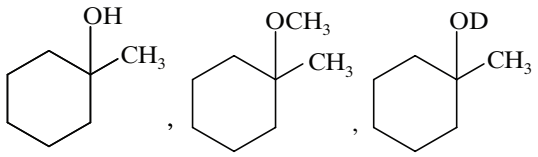
(c) 

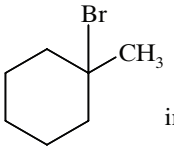
(d) 

23. The major products obtained R_1, R_2 and R_3 in the following reactions, respectively, is

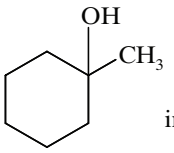


(a) 

(b) 

(c) 

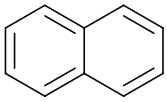
in all three reactions

(d) 

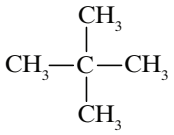
in all three reactions

24. The compound most likely to decolorize a solution of potassium permanganate is

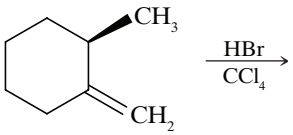
(a) CH_3CH_3

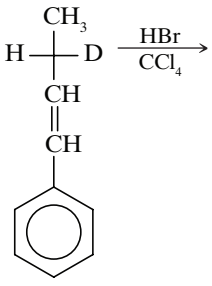
(b) 

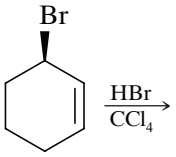
(c) $CH_3CH{=}CHCH_2CH_3$

(d) 

25. In which of the following reactions, diastereomers will be formed?

(a) 

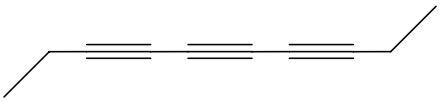
(b) 

(c) 

(d) All of these

Integer Type

1. What is the greatest number of atoms that you would expect to be co-linear in the molecule shown below?



2. The number of stereoisomers obtained by bromination of *trans*-2-butene is

(a) 1 **(b)** 2 **(c)** 3 **(d)** 4

Matrix Match Type

1.

Column I	Column II
(a) $CH_3—C{\equiv}C—CH_3$	**(p)** *cis*-product with H_2/Pd-$BaSO_4$
(b) $CH_3—CH_2—C{\equiv}CH$	**(q)** *trans*-product with Na/liq.NH_3

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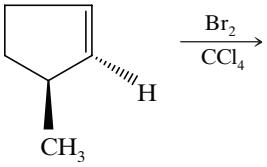
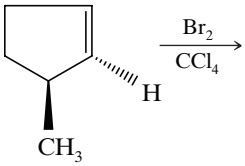
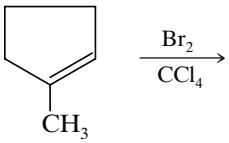
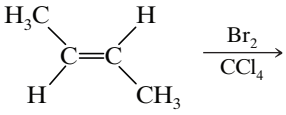
(c) $CH_3—C\equiv CH$ (r) white with amm. $AgNO_3$

(d) $CH_3—C\equiv C—Et$ (s) H_2 gas with Na

2.

Column I Reaction	Column II Nature of products formed	Column III Number of chiral center present in product. (Consider only one isomer in case of racemic mixture of diastereomer)
	(p) Racemic mixture	(w) 0
	(q) Meso	(x) 1
	(r) Diastereomer	(y) 2
	(s) Vicinal dihalide	(z) 3

ANSWER KEY

Single Correct Choice Type

1. (c)	**2.** (a)	**3.** (a)	**4.** (a)
5. (d)	**6.** (b)	**7.** (a)	**8.** (b)
9. (d)	**10.** (a)	**11.** (c)	**12.** (b)
13. (a)	**14.** (d)	**15.** (c)	**16.** (a)
17. (d)	**18.** (c)	**19.** (c)	**20.** (c)
21. (d)	**22.** (c)	**23.** (c)	**24.** (c)
25. (d)			

Integer Type

1. (8) **2.** (1)

Matrix Match Type

1. a →(p, q); b→(r, s); c→(r, s); d→(p, q)

2. a→(r, s, z); b→(p, s, y); c→(p, s, y); d→(q, s, y)

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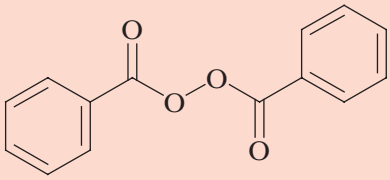
9

Radical Reactions



Benzoyl peroxide

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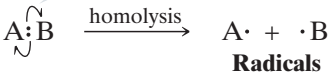
9.1 | Introduction: How Radicals Form and How They React
9.2 | Homolytic Bond Dissociation Energies ($\Delta H°$)
9.3 | Reactions of Alkanes with Halogens
9.4 | Chlorination of Methane: Mechanism of Reaction
9.5 | Halogenation of Higher Alkanes
9.6 | Reactions That Generate Tetrahedral Chirality Centers
9.7 | Allylic Substitution and Allylic Radicals
9.8 | Benzylic Substitution and Benzylic Radicals
9.9 | Radical Addition to Alkenes: The Anti-Markovnikov Addition of Hydrogen Bromide
9.10 | Other Important Radical Reactions

9.1 | INTRODUCTION: HOW RADICALS FORM AND HOW THEY REACT

So far almost all of the reactions whose mechanisms we have studied have been **ionic reactions**. Ionic reactions are those in which covalent bonds break **heterolytically** and in which ions are involved as reactants, intermediates, or products.

Another broad category of reactions has mechanisms that involve **homolysis** of covalent bonds with the production of intermediates possessing unpaired electrons called **radicals** (or **free radicals**):

Each atom takes one electron from the covalent bond that joined them.



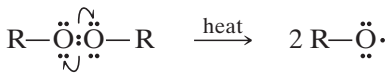
Radicals

This simple example illustrates the way we use **single-barbed curved arrows** to show the movement of **a single electron** (not of an electron pair as we have done earlier). In this instance, each group, A and B, comes away with one of the electrons of the covalent bond that joined them.

9.1A Production of Radicals

- Energy in the form of heat or light must be supplied to cause homolysis of covalent bonds (Section 9.2).

For example, compounds with an oxygen–oxygen single bond, called **peroxides**, undergo homolysis readily when heated, because the oxygen–oxygen bond is weak. The products are two radicals, called alkoxyl radicals:



Dialkyl peroxide **Alkoxyl radicals**

Homolysis of a dialkyl peroxide.

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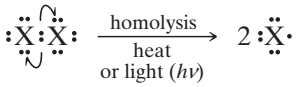
Halogen molecules (X_2) also contain a relatively weak bond. As we shall soon see, halogens undergo homolysis readily when heated or when irradiated with light of a wavelength that can be absorbed by the halogen molecule:



Homolysis of a halogen molecule.

The products of this homolysis are halogen atoms, and because halogen atoms contain an unpaired electron, they are radicals.

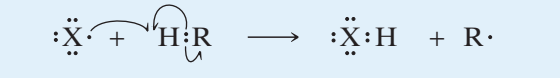
9.1B Reactions of Radicals

- Almost all small radicals are short-lived, highly reactive species.

When radicals collide with other molecules, they tend to react in a way that leads to pairing of their unpaired electron. One way they can do this is by abstracting an atom from another molecule. To abstract an atom means to remove an atom by homolytic bond cleavage as the atom forms a bond with another radical. For example, a halogen atom may abstract a hydrogen atom from an alkane. This **hydrogen abstraction** gives the halogen atom an electron (from the hydrogen atom) to pair with its unpaired electron. Notice, however, that the other product of this abstraction *is another radical intermediate*, in this case, an alkyl radical, R·, which goes on to react further, as we shall see in this chapter.

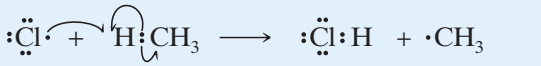
A MECHANISM FOR THE REACTION — Hydrogen Atom Abstraction

General Reaction



Reactive radical intermediate **Alkane** **Alkyl radical intermediate (reacts further)**

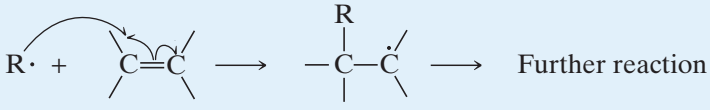
Specific Example



Chlorine atom (a radical) **Methane** **Methyl radical intermediate (reacts further)**

This behavior is characteristic of **radical reactions**. Consider another example, one that shows another way in which radicals can react: they can combine with a compound containing a multiple bond to produce a new radical, which goes on to react further. (We shall study reactions of this type in Section 9.10.)

A MECHANISM FOR THE REACTION — Radical Addition to a π Bond



Reactive alkyl radical intermediate **Alkene** **New radical intermediate**

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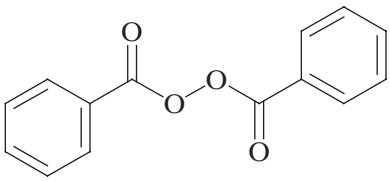
The Chemistry of... ACNE MEDICATIONS

It turns out that although certain peroxides are great at initiating radical reactions, peroxy radicals also have many valuable uses on their own. For example, benzoyl peroxide is an active ingredient typically found in many acne medications that breaks apart and forms radicals through the warmth of our skin and exposure to light. These radicals can then kill the bacteria that cause break-outs.

The same compound is also used as a whitening and bleaching agent. As we will see in Chapter 13, many colored compounds possess double bonds in conjugation; the benzoyl peroxide radicals can add to those bonds, break their conjugation, and remove their color to leave behind new white materials. If you have ever wiped your face after using an acne medication with a colored towel, you may already have seen these effects!



Benzoyl peroxide

9.2 | HOMOLYTIC BOND DISSOCIATION ENERGIES (ΔH°)

When atoms combine to form molecules, energy is released as covalent bonds form. The molecules of the products have lower enthalpy than the separate atoms. When hydrogen atoms combine to form hydrogen molecules, for example, the reaction is *exothermic*; it evolves 436 kJ of heat for every mole of hydrogen that is produced. Similarly, when chlorine atoms combine to form chlorine molecules, the reaction evolves 243 kJ mol^{-1} of chlorine produced:

$$H\cdot + H\cdot \longrightarrow H{-}H \qquad \Delta H^\circ = -436 \text{ kJ mol}^{-1}$$

$$Cl\cdot + Cl\cdot \longrightarrow Cl{-}Cl \qquad \Delta H^\circ = -243 \text{ kJ mol}^{-1}$$

Bond formation is an exothermic process: ΔH° is negative.

Reactions in which only bond breaking occurs are always endothermic. The energy required to break the covalent bonds of hydrogen or chlorine homolytically is exactly equal to that evolved when the separate atoms combine to form molecules. In the bond cleavage reaction, however, ΔH° is positive:

$$H{-}H \longrightarrow H\cdot + H\cdot \qquad \Delta H^\circ = +436 \text{ kJ mol}^{-1}$$

$$Cl{-}Cl \longrightarrow Cl\cdot + Cl\cdot \qquad \Delta H^\circ = +243 \text{ kJ mol}^{-1}$$

Bond breaking is an endothermic process: ΔH° is positive.

- Energy must be supplied to break covalent bonds.
- The energies required to break covalent bonds homolytically are called **homolytic bond dissociation energies**, and they are usually abbreviated by the symbol ΔH°.

The homolytic bond dissociation energies of hydrogen and chlorine, for example, can be written in the following way:

H—H	Cl—Cl
(ΔH° = 436 kJ mol^{-1})	**(ΔH° = 243 kJ mol^{-1})**

The homolytic bond dissociation energies of a variety of covalent bonds have been determined experimentally or calculated from related data. Some of these ΔH° values are listed in Table 9.1.

9.2A HOW TO Use Homolytic Bond Dissociation Energies to Determine the Relative Stabilities of Radicals

Homolytic bond dissociation energies also provide us with a convenient way to estimate the relative stabilities of radicals. If we examine the data given in Table 9.1, we find the following values of ΔH° for the primary and secondary C—H bonds of propane:

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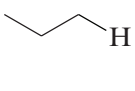


($\Delta H^\circ = 423$ kJ mol^{-1})



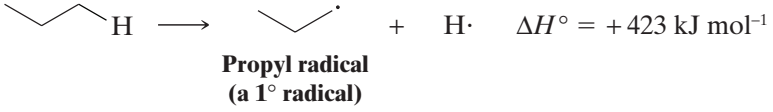
($\Delta H^\circ = 413$ kJ mol^{-1})

Table 9.1 Single-Bond Homolytic Dissociation Energies (ΔH°) at 25 °C[a]

A:B → A· + B·					
Bond Broken (shown in red)	kJ mol^{-1}	Bond Broken (shown in red)	kJ mol^{-1}	Bond Broken (shown in red)	kJ mol^{-1}
H—H	436	CH_3CH_2—OCH_3	352	CH_2=$CHCH_2$—H	369
D—D	443	$CH_3CH_2CH_2$—H	423	CH_2=CH—H	465
F—F	159	$CH_3CH_2CH_2$—F	444	C_6H_5—H	474
Cl—Cl	243	$CH_3CH_2CH_2$—Cl	354	HC≡C—H	547
Br—Br	193	$CH_3CH_2CH_2$—Br	294	CH_3—CH_3	378
I—I	151	$CH_3CH_2CH_2$—I	239	CH_3CH_2—CH_3	371
H—F	570	$CH_3CH_2CH_2$—OH	395	$CH_3CH_2CH_2$—CH_3	374
H—Cl	432	$CH_3CH_2CH_2$—OCH_3	355	CH_3CH_2—CH_2CH_3	343
H—Br	366	$(CH_3)_2CH$—H	413	$(CH_3)_2CH$—CH_3	371
H—I	298	$(CH_3)_2CH$—F	439	$(CH_3)_3C$—CH_3	363
CH_3—H	440	$(CH_3)_2CH$—Cl	355	HO—H	499
CH_3—F	461	$(CH_3)_2CH$—Br	298	HOO—H	356
CH_3—Cl	352	$(CH_3)_2CH$—I	222	HO—OH	214
CH_3—Br	293	$(CH_3)_2CH$—OH	402	$(CH_3)_3CO$—$OC(CH_3)_3$	157
CH_3—I	240	$(CH_3)_2CH$—OCH_3	359	C_6H_5CO—OCC_6H_5	139
CH_3—OH	387	$(CH_3)_2CHCH_2$—H	422	CH_3CH_2O—OCH_3	184
CH_3—OCH_3	348	$(CH_3)_3C$—H	400	CH_3CH_2O—H	431
CH_3CH_2—H	421	$(CH_3)_3C$—Cl	349	CH_3C—H	364
CH_3CH_2—F	444	$(CH_3)_3C$—Br	292		
CH_3CH_2—Cl	353	$(CH_3)_3C$—I	227		
CH_3CH_2—Br	295	$(CH_3)_3C$—OH	400		
CH_3CH_2—I	233	$(CH_3)_3C$—OCH_3	348		
CH_3CH_2—OH	393	$C_6H_5CH_2$—H	375		

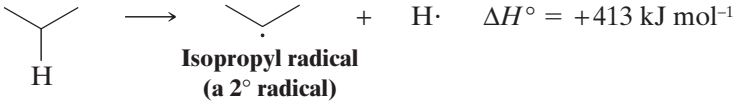
[a]Data compiled from the National Institute of Standards (NIST) Standard Reference Database Number 69, July 2001 Release, Accessed via NIST Chemistry WebBook (http://webbook.nist.gov/chemistry/) Copyright 2000. Data from CRC Handbook of Chemistry and Physics, Updated 3rd Electronic Edition; Lide, David R., ed. DH° values were obtained directly or calculated from heat of formation (Hf) data using the equation DH° [A-B] = Hf [A.] + Hf [B.] - Hf [A-B].

This means that for the reaction in which the designated C—H bonds are broken homolytically, the values of ΔH° are those given here.



Propyl radical (a 1° radical)

$\Delta H^\circ = +423$ kJ mol^{-1}



Isopropyl radical (a 2° radical)

$\Delta H^\circ = +413$ kJ mol^{-1}

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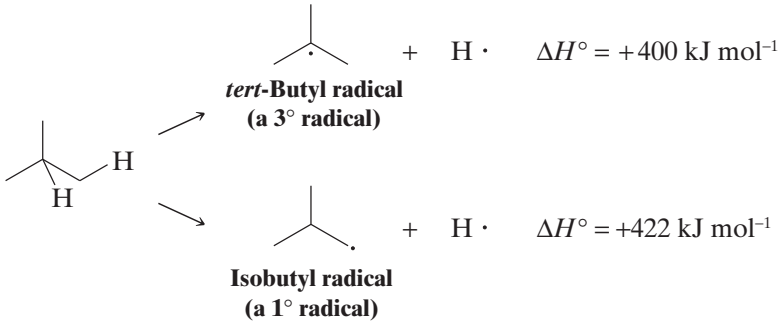
These reactions resemble each other in two respects: they both begin with the same alkane (propane), and they both produce an alkyl radical and a hydrogen atom. They differ, however, in the amount of energy required and in the type of carbon radical produced. These two differences are related to each other.

- Alkyl radicals are classified as being 1°, 2°, or 3° based on the carbon atom that has the unpaired electron, the same way that we classify carbocations based on the carbon atom with the positive charge.

More energy must be supplied to produce a primary alkyl radical (the propyl radical) from propane than is required to produce a secondary carbon radical (the isopropyl radical) from the same compound. This must mean that the primary radical has absorbed more energy and thus has greater *potential energy*. Because the relative stability of a chemical species is inversely related to its potential energy, the secondary radical must be the *more stable* radical (Fig. 9.1*a*). In fact, the secondary isopropyl radical is more stable than the primary propyl radical by 10 kJ mol^{-1}.

We can use the data in Table 9.1 to make a similar comparison of the *tert*-butyl radical (a 3° radical) and the isobutyl radical (a 1° radical) relative to isobutane:



Here we find (Fig. 9.1*b*) that the difference in stability of the two radicals is even larger. The tertiary radical is more stable than the primary radical by 22 kJ mol^{-1}.

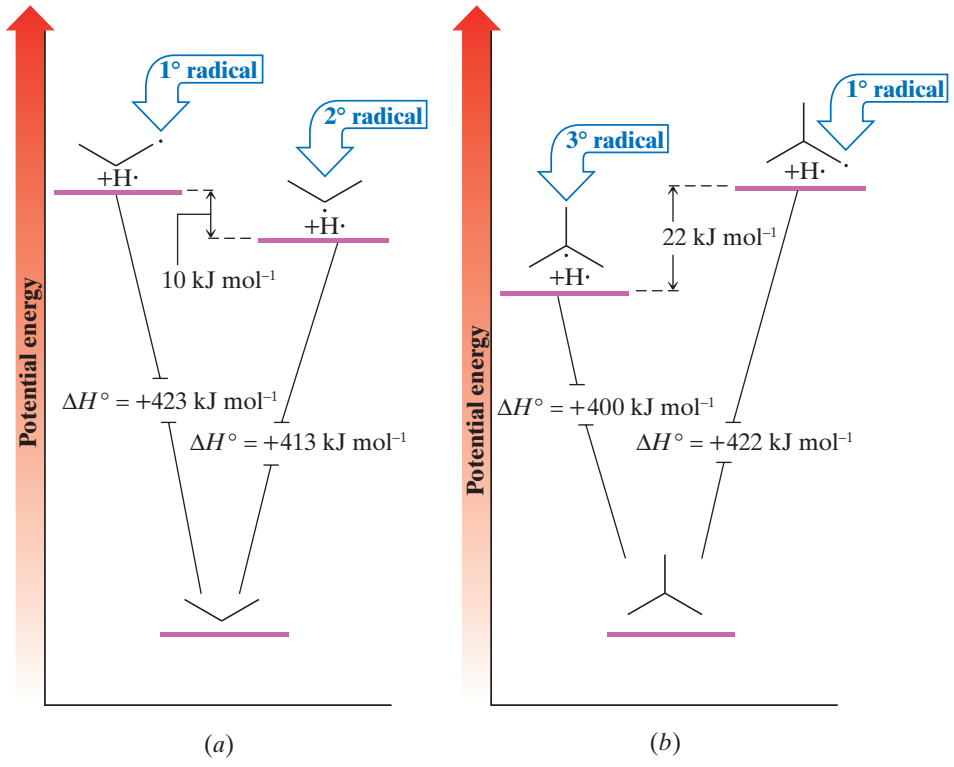


Figure 9.1 (*a*) Comparison of the potential energies of the propyl radical (+H·) and the isopropyl radical (+H·) relative to propane. The isopropyl radical (a 28 radical) is more stable than the 18 radical by 10 kJ mol^{-1}. (*b*) Comparison of the potential energies of the *tert*-butyl radical (+H·) and the isobutyl radical (+H·) relative to isobutane. The 38 radical is more stable than the 18 radical by 22 kJ mol^{-1}.

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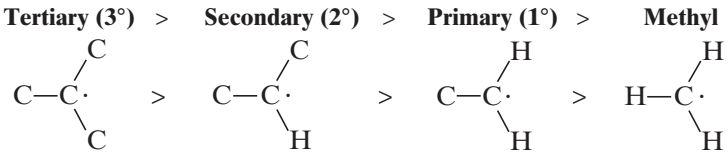
The kind of pattern that we find in these examples is found with alkyl radicals generally.

- **Overall, the relative stabilities of radicals are 3° > 2° > 1° > methyl.**

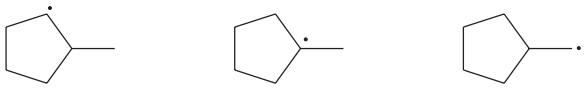


- **The order of stability of alkyl radicals is the same as for carbocations** (Section 6.11B).

Although alkyl radicals are uncharged, the carbon that bears the odd electron is *electron deficient*. Therefore, alkyl groups attached to this carbon provide a stabilizing effect through hyperconjugation, and the more alkyl groups bonded to it, the more stable the radical is. Thus, the reasons for the relative stabilities of radicals and carbocations are similar.

Solved Problem 9.1

Classify each of the following radicals as being 1°, 2°, or 3°, and rank them in order of decreasing stability.



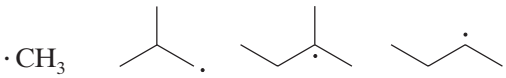
A **B** **C**

Answer

We examine the carbon bearing the unpaired electron in each radical to classify the radical as to its type. **B** is a tertiary radical (the carbon bearing the unpaired electron is tertiary) and is, therefore, most stable. **C** is a primary radical and is least stable. **A**, being a secondary radical, falls in between. The order of stability is **B > A > C**.

Practice Problem 9.1

List the following radicals in order of decreasing stability:



9.3 | REACTIONS OF ALKANES WITH HALOGENS

- Alkanes react with molecular halogens to produce alkyl halides by a **substitution reaction** called **radical halogenation**.

A general reaction showing formation of a monohaloalkane by radical halogenation is shown below. It is called radical halogenation because, as we shall see, the mechanism involves species with unpaired electrons called radicals. This reaction is not a nucleophilic substitution reaction.

$$R{-}H + X_2 \rightarrow R{-}X + HX$$

- A halogen atom replaces one or more of the hydrogen atoms of the alkane, and the corresponding hydrogen halide is formed as a by-product.

Only fluorine, chlorine, and bromine react this way with alkanes. Iodine is essentially unreactive due to unfavorable reaction energetics.

9.3A Multiple Halogen Substitution

One complicating factor of alkane halogenations is that multiple substitutions almost always occur unless we use an excess of the alkane (see Solved Problem 9.2). The following example illustrates this phenomenon. If we mix an

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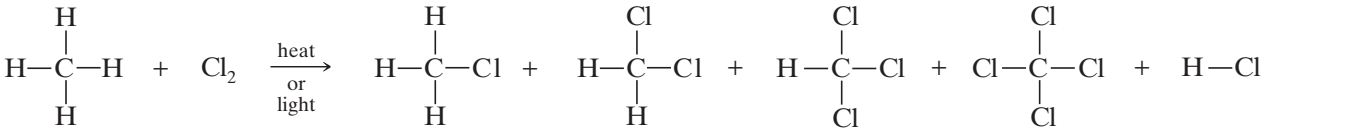
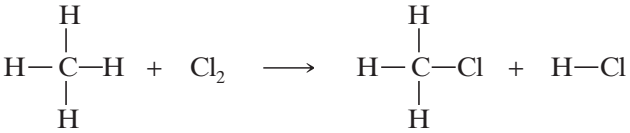
equimolar ratio of methane and chlorine (both substances are gases at room temperature) and then either heat the mixture or irradiate it with light of the appropriate wavelength, a reaction begins to occur vigorously and ultimately produces the following mixture of products:



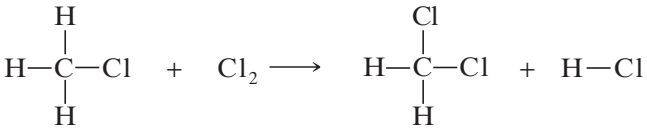
Methane **Chlorine** **Chloromethane** **Dichloromethane** **Trichloromethane** **Tetrachloromethane** **Hydrogen chloride**

(The sum of the number of moles of each chlorinated methane produced equals the number of moles of methane that reacted.)

To understand the formation of this mixture, we need to consider how the concentration of reactants and products changes as the reaction proceeds. At the outset, the only compounds that are present in the mixture are chlorine and methane, and the only reaction that can take place is one that produces chloromethane and hydrogen chloride:



As the reaction progresses, however, the concentration of chloromethane in the mixture increases, and a second substitution reaction begins to occur. Chloromethane reacts with chlorine to produce dichloromethane:



The dichloromethane produced can then react to form trichloromethane, and trichloromethane, as it accumulates in the mixture, can react with chlorine to produce tetrachloromethane. Each time a substitution of —Cl for —H takes place, a molecule of H—Cl is produced.

Solved Problem 9.2

If the goal of a synthesis is to prepare chloromethane (CH_3Cl), its formation can be maximized and the formation of CH_2Cl_2, $CHCl_3$, and CCl_4 minimized by using a large excess of methane in the reaction mixture. Explain why this is possible.

Answer

The use of a large excess of methane maximizes the probability that chlorine will attack methane molecules because the concentration of methane in the mixture will always be relatively large. It also minimizes the probability that chlorine will attack molecules of CH_3Cl, CH_2Cl_2, and $CHCl_3$, because their concentrations will always be relatively small. After the reaction is over, the unreacted excess methane can be recovered and recycled.

9.3B Lack of Chlorine Selectivity

Chlorination of most higher alkanes gives a mixture of isomeric monochlorinated products as well as more highly halogenated compounds.

- Chlorine is relatively ***unselective***; it does not discriminate greatly among the different types of hydrogen atoms (primary, secondary, and tertiary) in an alkane.

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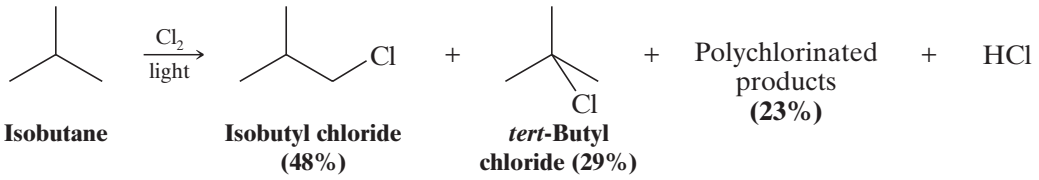
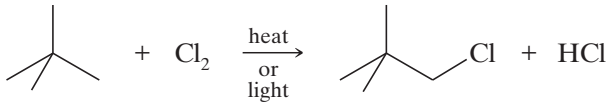
An example is the light-promoted chlorination of isobutane:



Isobutane — **Isobutyl chloride (48%)** — ***tert*-Butyl chloride (29%)**

- Because alkane chlorinations usually yield a complex mixture of products, they are not useful as synthetic methods when the goal is preparation of a specific alkyl chloride.
- An exception is the halogenation of an alkane (or cycloalkane) whose hydrogen atoms *are all equivalent* (i.e., homotopic). [Homotopic hydrogen atoms are defined as those that on replacement by some other group (e.g., chlorine) yield the same compound]

Neopentane, for example, can form only one monohalogenation product, and the use of a large excess of neopentane minimizes polychlorination:



Neopentane (excess) — **Neopentyl chloride**

- Bromine is generally less reactive toward alkanes than chlorine, and bromine is ***more selective*** in the site of attack when it does react.

We shall examine the selectivity of bromination further in Section 9.5A.

9.4 | CHLORINATION OF METHANE: MECHANISM OF REACTION

The reaction of methane with chlorine (in the gas phase) provides a good example for studying the mechanism of radical **halogenation**.

$$CH_4 + Cl_2 \longrightarrow CH_3Cl + HCl \ (+ CH_2Cl_2,\ CHCl_3,\ \text{and}\ CCl_4)$$

Several experimental observations help in understanding the mechanism of this reaction:

1. **The reaction is promoted by heat or light**. At room temperature methane and chlorine do not react at a perceptible rate as long as the mixture is kept away from light. Methane and chlorine do react, however, at room temperature if the gaseous reaction mixture is irradiated with UV light at a wavelength absorbed by Cl_2, and they react in the dark if the gaseous mixture is heated to temperatures greater than 100 °C.
2. **The light-promoted reaction is highly efficient**. A relatively small number of light photons permits the formation of relatively large amounts of chlorinated product.

A mechanism that is consistent with these observations has several steps, shown below. The first step involves the dissociation of a chlorine molecule, by heat or light, into two chlorine atoms. The second step involves hydrogen abstraction by a chlorine atom.

A MECHANISM FOR THE REACTION — Radical Chlorination of Methane

Reaction

$$CH_4 + Cl_2 \xrightarrow[\text{or light}]{\text{heat}} CH_3Cl + HCl$$

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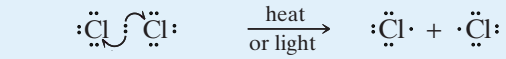
Mechanism

Chain Initiation

Step 1: Halogen dissociation

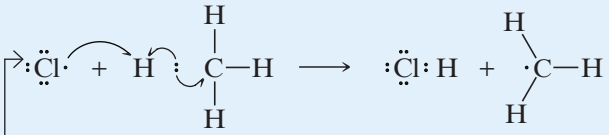


Under the influence of heat or light a molecule of chlorine dissociates; each atom takes one of the bonding electrons.

This step produces two highly reactive chlorine atoms.

Chain Propagation

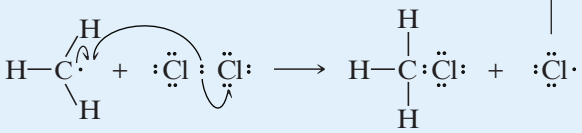
Step 2: Hydrogen abstraction



A chlorine atom abstracts a hydrogen atom from a methane molecule.

This step produces a molecule of hydrogen chloride and a methyl radical.

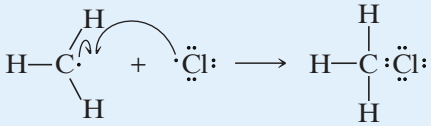
Step 3: Halogen abstraction



A methyl radical abstracts a chlorine atom from a chlorine molecule.

This step produces a molecule of chloromethane and a chlorine atom. The chlorine atom can now cause a repetition of step 2.

Chain Termination



Coupling of any two radicals depletes the supply of reactive intermediates and terminates the chain. Several pairings are possible for radical coupling termination steps (see the text).

In step 3 the highly reactive methyl radical reacts with a chlorine molecule by abstracting a chlorine atom. This results in the formation of a molecule of chloromethane (one of the ultimate products of the reaction) and a *chlorine atom*. The latter product is particularly significant, for the chlorine atom formed in step 3 can attack another methane molecule and cause a repetition of step 2. Then, step 3 is repeated, and so forth, for hundreds or thousands of times. (With each repetition of step 3 a molecule of chloromethane is produced.)

- This type of sequential, stepwise mechanism, in which each step generates the reactive intermediate that causes the next cycle of the reaction to occur, is called a **chain reaction**.

Step 1 is called the **chain-initiating step**. In the chain-initiating step ***radicals are created***. Steps 2 and 3 are called **chain-propagating steps**. In chain-propagating steps ***one radical generates another***.

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Chain Initiation: *creation of radicals*

Step 1 $Cl_2 \xrightarrow[\text{or light}]{\text{heat}} 2Cl\cdot$

Chain Propagation: *reaction and regeneration of radicals*

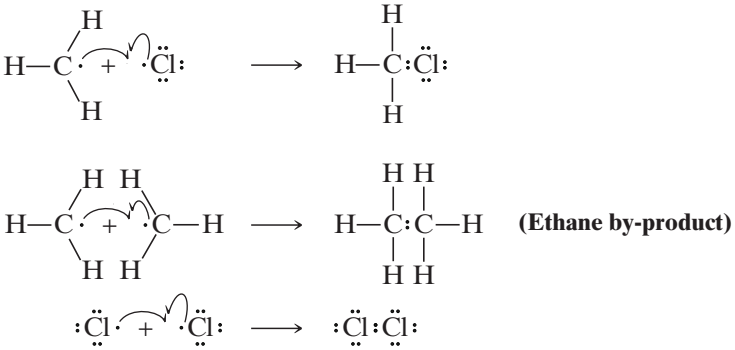
Step 2 $CH_4 + Cl\cdot \longrightarrow \cdot CH_3 + H{-}Cl$

Step 3 $\cdot CH_3 + Cl_2 \longrightarrow CH_3Cl + Cl\cdot$

The chain nature of the reaction accounts for the observation that the light-promoted reaction is highly efficient. The presence of a relatively few atoms of chlorine at any given moment is all that is needed to cause the formation of many thousands of molecules of chloromethane.

What causes the chain reaction to terminate? Why does one photon of light not promote the **chlorination** of all of the methane molecules present? We know that this does not happen because we find that, at low temperatures, continuous irradiation is required or the reaction slows and stops. The answer to these questions is the existence of ***chain-terminating steps***: steps that happen infrequently but occur often enough to *use up one or both of the reactive intermediates*. The continuous replacement of intermediates used up by chain-terminating steps requires continuous irradiation. Plausible chain-terminating steps are as follows.

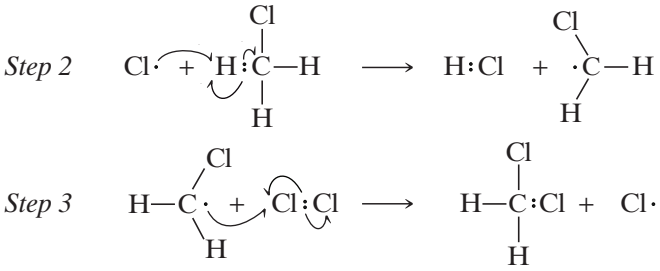
Chain Termination: *consumption of radicals (e.g., by coupling)*



(Ethane by-product)

Our radical mechanism also explains how the reaction of methane with chlorine produces the more highly halogenated products, CH_2Cl_2, $CHCl_3$, and CCl_4 (as well as additional HCl). As the reaction progresses, chloromethane (CH_3Cl) accumulates in the mixture and its hydrogen atoms, too, are susceptible to abstraction by chlorine. Thus chloromethyl radicals are produced that lead to dichloromethane (CH_2Cl_2).

Side Reactions: *multihalogenated by-product formation*



(Dichloromethane)

Then step 2 is repeated, then step 3 is repeated, and so on. Each repetition of step 2 yields a molecule of HCl, and each repetition of step 3 yields a molecule of CH_2Cl_2.

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Solved Problem 9.3

When methane is chlorinated, among the products found are traces of chloroethane. How is it formed? Of what significance is its formation?

Answer

A small amount of ethane is formed by the combination of two methyl radicals:

$$2 \cdot CH_3 \longrightarrow CH{:}CH_3$$

The ethane byproduct formed by coupling then reacts with chlorine in a radical halogenation reaction (see Section 9.5) to form chloroethane.

The significance of this observation is that it is evidence for the proposal that the combination of two methyl radicals is one of the chain-terminating steps in the chlorination of methane.

9.5 | HALOGENATION OF HIGHER ALKANES

Higher alkanes react with halogens by the same kind of **chain mechanism** as those that we have just seen. Ethane, for example, reacts with chlorine to produce chloroethane (ethyl chloride). The mechanism is as follows:

A MECHANISM FOR THE REACTION — Radical Halogenation of Ethane

Chain Initiation

Step 1

$$Cl_2 \xrightarrow[\text{or heat}]{\text{light}} 2\ Cl\cdot$$

Chain Propagation

Step 2

$$CH_3CH_2{:}H + \cdot Cl \longrightarrow CH_3CH_2\cdot + H{:}Cl$$

Step 3

$$CH_3CH_2\cdot + Cl{:}Cl \longrightarrow CH_3CH_2{:}Cl + Cl\cdot$$

Chain propagation continues with steps 2, 3, 2, 3, and so on.

Chain Termination

$$CH_3CH_2\cdot + \cdot Cl \longrightarrow CH_3CH_2{:}Cl$$

$$CH_3CH_2\cdot + \cdot CH_2CH_3 \longrightarrow CH_3CH_2{:}CH_2CH_3$$

$$Cl\cdot + \cdot Cl \longrightarrow Cl{:}Cl$$

Practice Problem 9.2

When ethane is chlorinated, 1,1-dichloroethane and 1,2-dichloroethane, as well as more highly chlorinated ethanes, are formed in the mixture (see Section 9.3A). Write chain reaction mechanisms accounting for the formation of 1,1-dichloroethane and 1,2-dichloroethane.

Chlorination of most alkanes whose molecules contain more than two carbon atoms gives a mixture of isomeric monochloro products (as well as more highly chlorinated compounds). Several examples follow. The percentages given are based on the total amount of monochloro products formed in each reaction.

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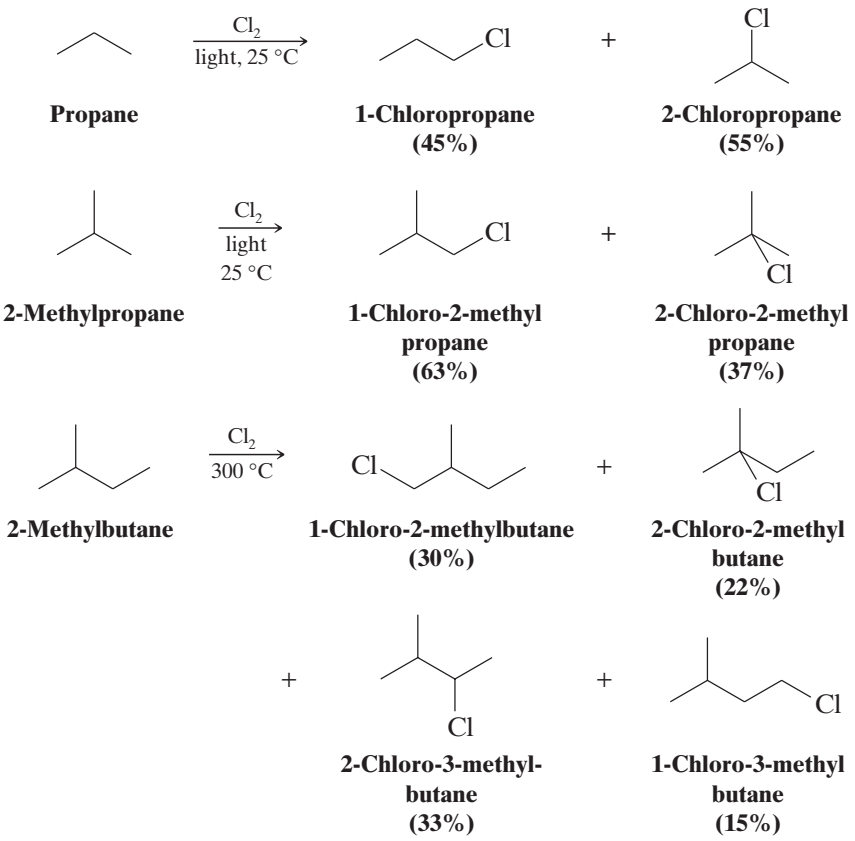
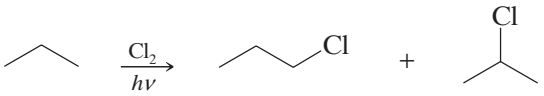
These examples show the nonselectivity of chlorination.



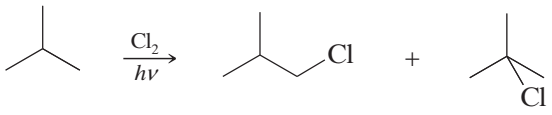
The ratios of products that we obtain from chlorination reactions of higher alkanes are not identical to what we would expect if all the hydrogen atoms of the alkane were equally reactive. We find that there is a correlation between reactivity of different hydrogen atoms and the type of hydrogen atom (1°, 2°, or 3°) being replaced. The tertiary hydrogen atoms of an alkane are most reactive, secondary hydrogen atoms are next most reactive, and primary hydrogen atoms are the least reactive (see Practice Problem 9.3).

Practice Problem 9.3

(a) What percentages of 1-chloropropane and 2-chloropropane would you expect to obtain from the chlorination of propane if 1° and 2° hydrogen atoms were equally reactive?



(b) What percentages of 1-chloro-2-methylpropane and 2-chloro-2-methylpropane would you expect from the chlorination of 2-methylpropane if the 1° and 3° hydrogen atoms were equally reactive?



(c) Compare these calculated answers with the results actually obtained (above in Section 9.5) and justify the assertion that the order of reactivity of the hydrogen atoms is 3° > 2° > 1°.

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We can account for the relative reactivities of the primary, secondary, and tertiary hydrogen atoms in a chlorination reaction on the basis of the homolytic bond dissociation energies we saw earlier (Table 9.1). Of the three types, breaking a tertiary C—H bond requires the least energy, and breaking a primary C—H bond requires the most. Since the step in which the C—H bond is broken (i.e., the hydrogen atom–abstraction step) determines the location or orientation of the chlorination, we would expect the E_{act} for abstracting a tertiary hydrogen atom to be least and the E_{act} for abstracting a primary hydrogen atom to be greatest. Thus tertiary hydrogen atoms should be most reactive, secondary hydrogen atoms should be the next most reactive, and primary hydrogen atoms should be the least reactive.

The differences in the rates with which primary, secondary, and tertiary hydrogen atoms are replaced by chlorine are not large, however.

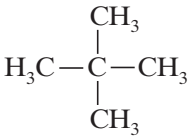
- Chlorine does not discriminate among the different types of hydrogen atoms in a way that makes chlorination of higher alkanes a generally useful laboratory synthesis.

Solved Problem 9.4

An alkane with the formula C_5H_{12} undergoes chlorination to give only one product with the formula $C_5H_{11}Cl$. What is the structure of this alkane?

Answer

The hydrogen atoms of the alkane must all be equivalent (homotopic), so that replacing any one of them leads to the same product. The only five-carbon alkane for which this is true is neopentane.

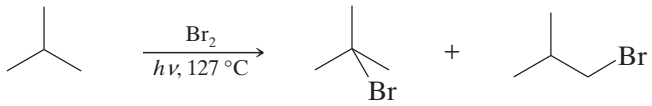


9.5A Selectivity of Bromine

Bromine shows a much greater ability to discriminate among the different types of hydrogen atoms.

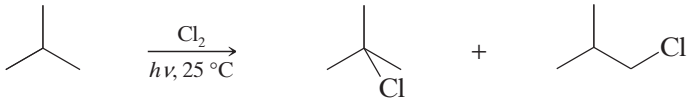
- Bromine is less reactive than chlorine toward alkanes in general but bromine is more *selective* in the site of attack.
- Bromination is selective for substitution where the most stable radical intermediate can be formed.

The reaction of 2-methylpropane and bromine, for example, gives almost exclusive replacement of the tertiary hydrogen atom:



(>99%) **(trace)**

A very different result is obtained when 2-methylpropane reacts with chlorine:



(37%) **(63%)**

Fluorine, being much more reactive than chlorine, *is even less selective than chlorine*. Because the **energy of activation** for the abstraction of any type of hydrogen by a fluorine atom is low, there is very little difference in the rate at which a 1°, 2°, or 3° hydrogen reacts with fluorine. Reactions of alkanes with fluorine give (almost) the distribution of products that we would expect if all of the hydrogens of the alkane were equally reactive.

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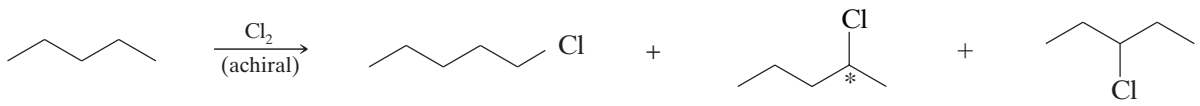
9.6 | REACTIONS THAT GENERATE TETRAHEDRAL CHIRALITY CENTERS

- When **achiral molecules** react to produce a compound with a single tetrahedral **chirality center**, the product will be a **racemic form**.

This will always be true in the absence of any chiral influence on the reaction such as an enzyme or the use of a chiral reagent or solvent.

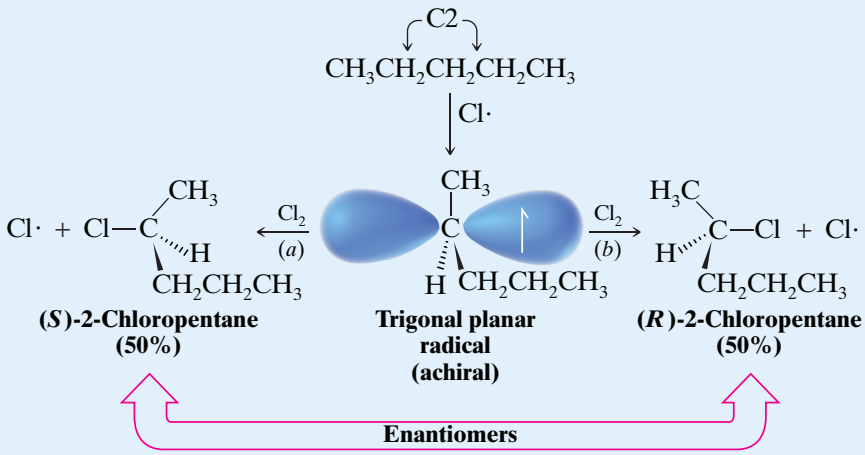
Let us examine a reaction that illustrates this principle, the **radical** chlorination of pentane:



Pentane (achiral) | **1-Chloropentane (achiral)** | **(±)-2-Chloropentane (a racemic form)** | **3-Chloropentane (achiral)**

The reaction will lead to the products shown here, as well as more highly chlorinated products. (We can use an excess of pentane to minimize multiple chlorinations.) Neither 1-chloropentane nor 3-chloropentane contains a chirality center, but 2-chloropentane does, and it is *obtained as a racemic form*. If we examine the mechanism we shall see why.

A MECHANISM FOR THE REACTION — The Stereochemistry of Chlorination at C2 of Pentane



Abstraction of a hydrogen atom from C2 produces a trigonal planar radical that is achiral. This radical then reacts with chlorine at either face [by path (*a*) or path (*b*)]. Because the radical is achiral, the probability of reaction by either path is the same; therefore, the two enantiomers are produced in equal amounts, and a racemic form of 2-chloropentane results.

We can also say that the C2 hydrogens of pentane are **enantiotopic** because enantiomers are formed by reaction at each C2 hydrogen.

9.6A Generation of a Second Chirality Center in a Radical Halogenation

Let us now examine what happens when a chiral molecule (containing one chirality center) reacts so as to yield a product with a second chirality center. As an example consider what happens when (*S*)-2-chloropentane undergoes chlorination at C3 (other products are formed, of course, by chlorination at other carbon atoms). The results of chlorination at C3 are shown in the box below.

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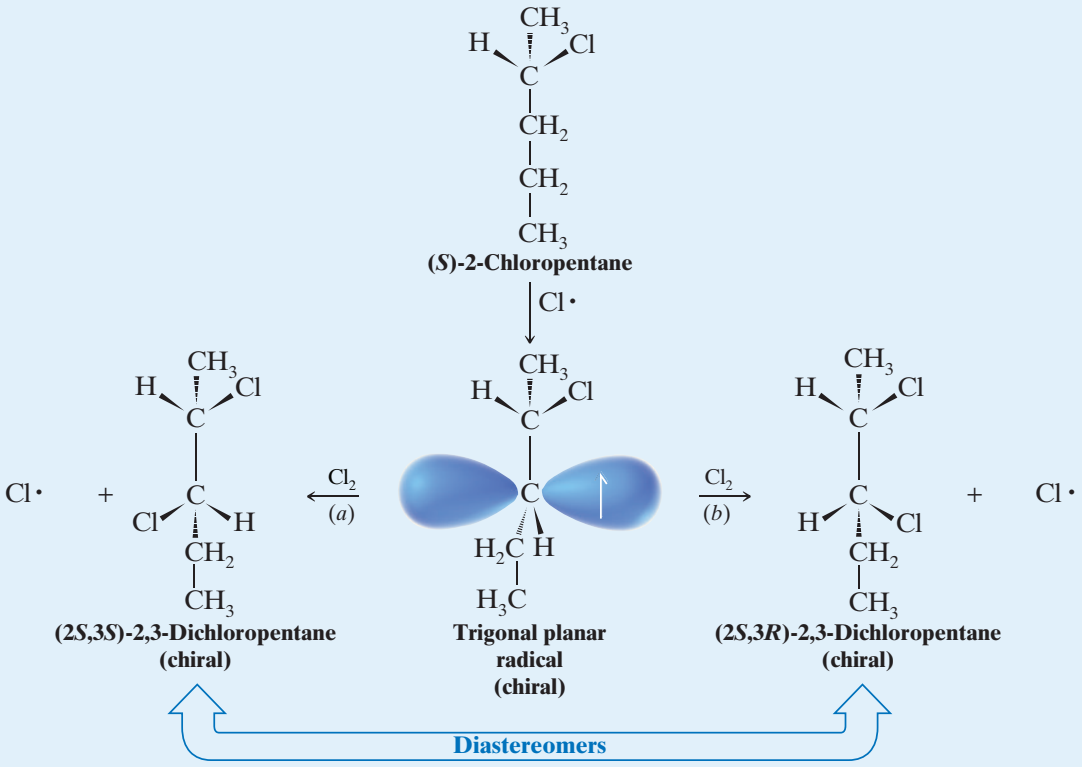
The products of the reactions are (2*S*,3*S*)-2,3-dichloropentane and (2*S*,3*R*)-2,3-dichloropentane. These two compounds are **diastereomers**. (They are stereoisomers but they are not mirror images of each other.) They each resulted by substitution of one of the **diastereotopic** hydrogens at C3. The two diastereomers are *not* produced in equal amounts. Because the intermediate radical itself is chiral, reactions at the two faces are not equally likely. The radical reacts with chlorine to a greater extent at one face than the other (although we cannot easily predict which). That is, the presence of a chirality center in the radical (at C2) influences the reaction that introduces the new chirality center (at C3).

Both of the 2,3-dichloropentane diastereomers are chiral and, therefore, each exhibits optical activity. Moreover, because the two compounds are *diastereomers*, they have different physical properties (e.g., different melting points and boiling points) and are separable by conventional means (by gas chromatography or by careful fractional distillation).

A MECHANISM FOR THE REACTION — The Stereochemistry of Chlorination at C3 of (*S*)-2-Chloropentane



Abstraction of a hydrogen atom from C3 of (*S*)-2-chloropentane produces a radical that is chiral (it contains a chirality center at C2). This chiral radical can then react with chlorine at one face [path (a)] to produce (2*S*, 3*S*)-2,3-dichloropentane and the other face [path (b)] to yield (2*S*, 3*R*)-2,3-dichloropentane. These two compounds are diastereomers, and they are not produced in equal amounts. Each product is chiral, and each alone would be optically active.

Practice Problem 9.4

Consider the chlorination of (*S*)-2-chloropentane at C4. **(a)** Write structural formulas for the products, showing three dimensions at all chirality centers. Give each its proper (*R*,*S*) designation. **(b)** What is the stereoisomeric relationship between these products? **(c)** Are both products chiral? **(d)** Are both optically active? **(e)** Could the products be separated by conventional means? **(f)** What other dichloropentanes would be obtained by chlorination of (*S*)-2-chloropentane? **(g)** Which of these are optically active?

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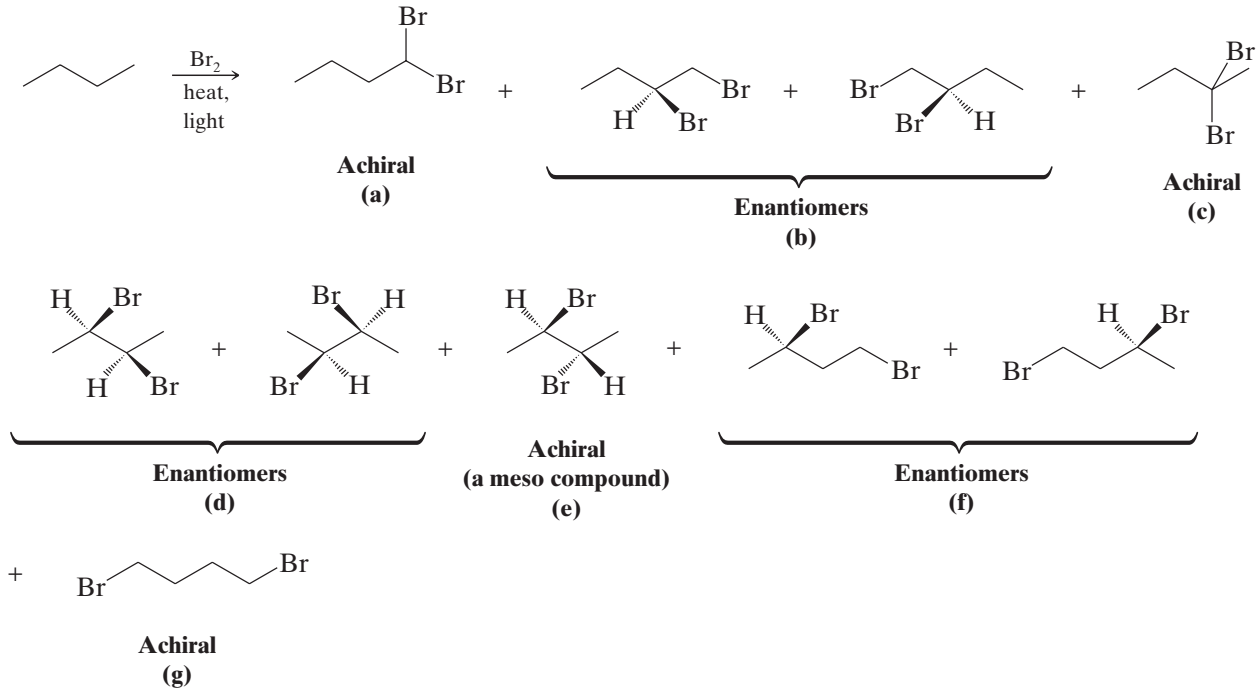
Solved Problem 9.5

Consider the bromination of butane using sufficient bromine to cause dibromination. After the reaction is over, you separate all the dibromobutane isomers by gas chromatography or by fractional distillation. How many fractions would you obtain, and what compounds would the individual fractions contain? Which if any of the fractions would be optically active?

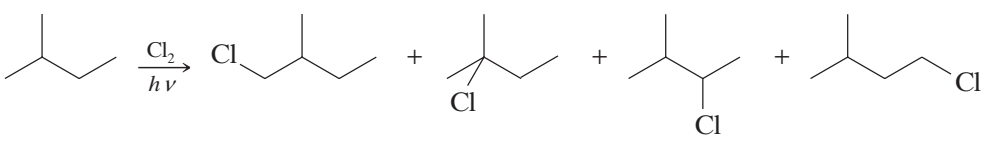
Answer

The construction of handheld models will help in solving this problem. First, decide how many constitutional isomers are possible by replacing two hydrogens of butane with two bromine atoms. There are six: 1,1-dibromobutane, 1,2-dibromobutane, 2,2-dibromobutane, 2,3-dibromobutane, 1,3-dibromobutane, and 1,4-dibromobutane. Then recall that constitutional isomers have different physical properties (i.e., boiling points and retention times in a gas chromatograph), so there should be at least six fractions. In actuality there are seven. See fractions **(a)**–**(g)** below. We soon see why there are seven fractions if we examine each constitutional isomer looking for chirality centers and stereoisomers. Isomers **(a)**, **(c)**, and **(g)** have no chirality centers and are, therefore, achiral and are optically inactive. 1,2-Dibromobutane in fraction **(b)** and 1,4-dibromobutane in fraction **(f)** each have one chirality center and, because there is no chiral influence on the reaction, they will be formed as a 50:50 mixture of enantiomers (a racemate). A racemate cannot be separated by distillation or conventional gas chromatography; therefore, fractions **(b)** and **(f)** will not be optically active. 2,3-Dibromobutane has two chirality centers and will be formed as a racemate [fraction **(d)**] and as a meso compound, fraction **(e)**. Both fractions will be optically inactive. The meso compound is a diastereomer of the enantiomers in fraction **(d)** (and has different physical properties from them); therefore, it is separated from them by distillation or gas chromatography.



Practice Problem 9.5

Consider the monochlorination of 2-methylbutane.



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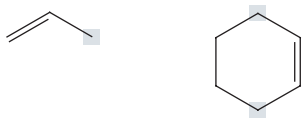
(a) Assuming that the product mixture was subjected to fractional distillation, which fractions, if any, would show optical activity? **(b)** Could any of these fractions be resolved, theoretically, into enantiomers?

9.7 | ALLYLIC SUBSTITUTION AND ALLYLIC RADICALS

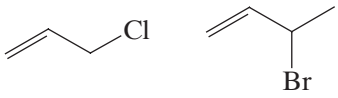
- An atom or group that is bonded to an sp^3-hybridized carbon adjacent to an alkene double bond is called an **allylic group**. The group is said to be bonded at the **allylic position**.

The following are some examples.

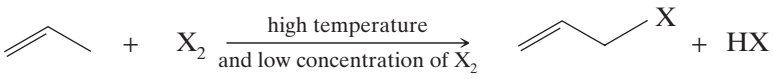
The hydrogen atoms bonded to the highlighted carbons below are allylic hydrogens.



The chlorine and bromine atoms below are bonded at allylic positions.



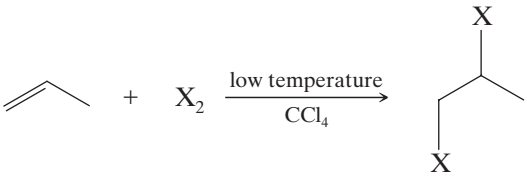
Allylic hydrogens are especially reactive in radical substitution reactions. We can synthesize allylic halides by substitution of allylic hydrogens. For example, when propene reacts with bromine or chlorine at high temperatures or under radical conditions where the concentration of the halogen is small, the result is **allylic substitution**.



Propene

At high temperature (or in the presence of a radical initiator) and low concentration of X_2 a substitution reaction occurs.

On the other hand, when propene reacts with bromine or chlorine at low temperatures, an addition reaction of the type we studied in Chapter 8 occurs.

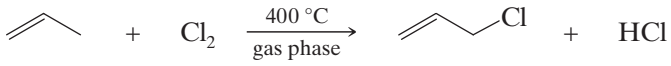


At low temperature an addition reaction occurs.

To bias the reaction toward allylic substitution we need to use reaction conditions that favor formation of radicals and that provide a low but steady concentration of halogen.

9.7A Allylic Chlorination (High Temperature)

Propene undergoes allylic chlorination when propene and chlorine react in the gas phase at 400 °C.



Propene **3-Chloropropene (allyl chloride)**

The mechanism for allylic substitution is the same as the chain mechanism for alkane **halogenations** that we saw earlier in the chapter. In the chain-initiating step, the chlorine molecule dissociates into chlorine atoms.

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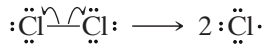
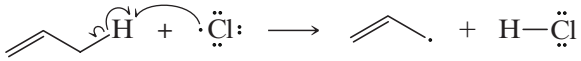
Chain-Initiating Step



In the first chain-propagating step the chlorine atom abstracts one of the allylic hydrogen atoms. The radical that is produced in this step is called an **allylic radical**.

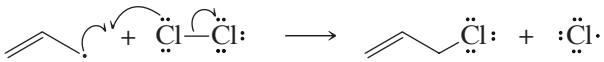
First Chain-Propagating Step



An allylic radical

In the second chain-propagating step the allyl radical reacts with a molecule of chlorine.

Second Chain-Propagating Step



Allyl chloride

This step results in the formation of a molecule of allyl chloride (2-chloro-1-propene) and a chlorine atom. The chlorine atom then brings about a repetition of the first chain-propagating step. The chain reaction continues until the usual chain-terminating steps (see Section 9.4) consume the radicals.

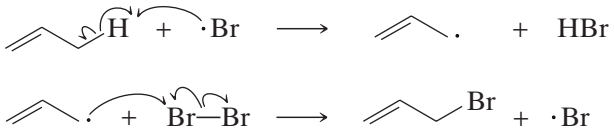
9.7B Allylic Bromination with *N*-Bromosuccinimide (Low Concentration of Br_2)

Propene undergoes allylic bromination when it is treated with *N*-bromosuccinimide (NBS) in the presence of peroxides or light:

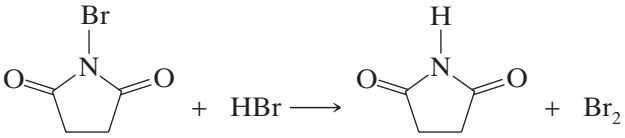


***N*-Bromosuccinimide (NBS)** | **3-Bromopropene (allyl bromide)** | **Succinimide**

The reaction is initiated by the formation of a small amount of Br· (possibly formed by dissociation of the N—Br bond of the NBS). The main propagation steps for this reaction are the same as for allylic chlorination (Section 9.2A):



N-Bromosuccinimide is a solid that provides a constant but very low concentration of bromine in the reaction mixture. It does this by reacting very rapidly with the HBr formed in the substitution reaction. Each molecule of HBr is replaced by one molecule of Br_2.



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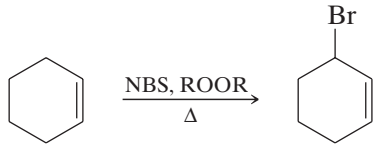
Under these conditions, that is, *in a nonpolar solvent and with a very low concentration of bromine*, very little bromine adds to the double bond; it reacts by substitution and replaces an allylic hydrogen atom instead.

The following reaction with cyclohexene is another example of allylic bromination with NBS:

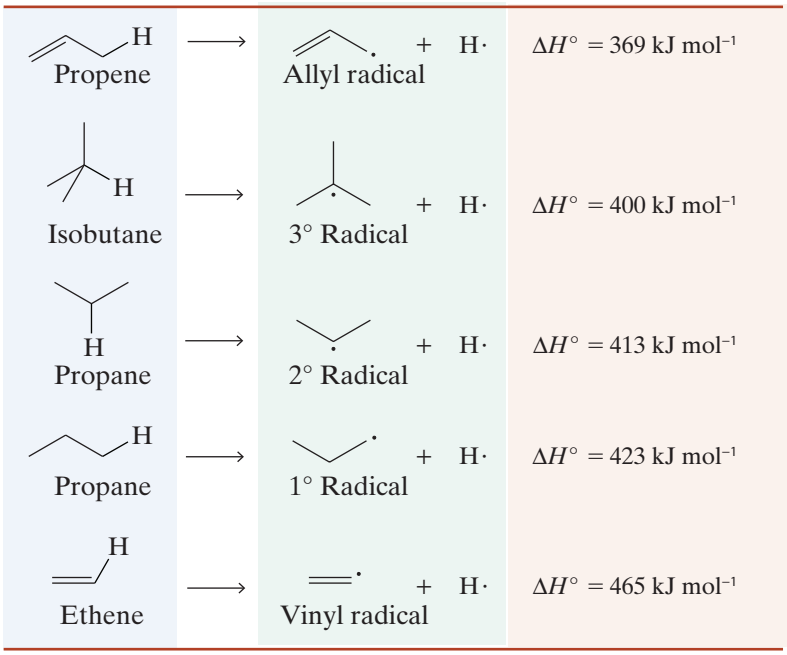


82–87%

- In general, NBS is a good reagent to use for allylic bromination.

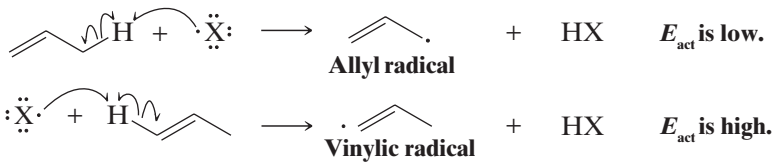
9.7C Allylic Radicals Are Stabilized by Electron Delocalization

Let us examine the bond dissociation energy of an allylic carbon–hydrogen bond and compare it with the bond dissociation energies of other carbon–hydrogen bonds.



See Table 9.1 for a list of additional bond dissociation energies.

We see that an allylic carbon–hydrogen bond of propene is broken with greater ease than even the tertiary carbon–hydrogen bond of isobutane and with far greater ease than a vinylic carbon–hydrogen bond:



- The ease with which an allylic carbon–hydrogen bond is broken means that relative to primary, secondary, tertiary, and vinylic free radicals an allylic radical is the *most stable* (Fig. 9.2):

Relative stability: allylic or allyl > 3° > 2° > 1° > vinyl or vinylic

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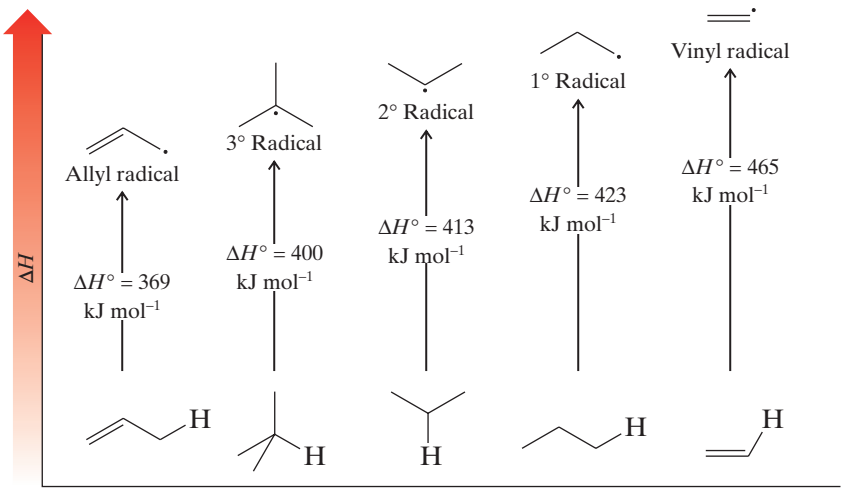


Figure 9.2 The relative stability of the allyl radical compared to 1°, 2°, 3°, and vinyl radicals. (The stabilities of the radicals are relative to the hydrocarbon from which each was formed, and the overall order of stability is allyl > 3° > 2° > 1° > vinyl.)

The reason that allylic radicals are more stable than alkyl radicals is due to electron delocalization. For example, we can draw the following contributing resonance structures and the corresponding resonance hybrid for the allylic radical from propene.



Contributing Resonance Structures



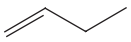
Resonance Hybrid

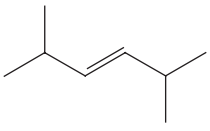
Resonance delocalization of allylic radicals means that bonding of the halogen can occur at either end of an allylic radical. With the allylic radical from propene the two possible substitutions are the same, but unsymmetrical allylic radicals lead to products that are constitutional isomers.

Practice Problem 9.6

(a) What monobromo allylic substitution products would result from reaction of each of the following compounds with NBS in the presence of peroxides and/or light? **(b)** In the case of isomeric products for any reaction, which would you predict to be the most stable based on the double bond in the product? **(c)** Draw the resonance hybrid(s) for the allylic radical that would be involved in each reaction.

(i) 

(ii) 

(iii) 

9.8 | BENZYLIC SUBSTITUTION AND BENZYLIC RADICALS

- An atom or group bonded to an sp^3-hybridized carbon adjacent to a benzene ring is called a **benzylic group**. The group is said to be bonded at the **benzylic position**.

The following are some examples.

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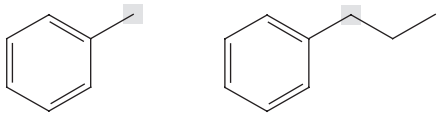
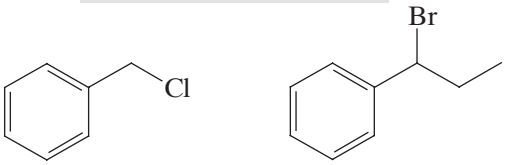
The hydrogen atoms bonded at the highlighted carbons are benzylic hydrogens.

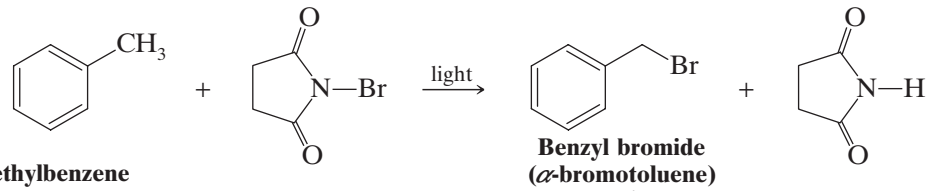


The chlorine and bromine atoms are bonded at benzylic positions.



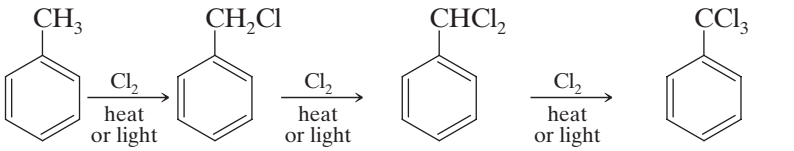
Benzylic hydrogens are even more reactive than allylic hydrogens in radical substitution reactions due to the additional delocalization that is possible for a benzylic radical intermediate (see Practice Problem 9.7).

When methylbenzene (toluene) reacts with *N*-bromosuccinimide (NBS) in the presence of light, for example, the major product is benzyl bromide. *N*-Bromosuccinimide furnishes a low concentration of Br_2, and the reaction is analogous to that for allylic bromination that we studied in Section 9.7B.



Methylbenzene (Toluene) **NBS** **Benzyl bromide (α-bromotoluene) (64%)**

Benzylic chlorination of methylbenzene takes place in the gas phase at 400–600 °C or in the presence of UV light. When an excess of chlorine is used, multiple chlorinations of the side chain occur:



Benzyl chloride **Dichloromethyl benzene** **Trichloromethyl benzene**

These halogenations take place through the same radical mechanism we saw for alkanes in Section 9.4. The halogens dissociate to produce halogen atoms and then the halogen atoms initiate chain reactions by abstracting hydrogens of the methyl group.

Practice Problem 9.7

Benzylic radicals, due to the adjacent benzene ring, have even greater possibility for delocalization than allylic radicals. Draw contributing resonance structures that show this delocalization for the benzylic radical derived from methylbenzene. (*Hint:* There are four contributing resonance structures for this benzylic radical.)

The greater stability of benzylic radicals accounts for the fact that when ethylbenzene is halogenated, the major product is the 1-halo-1-phenylethane. The benzylic radical is formed much faster than the 1° radical:

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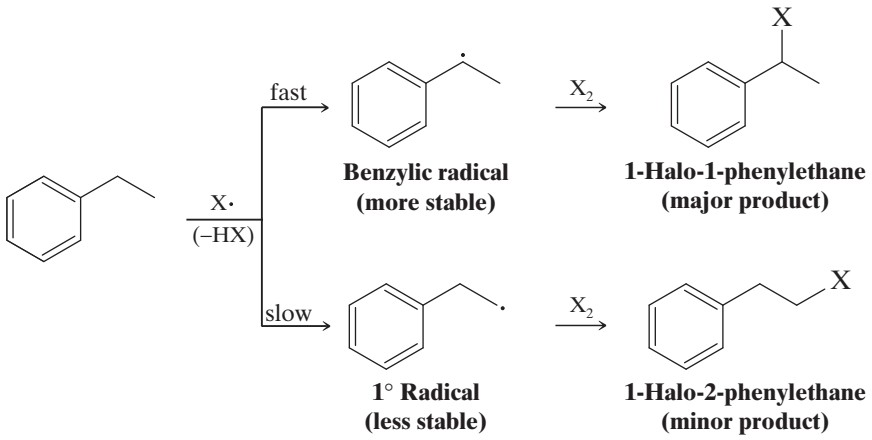


Practice Problem 9.8

When propylbenzene reacts with chlorine in the presence of UV radiation, the major product is 1-chloro-1-phenylpropane. Both 2-chloro-1-phenylpropane and 3-chloro-1-phenylpropane are minor products. Write the structure of the radical leading to each product and account for the fact that 1-chloro-1-phenylpropane is the major product.

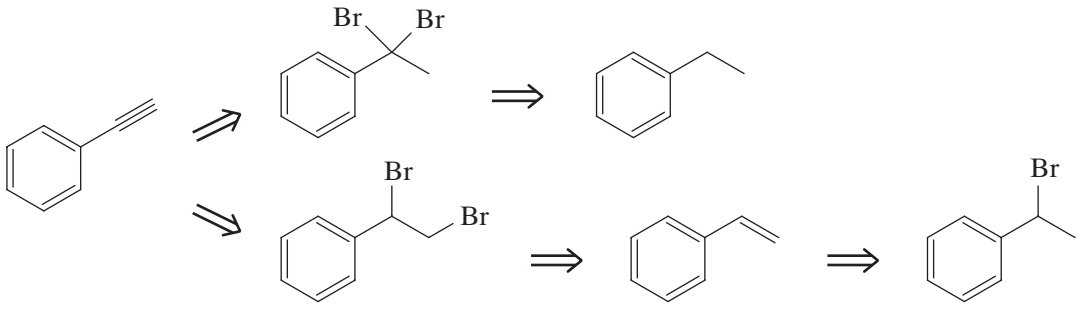
Benzylic halogenation is useful for introducing a leaving group where none may have been present before. Consider the following solved problem regarding multistep synthesis, where introduction of a leaving group is a necessary step.

Solved Problem 9.6

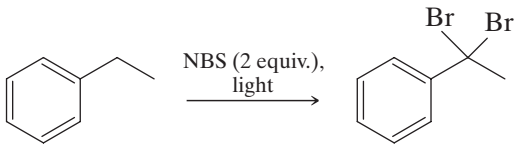
Show how phenylacetylene ($C_6H_5C{\equiv}CH$) could be synthesized from ethylbenzene (phenylethane). Begin by writing a retrosynthetic analysis, and then write reactions needed for the synthesis.

Answer

Working backward, that is, using *retrosynthetic analysis*, we find that we can easily envision two syntheses of phenylacetylene. We can make phenylacetylene by dehydrohalogenation of 1,1-dibromo-1-phenylethane, which could have been prepared by allowing ethylbenzene (phenylethane) to react with 2 mol of NBS. Alternatively, we can prepare phenylacetylene from 1,2-dibromo-1-phenylethane, which could be prepared from styrene (phenylethene). Styrene can be made from 1-bromo-1-phenylethane, which can be made from ethylbenzene.



Following are the synthetic reactions we need for the two retrosynthetic analyses above:



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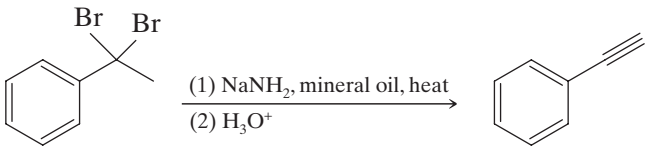

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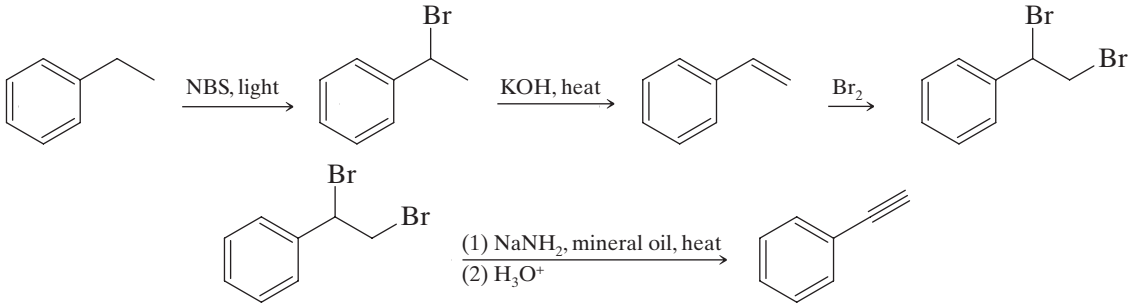


Practice Problem 9.9

Show how the following compounds could be synthesized from phenylacetylene ($C_6H_5C{\equiv}CH$): **(a)** 1-phenylpropyne, **(b)** 1-phenyl-1-butyne, **(c)** (*Z*)-1-phenylpropene, and **(d)** (*E*)-1-phenylpropene. Begin each synthesis by writing a retrosynthetic analysis.

9.9 | RADICAL ADDITION TO ALKENES: THE ANTI-MARKOVNIKOV ADDITION OF HYDROGEN BROMIDE

Before 1933, the orientation of the addition of hydrogen bromide to alkenes was the subject of much confusion. At times addition occurred in accordance with Markovnikov's rule; at other times it occurred in just the opposite manner. Many instances were reported where, under what seemed to be the same experimental conditions, Markovnikov additions were obtained in one laboratory and anti-Markovnikov additions in another. At times even the same chemist would obtain different results using the same conditions but on different occasions.

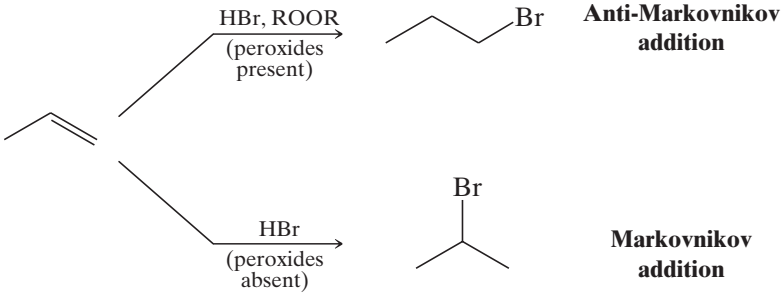
The mystery was solved in 1933 by the research of M. S. Kharasch and F. R. Mayo (of the University of Chicago). The explanatory factor turned out to be organic peroxides present in the alkenes—peroxides that were formed by the action of atmospheric oxygen on the alkenes.



An organic peroxide **An organic hydroperoxide**

- When alkenes containing peroxides or hydroperoxides react with hydrogen bromide, anti-Markovnikov addition of HBr occurs.

For example, in the *presence* of peroxides propene yields 1-bromopropane. In the *absence* of peroxides, or in the presence of compounds that "trap" radicals, normal Markovnikov addition occurs.



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- Hydrogen bromide is the only hydrogen halide that gives anti-Markovnikov addition when peroxides are present.

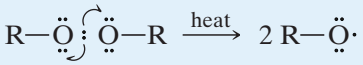
Hydrogen fluoride, hydrogen chloride, and hydrogen iodide *do not* give anti-Markovnikov addition even when peroxides are present.

The mechanism for **anti-Markovnikov addition of hydrogen bromide** is a **radical chain reaction** initiated by peroxides.

A MECHANISM FOR THE REACTION — Anti-Markovnikov Addition of HBr

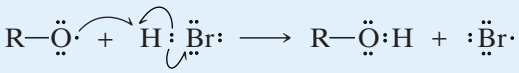
Chain Initiation

Step 1



Heat brings about homolytic cleavage of the weak oxygen–oxygen bond.

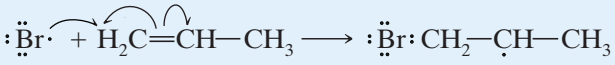
Step 2



The alkoxyl radical abstracts a hydrogen atom from HBr, producing a bromine radical.

Chain Propagation

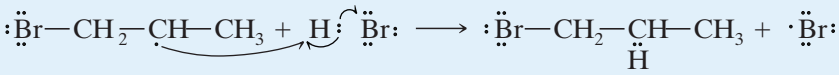
Step 3



2° Radical

A bromine radical adds to the double bond to produce the more stable 2° alkyl radical.

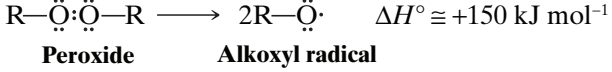
Step 4



1-Bromopropane

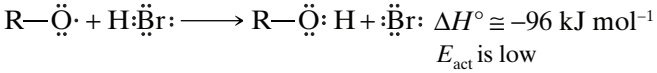
The alkyl radical abstracts a hydrogen atom from HBr. This leads to the product and regenerates a bromine radical. Then repetitions of steps 3 and 4 lead to a chain reaction.

Step 1 is the simple homolytic cleavage of the peroxide molecule to produce two alkoxyl radicals. The oxygen–oxygen bond of peroxides is weak, and such reactions are known to occur readily:

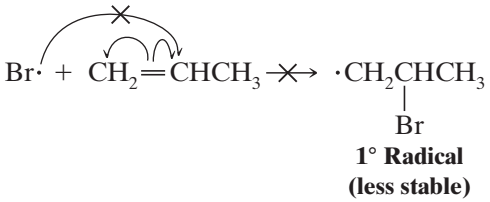


Peroxide **Alkoxyl radical**

Step 2 of the mechanism, abstraction of a hydrogen atom by the radical, is exothermic and has a low energy of activation:



Step 3 of the mechanism determines the final orientation of bromine in the product. It occurs as it does because a *more stable secondary radical* is produced and because *attack at the primary carbon atom is less hindered*. Had the bromine attacked propene at the secondary carbon atom, a less stable, primary radical would have been the result,



1° Radical (less stable)

and attack at the secondary carbon atom would have been more hindered.

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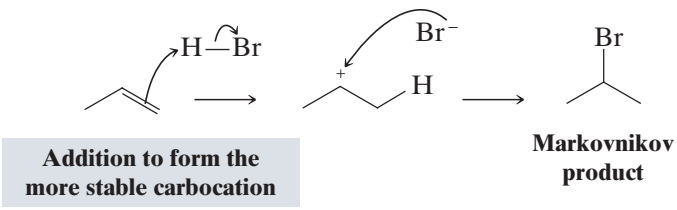
Step 4 of the mechanism is simply the abstraction of a hydrogen atom from hydrogen bromide by the radical produced in step 3. This hydrogen atom abstraction produces a bromine atom (which, of course, is a radical due to its unpaired electron) that can bring about step 3 again; then step 4 occurs again—a chain reaction.

9.9A Summary of Markovnikov versus Anti-Markovnikov Addition of HBr to Alkenes

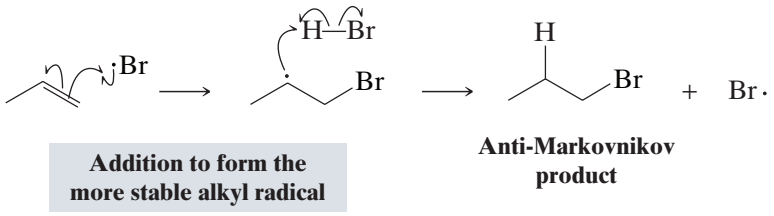
We can now see the contrast between the two ways that HBr can add to an alkene. In the *absence* of peroxides, the reagent that attacks the double bond first is a proton. Because a proton is small, steric effects are unimportant. It attaches itself to a carbon atom by an ionic mechanism so as to form the more stable carbocation. The result is Markovnikov addition. Polar, protic solvents favor this process.

Ionic Addition



In the *presence* of peroxides, the reagent that attacks the double bond first is the larger bromine atom. It attaches itself to the less hindered carbon atom by a radical mechanism, so as to form the more stable radical intermediate. The result is anti-Markovnikov addition. Nonpolar solvents are preferable for reactions involving radicals.

Radical Addition



9.10 | OTHER IMPORTANT RADICAL REACTIONS

Radical mechanisms are important in understanding many other organic reactions. We shall see other examples in later chapters, but let us examine a few important radicals and radical reactions here: oxygen and superoxide, the combustion of alkanes, DNA cleavage, autoxidation, antioxidants, and some reactions of chlorofluoromethanes that have threatened the protective layer of ozone in the stratosphere.

9.10A Reaction Involving Free Radicals – Dimerization

Given below are some reactions involving free radicals.

1. Pinacol formation.
2. Wurtz reaction.
3. Intramolecular Wurtz reaction.
4. Fittig reaction.
5. Wurtz–Fittig reaction.
6. Ullmann reaction.
7. Frankland reaction.
8. Kolbe's electrolysis.
9. Intramolecular Kolbe's reaction.
10. Acyloin condensation.

Each of these reactions is discussed as follows:

1. **Pinacol formation:** A simple example of pinacol formation is as follows:

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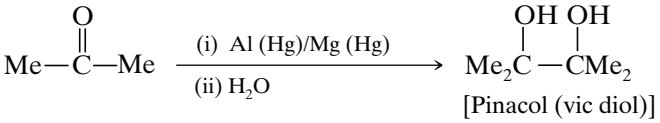
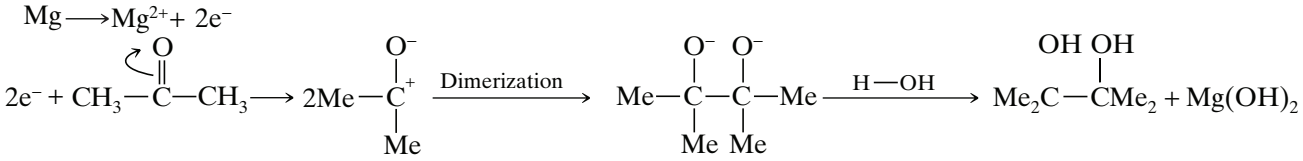
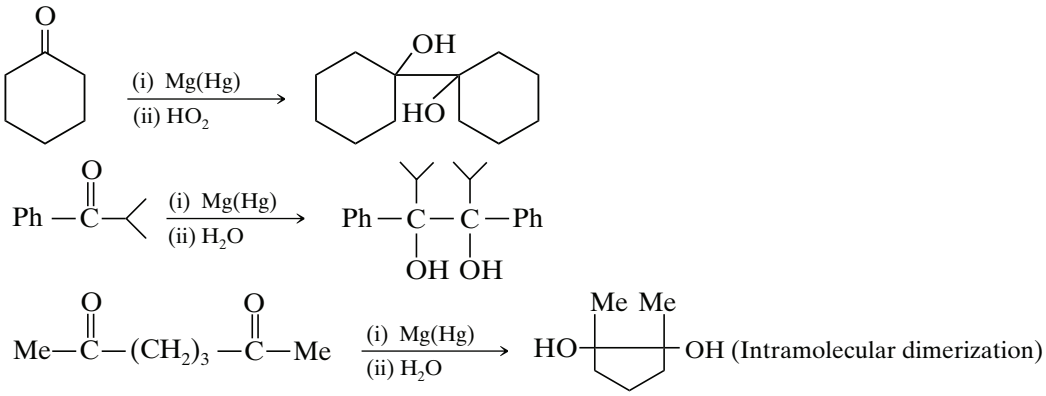


Benzene or ether is used as solvent in the above reaction.

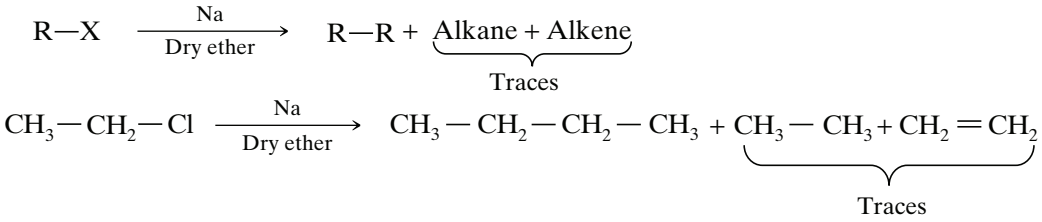
Mechanism: The mechanism of reaction is explained below:



Some examples of pinacol formation reaction are as follows:

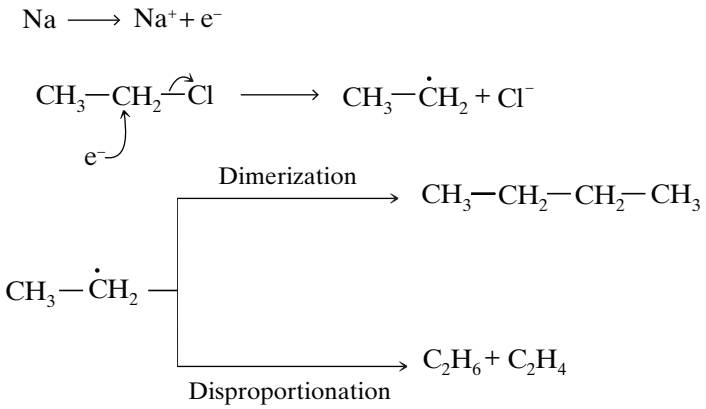


2. **Wurtz reaction:** Formation of higher alkanes from alkyl halides in the presence of sodium and dry ether is named Wurtz reaction.



This reaction may proceed involving free radical as well as ionic mechanisms.

(a) Free radicals mechanism:



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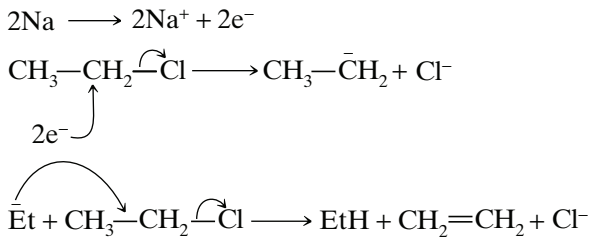
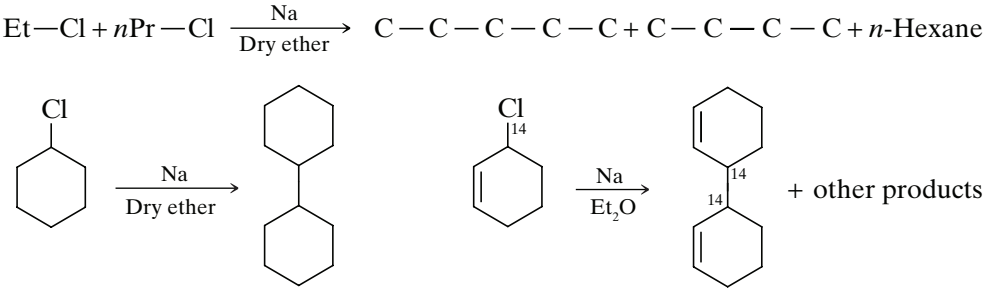
(b) Ionic mechanism:

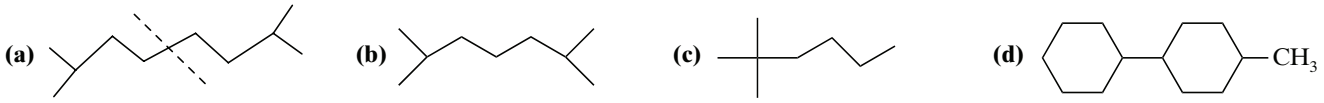


Some examples of this reaction are as follows:



Solved Problem 9.7

Which of the following alkanes would be produced in high yield in Wurtz reaction?



Answer

The Compound **(a)** will be produced in high yield. The other alkanes will be obtained in form of a mixture.

Solved Problem 9.8

Can methane (CH_4) be prepared by Wurtz reaction?

Answer

Methane cannot be prepared by Wurtz reaction

The characteristics of Wurtz reaction are as follows:

(a) Methane cannot be prepared by this method.
(b) The best yield is of a symmetrical alkane, such as *n*-butane, which is the favoured product of this reaction.
(c) When two different alkyl halides undergo Wurtz reaction, three products are expected to form.

The following points are worth noting:

(a) We cannot use those alkyl halides that contain an acidic hydrogen because in that case an intramolecular substitution reaction will take place.
(b) The dimerization product is the major product due to zero activation energy.
(c) The dimerization product is the minor product because of steric hindrance in tertiary free radicals.

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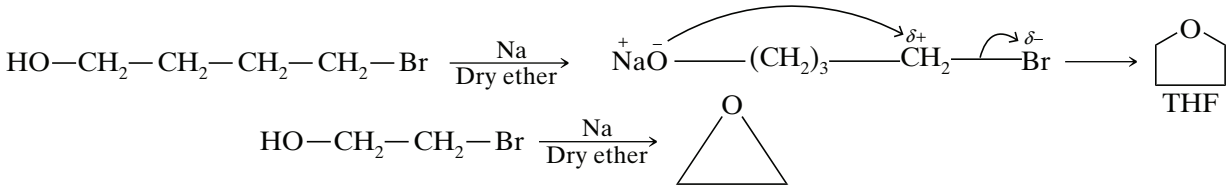
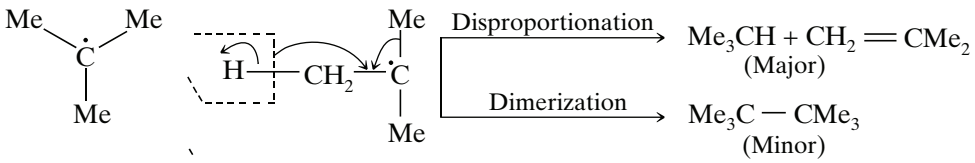
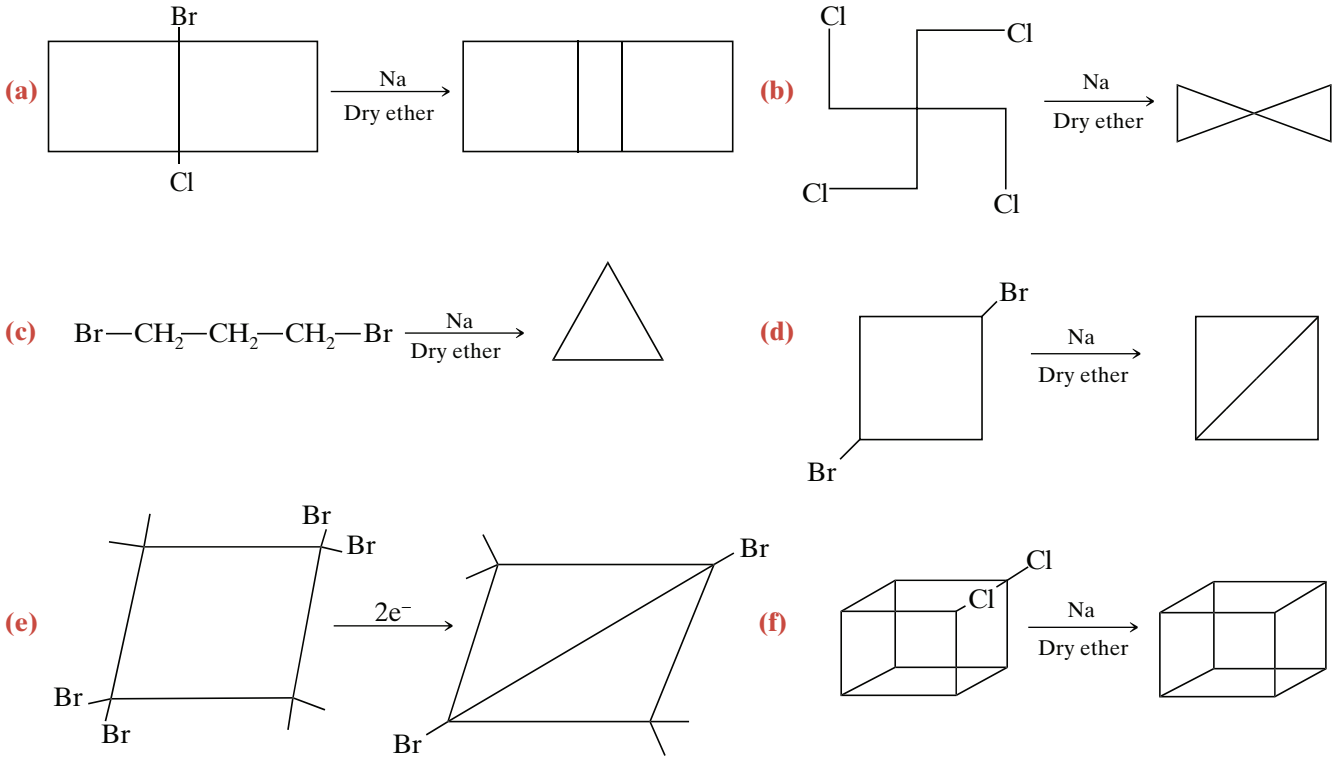
Some other examples are as follows:



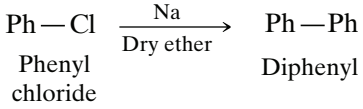


$$K_{Disproportionation} \cong 2K_{Dimerization}$$

3. **Intramolecular Wurtz reaction:** When the nucleophile and alkyl halide are present in the same compound, the compound is unstable because the two groups undergo intramolecular reaction. The following examples show this reaction:



4. **Fittig reaction:** This reaction is analogous to Wurtz reaction except that it involves aryl halides in place of alkyl halides. It is used for the preparation of biaryls. For example,



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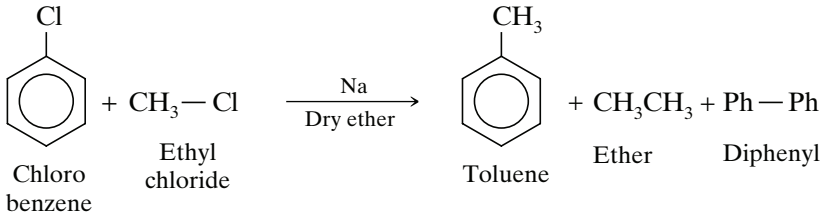
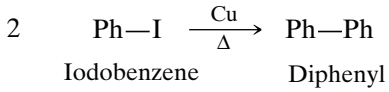
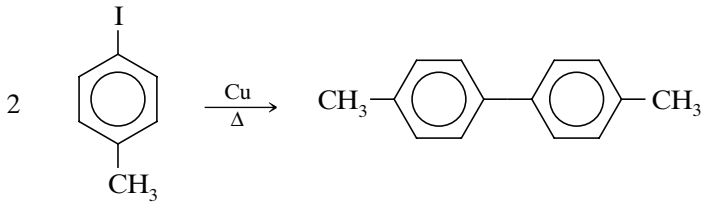
5. **Wurtz–Fittig reaction:** This reaction combines Wurtz and Fittig reactions; consists of treating a mixture of an alkyl halide and an aryl halide with sodium in presence of dry ether as the reaction medium. It is used for the preparation of arenes.

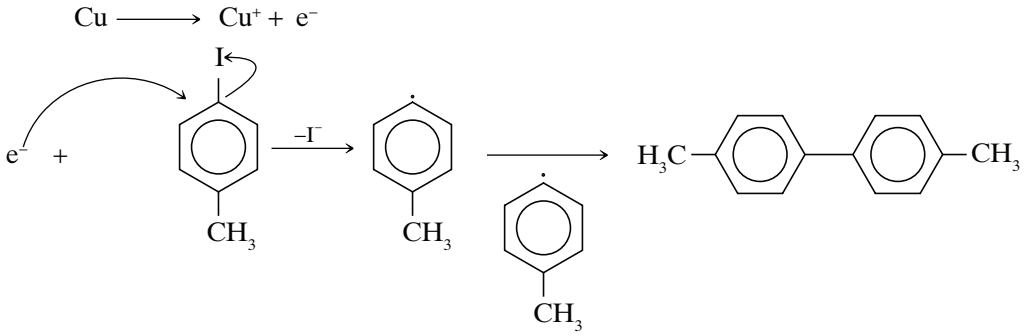


6. **Ullmann reaction:** Synthesis of biaryls by heating aryl iodides with copper powder in a sealed tube is named as Ullmann reaction. For example,

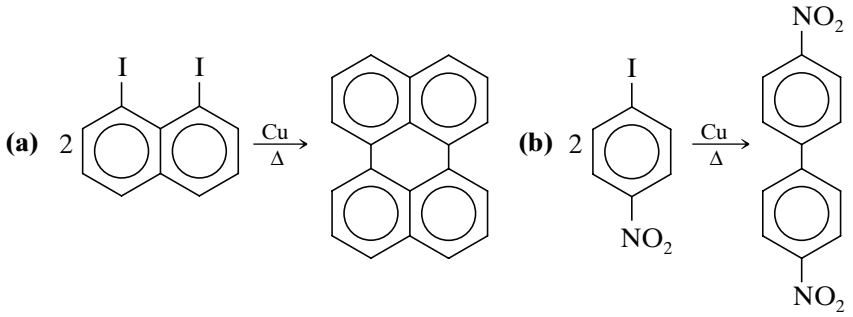




The mechanism of the reaction may be given as follows:



The reaction takes place at approximately 300°C. Some other examples of Ullmann reaction are as follows:



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7. **Frankland reaction:** Formation of alkenes by heating alkyl iodides with zinc is named as Frankland reaction.

The mechanism of the reaction is as follows:

$$R{-}I \xrightarrow[\Delta]{Zn} R{-}R$$

$$Zn \longrightarrow Zn^{2+} + 2e^-$$

$$2e^- + R{-}X \xrightarrow[-X^-]{} R^- + R{-}X^- \longrightarrow R{-}R + X^-$$

8. **Kolbe's electrolytic reaction:** The Kolbe's electrolytic reaction involves the electrolysis of a concentrated solution of sodium potassium salt of a carboxylic acid, leading to the formation of alkane.

$$2CH_3{-}CH_2{-}\overset{\overset{O}{\|}}{C}{-}O^-K^+ \xrightarrow{\text{Electrolysis}} CH_3{-}CH_2{-}CH_2{-}CH_3 + CH_3{-}CH_3 + H_2C{=}CH_2 + \overset{\overset{O}{\|}}{Et{-}C{-}O{-}Et}$$

K-propionate

At anode (oxidation)

$$Et{-}COO^- \longrightarrow Et{-}\overset{\overset{O}{\|}}{C}{-}\dot{O} + \dot{e} \longrightarrow \dot{E}t + CO_2$$

$$Et{-}Et \xleftarrow{\text{Dimerization}} \dot{E}t + CO_2 \xrightarrow{\text{Disproportionation}} CH_2{=}CH_2 + CH_3{-}CH_3$$

At cathode:

$$2H_2O + 2e^- \longrightarrow 2\,OH^- + H_2$$

The main characteristics of Kolbe's electrolysis are as follows:

(a) As the reaction proceeds in the forward direction, the pH will increase because of the formation of a strong base.
(b) Methane cannot be prepared by this method.
(c) Normal alkanes having even number of carbon atoms are obtained in good yield by this method.
(d) Normal alkane having odd number of carbon atoms are obtained in poor yield.

The example for Kolbe's reaction is as follows:

$$\begin{matrix} CH_2{-}\overset{\overset{O}{\|}}{C}{-}OH \\ | \\ CH_2{-}\underset{\underset{O}{\|}}{C}{-}OH \end{matrix} \xrightarrow[2\text{ moles}]{K^+OH^-} \begin{matrix} CH_2{-}\overset{\overset{O}{\|}}{C}{-}O^- \\ | \\ CH_2{-}\underset{\underset{O}{\|}}{C}{-}O^- \end{matrix} \xrightarrow{\text{Oxidation}} \begin{matrix} CH_2{-}\overset{\overset{O}{\|}}{C}{-}O\cdot \\ | \\ CH_2{-}\underset{\underset{O}{\|}}{C}{-}O\cdot \end{matrix} \xrightarrow{-2CO_2} CH_2{=}CH_2$$

9. **Intramolecular Kolbe's electrolysis:** The example for intramolecular Kolbe's electrolysis is as follows:

$$\begin{matrix} CH_3{-}CH{-}COOK \\ | \\ CH_3{-}CH{-}COOK \end{matrix} \xrightarrow{\text{Kolbe's electrolysis}} CH_3{-}CH{=}CH{-}CH_3$$

***trans* (Major product)**

The diradical formed in the reaction is more stable in *trans* form. So, *trans* isomer is the major product. Some other examples of this reaction are:

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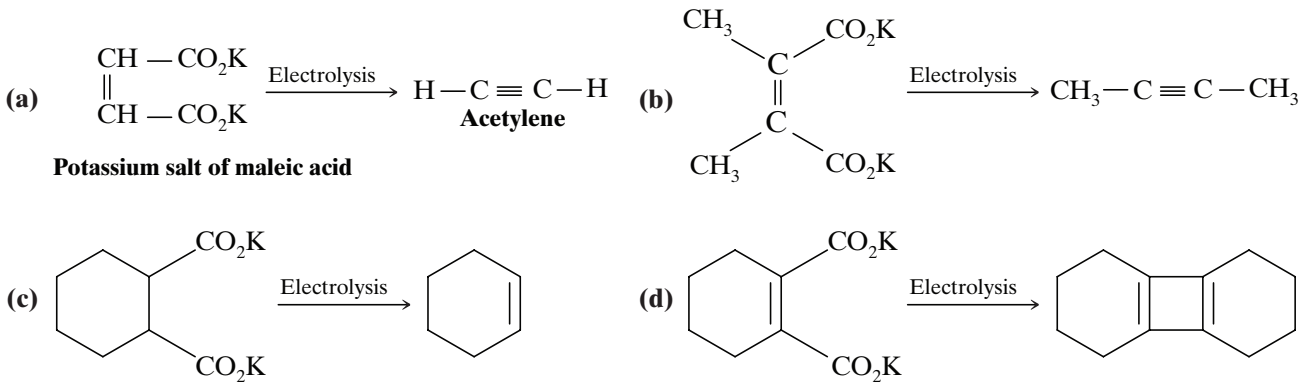
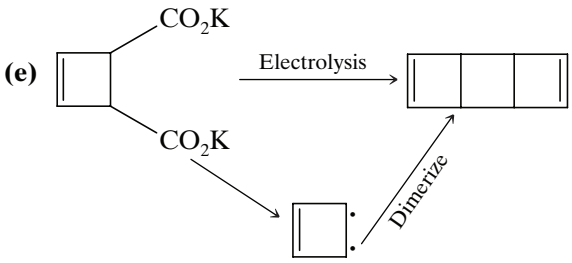


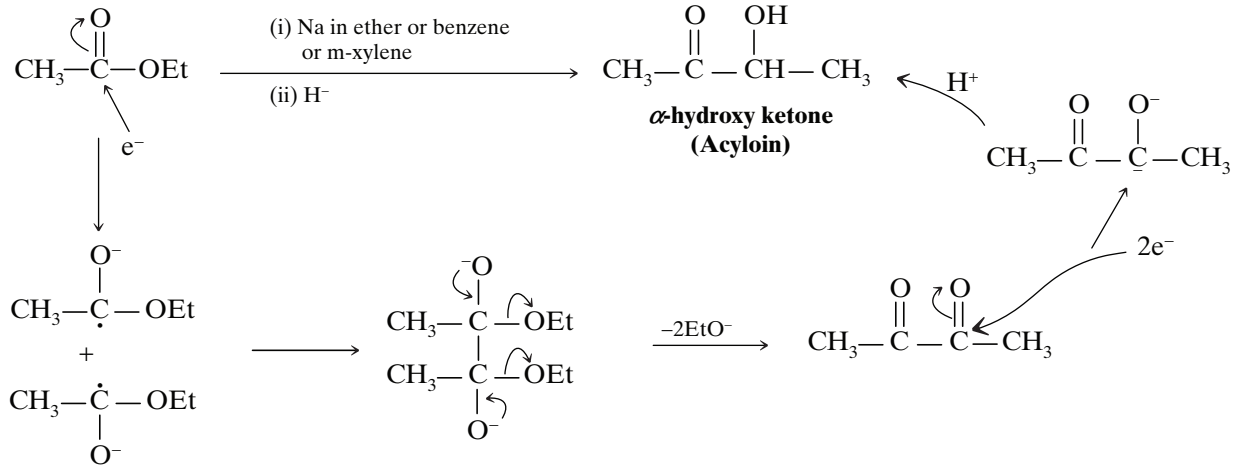
sp hybridized carbon is possible if the ring size is greater than or equal to eight carbons.



10. Acyloin condensation: When an ester (preferrably methyl or ethyl) is treated with sodium in an inert solvent (such as ether, benzene or toluene) and then with an acid, a product called acyloin is formed. This reaction is named acyloin (α-hydroxy ketone) condensation.

The reaction mechanism is as follows:

$$2Na \longrightarrow 2Na^{+} + 2e^{-}$$



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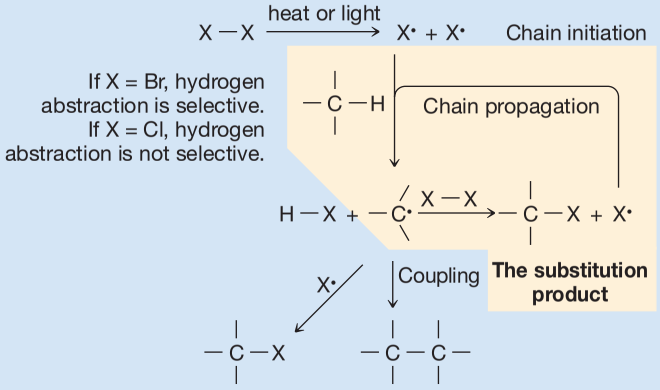
[CONCEPT MAP]

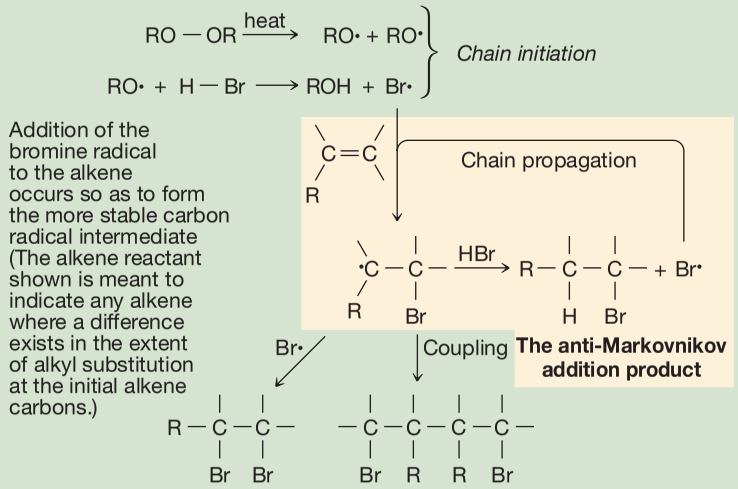
Mechanism Review of Radical Reactions

Radical Halogenation of Alkanes



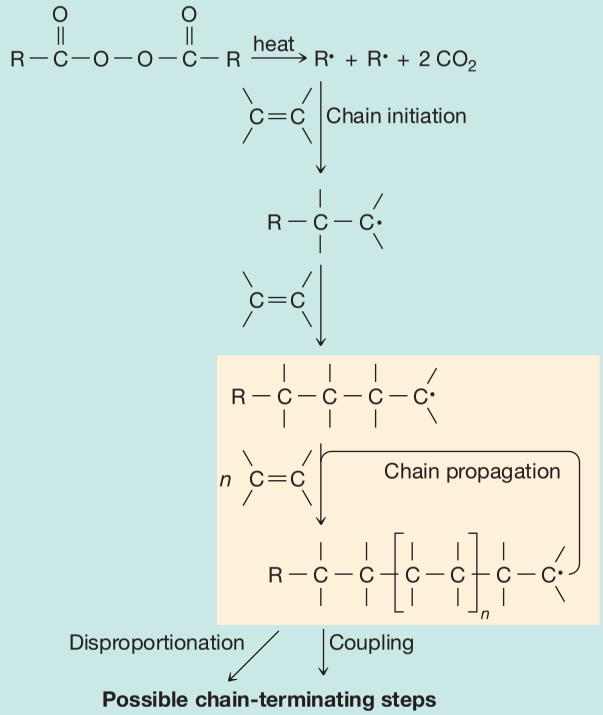
Some possible chain-terminating steps

Anti-Markovnikov Addition of HBr to Alkenes



Some possible chain-terminating steps

Radical Polymerization



Possible chain-terminating steps

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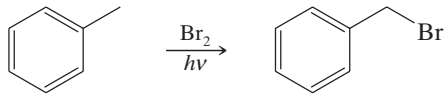
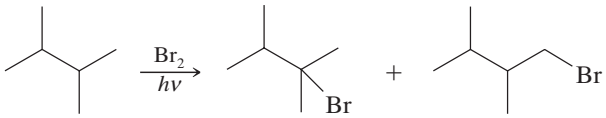
REVIEW PROBLEMS

Radical Mechanisms and Properties

9.10 Write a mechanism for the following radical halogenation reaction.

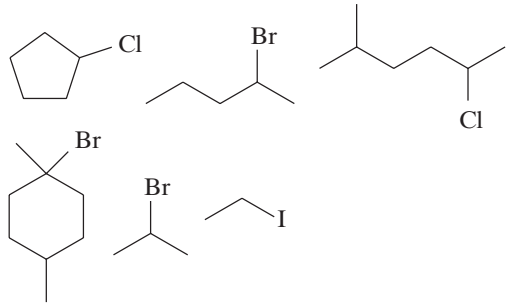


9.11 Explain the relative distribution of products below using reaction energy diagrams for the hydrogen abstraction step that leads to each product. (The rate-determining step in radical halogenation is the hydrogen abstraction step.) In energy diagrams for the two pathways, show the relative energies of the transition states and of the alkyl radical intermediate that results in each case.

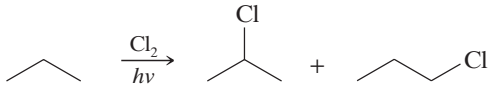


(92%) **(8%)**

9.12 Which of the following compounds can be prepared by radical halogenation with little complication by formation of isomeric by-products?

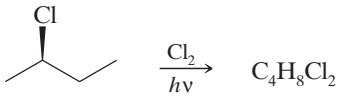


9.13 The radical reaction of propane with chlorine yields (in addition to more highly halogenated compounds) 1-chloropropane and 2-chloropropane.



Write chain-initiating and chain-propagating steps showing how each of the products above is formed.

9.14 Chlorination of (*R*)-2-chlorobutane yields a mixture of dichloro isomers.



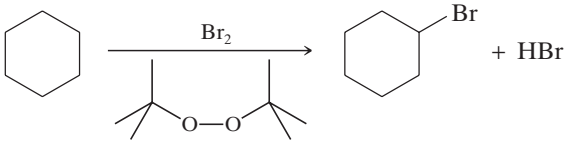
(multiple isomers)

(a) Taking into account stereochemistry, how many different isomers would you expect? Write their structures.

(b) How many fractions would be obtained upon fractional distillation?

(c) Which of these fractions would be optically active?

9.15 Peroxides are often used to initiate radical chain reactions such as in the following radical halogenation.



(Di-*tert*-butyl peroxide)

(a) Using bond dissociation energies in Table 9.1, explain why peroxides are especially effective as radical initiators.

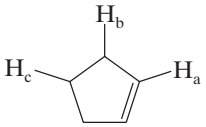
(b) Write a mechanism for the reaction above showing how it could be initiated by di-*tert*-butyl peroxide.

9.16 List in order of decreasing stability all of the radicals that can be obtained by abstraction of a hydrogen atom from 2-methylbutane.

9.17 Find examples of C—H bond dissociation energies in Table 9.1 that are as closely related as possible to the bonds to H_a, H_b, and H_c in the molecule at right. Use these values to answer the questions below.

(a) What can you conclude about the relative ease of radical halogenation at H_a?

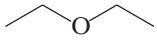
(b) Comparing H_b and H_c, which would more readily undergo substitution by radical halogenation?



Synthesis

9.18 Starting with the compound or compounds indicated in each part and using any other needed reagents, outline syntheses of each of the following compounds. (You need not repeat steps carried out in earlier parts of this problem.)

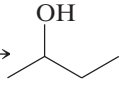
(a) $CH_3CH_3 \longrightarrow$ 

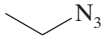
(b) $CH_3CH_3 \longrightarrow$ 

(c) 

(d) 

(e) $CH_4 + HC{\equiv}CH \longrightarrow$

(f) $CH_3CH_3 + HC{\equiv}CH \longrightarrow$ 

(g) $CH_3CH_3 \longrightarrow$ 

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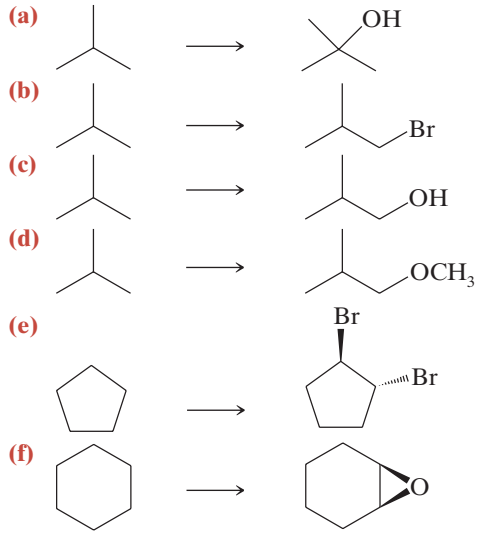
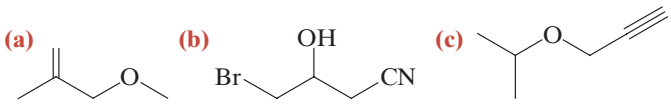
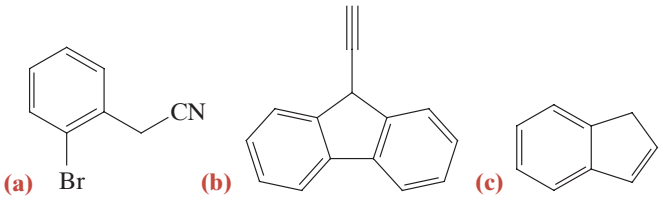
9.19 Provide the reagents necessary for the following synthetic transformations. More than one step may be required.



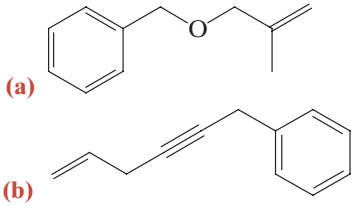
9.20 Synthesize each of the following compounds by routes that involve allylic bromination by NBS. Use starting materials having four carbons or fewer. Begin by writing a retrosynthetic analysis.



9.21 Synthesize each of the following compounds by routes that involve benzylic bromination by NBS and any other synthetic steps necessary. Begin by writing a retrosynthetic analysis.



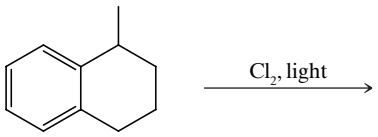
9.22 Synthesize each of the following compounds by routes that involve both allylic and benzylic bromination by NBS.

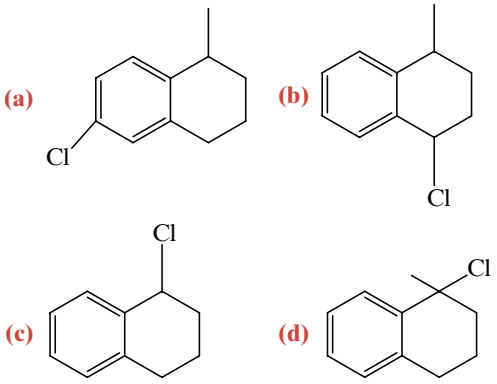


ADDITIONAL OBJECTIVE QUESTIONS

Single Correct Choice Type

1. Predict the major product of the following reaction.





2. A mixture of ethyl iodide and *n*-propyl iodide is subjected to Wurtz reaction. The hydrocarbon that will not be formed is

(a) *n*-butane. **(b)** *n*-propane.

(c) *n*-pentane. **(d)** *n*-hexane.

3. In the presence of peroxide, hydrogen chloride and hydrogen iodide do not give anti-Markovnikov addition to alkene because

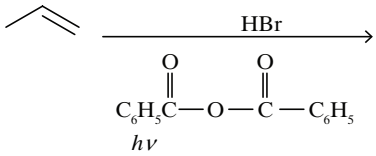
(a) both are highly ionic.

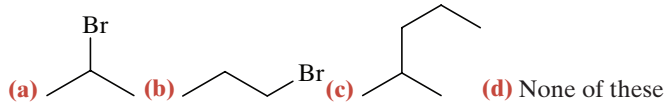
(b) one is oxidizing and the other is reducing.

(c) one of the steps is endothermic in both the cases.

(d) All the steps are exothermic in both cases.

4. Predict the final product of



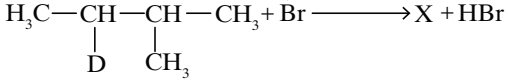


(d) None of these

5. Which of the following is the major product of the chlorination of methane if a large excess of methane is used?

(a) CH_3Cl **(b)** CH_2Cl_2 **(c)** CH_3CH_2Cl **(d)** CCl_4

6. Consider the following reactions:



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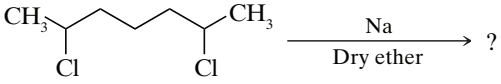
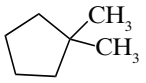
Identify the structure of the major product X.

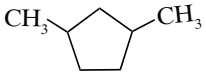
(a) $H_3C-\underset{\underset{D}{|}}{CH}-\underset{\underset{CH_3}{|}}{CH}-\dot{C}H_2$ **(b)** $H_3C-\underset{\underset{D}{|}}{CH}-\dot{\underset{\underset{CH_3}{|}}{C}}-CH_3$

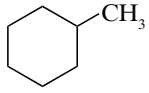
(c) $H_3C-\dot{\underset{\underset{D}{|}}{C}}-\underset{\underset{CH_3}{|}}{CH}-CH_3$ **(d)** $H_3C-\dot{C}H-\underset{\underset{CH_2}{|}}{CH}-CH_3$

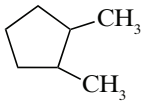
7. Identify the product formed.



(a) 

(b) 

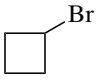
(c) 

(d) 

8. Which of the following acids adds to propene in the presence of peroxide to give anti-Markovnikov product?

(a) HF **(b)** HCl **(c)** HBr **(d)** HI

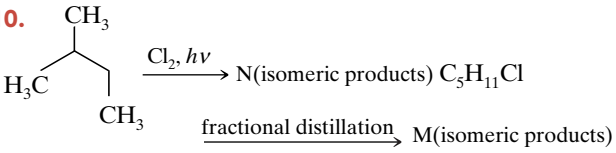
9. When 1-bromo-3-chlorocyclobutane is treated with two equivalents of Na, in the presence of ether which of the following will be formed?

(a) 

(b) 

(c) 

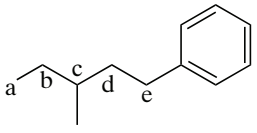
(d) 

10. 

What are N and M?

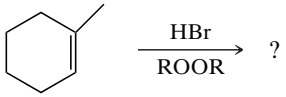
(a) 6, 6 **(b)** 6, 4 **(c)** 4, 4 **(d)** 3, 3

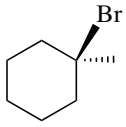
11. Consider the compound shown below. Suppose you treated the compound with Br_2 under a strong light to form a monobromonated product. At which carbon would you expect the greatest of amount of substitution to take place?

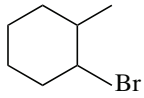


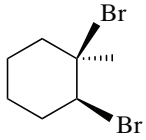
(a) b **(b)** c **(c)** d **(d)** e

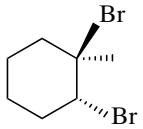
12. What is the major product of the following reaction?



(a) 

(b) 

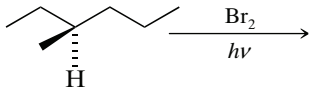
(c) 

(d) 

13. The number of possible enantiomeric pairs that can be produced during monochlorination of 2-methyl butane is

(a) 2 **(b)** 3 **(c)** 4 **(d)** 1

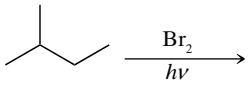
14. For the following reaction, the products formed are

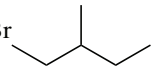


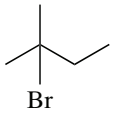
(a) racemic. **(b)** diastereomers.

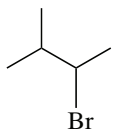
(c) meso compounds. **(d)** none of these.

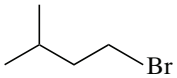
15. What is the major organic product obtained from the following reaction?



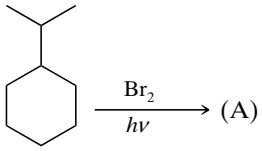
(a) 

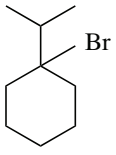
(b) 

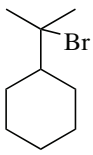
(c) 

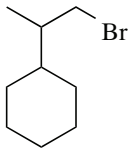
(d) 

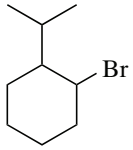
16. For the following reaction, the product (A) is



(a) 

(b) 

(C) 

(d) 

17. In the radical chlorination of methane, one propagation step is shown as

$$Cl^{\bullet} + CH_4 \longrightarrow HCl + {}^{\bullet}CH_3$$

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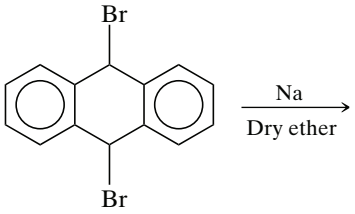
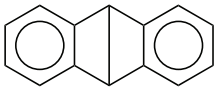
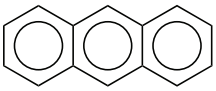
Why do we eliminate the possibility that this step goes as shown below?

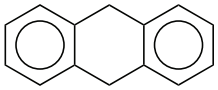
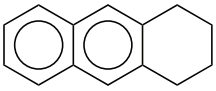
$$Cl\cdot + CH_4 \longrightarrow CH_3Cl + H\cdot$$

(a) Because in the next propagation step, H· would have to react with Cl_2 to form Cl· and HCl; this reaction is not feasible.
(b) Because this alternative step has a more endothermic ΔH° than the first.
(c) Because free hydrogen atoms cannot exist.
(d) Because this alternative step is not consistent with the high photochemical efficiency of this reaction.

18. For the reaction, 

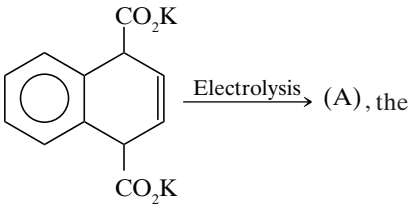
the product formed is

(a)  **(b)** 

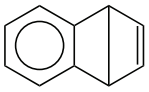
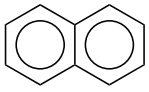
(c)  **(d)** 

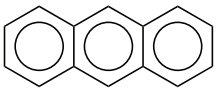
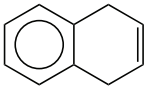
19. On mixing a certain alkane with chlorine and irradiating it with ultraviolet light, it forms only one monochloroalkane. This alkane could be

(a) propane. **(b)** pentane.
(c) isopentane. **(d)** neopentane.

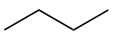
20. For the reaction 

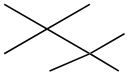
(A), the product (A) is

(a)  **(b)** 

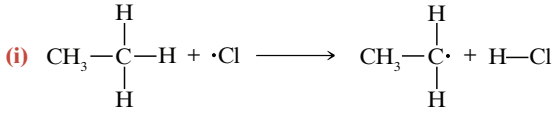
(c)  **(d)** 

21. In which of following reactions, enantiomer is formed?

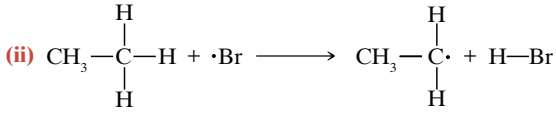
(a)  $\xrightarrow[h\nu]{Cl_2}$ **(b)**  $\xrightarrow[h\nu]{Cl_2}$

(c)  $\xrightarrow[h\nu]{Cl_2}$ **(d)**  $\xrightarrow[h\nu]{Cl_2}$

22. Choose the incorrect statement about the following two reactions.

(i) 

$\Delta H^\circ = -2$ kcal/mol

(ii) 

$\Delta H^\circ = +13$ kcal/mol

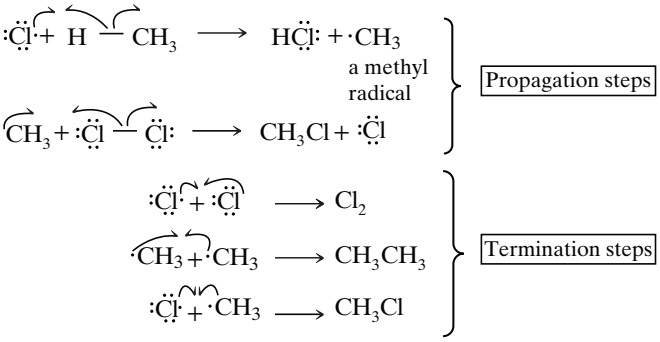
(a) Reaction (i) would be expected to be faster than reaction (ii).
(b) According to Hammound's postulate the transition state of reaction (ii) resembles the product.
(c) According to Hammound's postulate the transition state of reaction (i) resembles the reactant.
(d) The C–H bond of reaction (ii) is completely broken in the transition state.

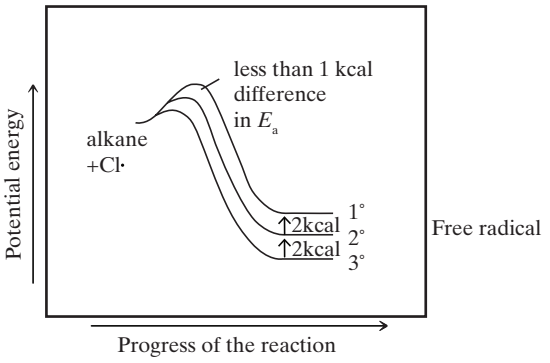
Linked Comprehension Type

Paragraph for Questions 1 to 3

Mechanism for the monochlorination of methane is as following:







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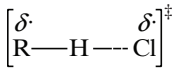
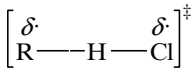
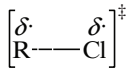
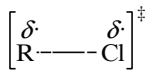
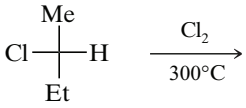
The reaction of a chlorine radical with an alkane to form a primary, secondary, or tertiary radical is exothermic; the transition states resemble the reactants more than the products. The reactants all have approximately the same energy, so there will be only a small difference in the activation energies for removal of a hydrogen atom from a primary, secondary, or tertiary carbon. In contrast, the reaction of a bromine radical with an alkane is endothermic, so the transition states resemble the products more than the reactants. In other words, because bromine radical is relatively unreactive it is very selective about which hydrogen atom it abstracts. In contrast, the much more reactive chlorine radical is much less selective. Reactivity–selectivity principle is followed which states that the greater the reactivity of a species, the less selective it will be.

1. Most appropriate transition state structure in chlorination is

(a)  **(b)** 

(c)  **(d)** 

2. Choose the correct statement for monochlorination of *R*-sec butyl chloride



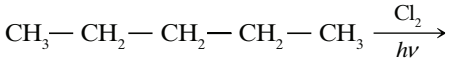
(a) There are four possible products; three are optically active and one is optically inactive.

(b) There are five possible products; three are optically inactive and two are optically active.

(c) There are five possible products; two are optically inactive and three are optically active.

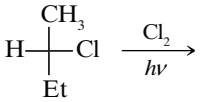
(d) There are four possible products; two are optically active and two are optically inactive.

3. Reaction 1:

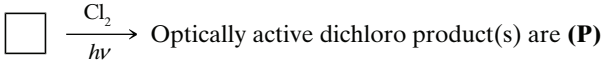


Optically active monochloro product(s) are **(R)**

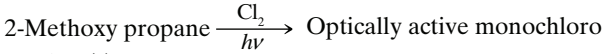
Reaction 2:

 Optically active dichloro product(s) are **(S)**

Reaction 3:

 Optically active dichloro product(s) are **(P)**

Reaction 4:

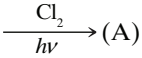
 Optically active monochloro product(s) are **(Q)**

The sum of the products (P), (Q), (R) and (S) is

(a) 8 **(b)** 9 **(c)** 10 **(d)** 11

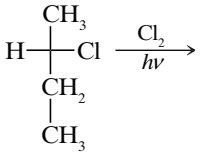
Integer Type

1. How many chiral compounds are possible on monochlorination of 2-methyl butane?

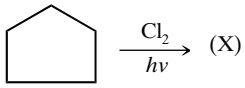
2. *n*-Pentane 

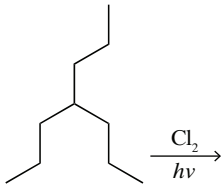
The number of monochloro products (including stereoisomers) for the above reaction is

3. For the following reaction, the number of dichloro products formed is

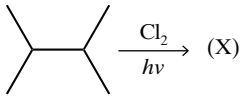


4. In the following reaction, the number of dichloro product is



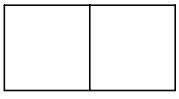
5.  (X), Monochloro products

6. In the following reaction, the number of monochloro products is_____.



Matrix Match Type

1.

Column I Compound	Column II Monochloro products (excluding steroisomerism)	Column III Monochloro products (including stereoisomerism)
(a) 	**(p)** 1	**(w)** 1

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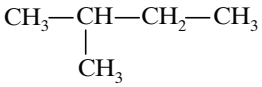
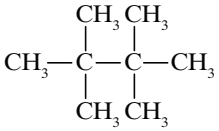
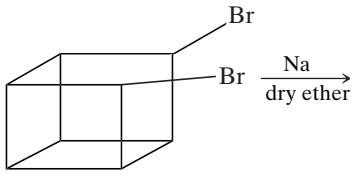
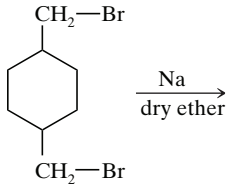
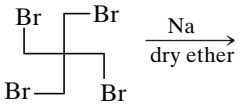
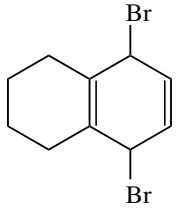
(b) 	(q) 2	(x) 3
(c) 	(r) 3	(y) 5
(d) $CH_3—CH_2—CH_2—CH_3$	(s) 4	(z) 6

2.

Column I	Column II
(a) 	(p) DBE (Double bond equivalent) of product is an odd number
(b) 	(q) DBE (Double bond equivalent) of product is an even number
(c) 	(r) Intramolecular Wurtz reaction
(d) 	(s) Free radical will be formed as an intermediate

3.

Column I Wurtz reaction	Column II Number of dimerization products
(a) $CH_3—Cl \xrightarrow[\text{dry ether}]{Na}$	(p) 5
(b) $CH_3—Cl + CH_3—CH_2—Cl \xrightarrow[\text{dry ether}]{Na}$	(s) 6
(c) $CH_3—Cl + CH_3—CH_2—Cl + CH_3—CH_2—CH_2—Cl \xrightarrow[\text{dry ether}]{Na}$	(r) 3
(d) $H_2C=CH—CH=CH—CH_2—Cl^+$ $CH_3—CH_2—Cl \xrightarrow[\text{dry ether}]{Na}$	(s) 1

ANSWER KEY

Single Correct Choice Type

1. (d)	**2.** (b)	**3.** (c)	**4.** (b)	**5.** (a)
6. (b)	**7.** (d)	**8.** (c)	**9.** (d)	**10.** (b)
11. (d)	**12.** (b)	**13.** (a)	**14.** (a)	**15.** (d)

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16. (b) **17.** (b) **18.** (b) **19.** (d) **20.** (b)
21. (b) **22.** (d)

Linked Comprehension Type

1. (a) **2.** (c) **3.** (b)

Integer Type

1. (4) **2.** (4) **3.** (1) **4.** (3) **5.** (6)
6. (1)

Matrix Match Type

1. a → (q, x); b → (s, z); c → (p, w); d → (q, x)
2. a → (p, r, s); b → (q, r, s); c → (q, r, s); d → (p, r, s)
3. a → (s); b → (r); c → (p); d → (q)

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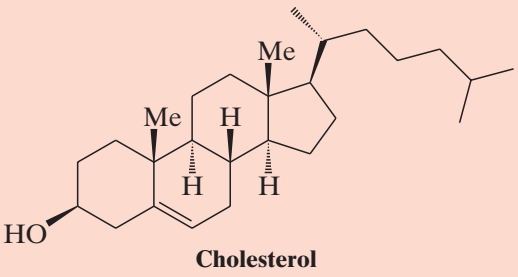
10

Alcohols and Ethers

Synthesis and Reactions



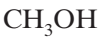
Cholesterol

Contents

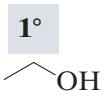
10.1 | Structure and Nomenclature
10.2 | Physical Properties of Alcohols and Ethers
10.3 | Synthesis of Alcohols from Alkenes
10.4 | Reactions of Alcohols
10.5 | Alcohols as Acids
10.6 | Conversion of Alcohols into Alkyl Halides
10.7 | Alkyl Halides from the Reaction of Alcohols with Hydrogen Halides
10.8 | Alkyl Halides from the Reaction of Alcohols with PBr_3 or $SOCl_2$
10.9 | Tosylates, Mesylates, and Triflates: Leaving Group Derivatives of Alcohols
10.10 | Rearrangements
10.11 | Synthesis of Ethers
10.12 | Reactions of Ethers
10.13 | Epoxides
10.14 | Reactions of Epoxides
10.15 | Anti 1,2-Dihydroxylation of Alkenes via Epoxides
10.16 | Crown Ethers

10.1 | STRUCTURE AND NOMENCLATURE

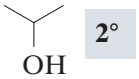
Alcohols have a hydroxyl (—OH) group bonded to a *saturated* carbon atom. The alcohol carbon atom may be part of a simple alkyl group, as in some of the following examples, or it may be part of a more complex molecule, such as cholesterol. Alcohols are also classified as 1°, 2°, or 3°, depending on the number of carbons bonded to the alcohol carbon.



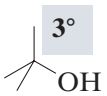
Methanol (methyl alcohol)



Ethanol (ethyl alcohol), *a 1° alcohol*

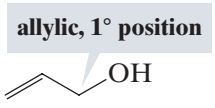


2-Propanol (isopropyl alcohol), *a 2° alcohol*

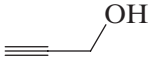


2-Methyl-2-propanol (*tert*-butyl alcohol), *a 3° alcohol*

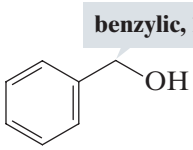
The alcohol carbon atom may also be a saturated carbon atom adjacent to an alkenyl or alkynyl group, or the carbon atom may be a saturated carbon atom that is attached to a benzene ring:



2-Propenol (or prop-2-en-1-ol, or allyl alcohol), *an allylic alcohol*



2-Propynol (or prop-2-yn-1-ol, or propargyl alcohol)



Benzyl alcohol (*a benzylic alcohol*)

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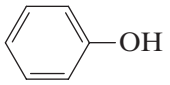
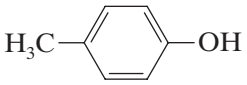
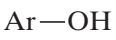
Compounds that have a hydroxyl group attached *directly* to a benzene ring are called **phenols**. (Phenols are discussed in detail in Chapter 19.)



Phenol

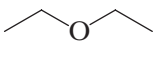


p*-Methylphenol, *a substituted phenol

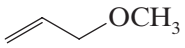


General formula for a phenol

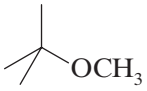
Ethers differ from alcohols in that the oxygen atom of an ether is bonded to two carbon atoms. The hydrocarbon groups may be alkyl, alkenyl, vinyl, alkynyl, or aryl. Several examples are shown here:



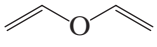
Diethyl ether



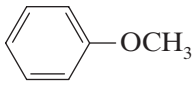
Allyl methyl ether



***tert*-Butyl methyl ether**



Divinyl ether



Methyl phenyl ether

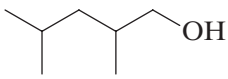
10.1A Nomenclature of Alcohols

We studied the IUPAC system of nomenclature for alcohols in Sections 2.5 and 5.3F. As a review consider the following problem.

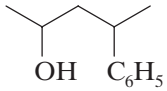
Solved Problem 10.1

Give IUPAC substitutive names for the following alcohols:

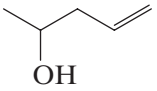
(a)



(b)



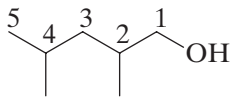
(c)



Answer

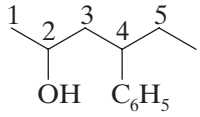
The longest chain ***to which the hydroxyl group is attached*** gives us the ***base name***. The ending is **-ol**. We then number ***the longest chain from the end that gives the carbon bearing the hydroxyl group the lower number***. Thus, the names, in both of the accepted IUPAC formats, are

(a)



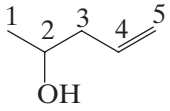
2,4-Dimethyl-1-pentanol
(or 2,4-dimethylpentan-1-ol)

(b)



4-Phenyl-2-pentanol
(or 4-phenylpentan-2-ol)

(c)



4-Penten-2-ol
(or pent-4-en-2-ol)

- The hydroxyl group has precedence over double bonds and triple bonds in deciding which functional group to name as the suffix [see example **(c)** above].

In common functional class nomenclature (Section 2.5) alcohols are called **alkyl alcohols** such as methyl alcohol, ethyl alcohol, and so on.

Practice Problem 10.1

What is wrong with the use of such names as "isopropanol" and "*tert*-butanol"?

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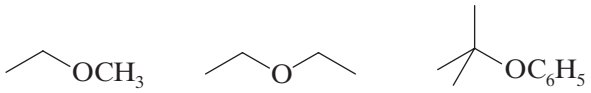
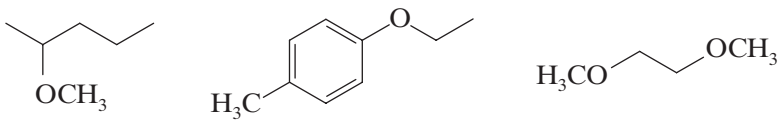
10.1B Nomenclature of Ethers

Simple ethers are frequently given common functional class names. One simply lists (in alphabetical order) both groups that are attached to the oxygen atom and adds the word *ether*:



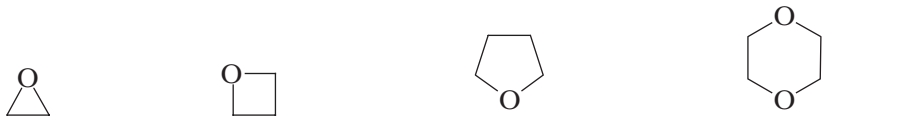
Ethyl methyl ether **Diethyl ether** ***tert*-Butyl phenyl ether**

IUPAC substitutive names should be used for complicated ethers, however, and for compounds with more than one ether linkage. In this IUPAC style, ethers are named as alkoxyalkanes, alkoxyalkenes, and alkoxyarenes. The RO— group is an **alkoxy** group.

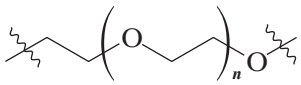


2-Methoxypentane **1-Ethoxy-4-methylbenzene** **1,2-Dimethoxyethane (DME)**

Cyclic ethers can be named in several ways. One simple way is to use **replacement nomenclature**, in which we relate the cyclic ether to the corresponding hydrocarbon ring system and use the prefix **oxa**- to indicate that an oxygen atom replaces a CH_2 group. In another system, a cyclic three-membered ether is named **oxirane** and a four-membered ether is called **oxetane.** Several simple cyclic ethers also have common names; in the examples below, these common names are given in parentheses. Tetrahydrofuran (THF) and 1,4-dioxane are useful solvents:



Oxacyclopropane or oxirane (ethylene oxide) **Oxacyclobutane or oxetane** **Oxacyclopentane (tetrahydrofuran or THF)** **1,4-Dioxacyclohexane (1,4-dioxane)**



Polyethylene oxide (PEO) (a water-soluble polymer made from ethylene oxide)

Ethylene oxide is the starting material for polyethylene oxide (PEO, also called polyethylene glycol, PEG). Polyethylene oxide has many practical uses, including covalent attachment to therapeutic proteins such as interferon, a use that has been found to increase the circulatory lifetime of the drug. PEO is also used in some skin creams, and as a laxative prior to digestive tract procedures.

Solved Problem 10.2

Albuterol (used in some commonly prescribed respiratory medications) and vanillin (from vanilla beans) each contain several functional groups. Name the functional groups in albuterol and vanillin and, if appropriate for a given group, classify them as primary (1°), secondary (2°), or tertiary (3°).

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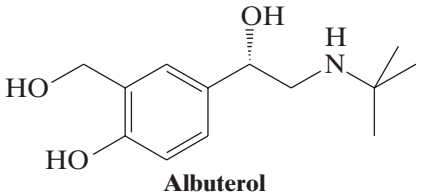
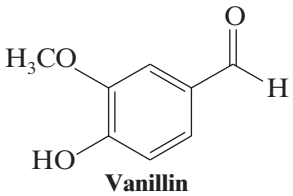


Albuterol
(an asthma medication)



Vanillin
(from vanilla beans)

Answer

Albuterol has the following functional groups: 1° alcohol, 2° alcohol, phenol, and 2° amine. Vanillin has aldehyde, ether, and phenol functional groups.

Practice Problem 10.2

Give bond-line formulas and appropriate names for all of the alcohols and ethers with the formulas **(a)** C_3H_8O and **(b)** $C_4H_{10}O$.

10.2 | PHYSICAL PROPERTIES OF ALCOHOLS AND ETHERS

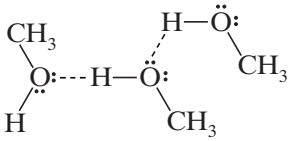
- Ethers have boiling points that are roughly comparable with those of hydrocarbons of the same molecular weight (MW).

For example, the boiling point of diethyl ether (MW = 74) is 34.6 °C; that of pentane (MW = 72) is 36 °C.

- Alcohols have much higher boiling points than comparable ethers or hydrocarbons.

The boiling point of butyl alcohol (MW = 74) is 117.7 °C. We learned the reason for this behavior in Section 2.12C.

- Alcohol molecules can associate with each other through **hydrogen bonding**, whereas those of ethers and hydrocarbons cannot.



Hydrogen bonding between molecules of methanol

Ethers, however, *are* able to form hydrogen bonds with compounds such as water. Ethers, therefore, have solubilities in water that are similar to those of alcohols of the same molecular weight and that are very different from those of hydrocarbons.

Diethyl ether and 1-butanol, for example, have the same solubility in water, approximately 8 g per 100 mL at room temperature. Pentane, by contrast, is virtually insoluble in water.

Methanol, ethanol, both propyl alcohols, and *tert*-butyl alcohol are completely miscible with water. The solubility of alcohols in water gradually decreases as the hydrocarbon portion of the molecule lengthens; long-chain alcohols are more "alkane-like" and are, therefore, less like water.

10.3 | SYNTHESIS OF ALCOHOLS FROM ALKENES

We have already studied the acid-catalyzed **hydration** of alkenes, **oxymercuration**–demercuration, and **hydroboration**–oxidation as methods for the synthesis of alcohols from alkenes (see Sections 8.4, 8.5, and 8.6, respectively). Below, we briefly summarize these methods.

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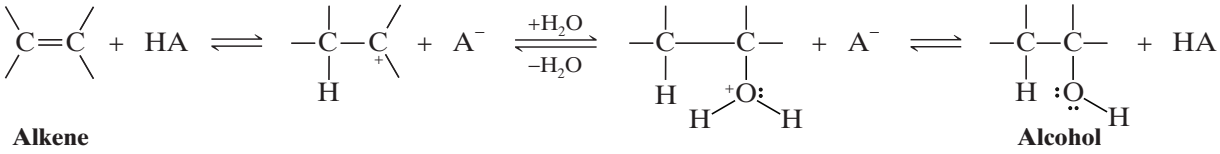
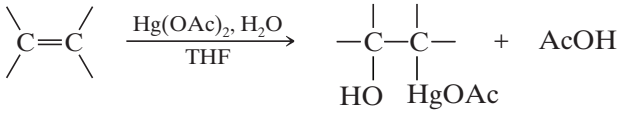
1. **Acid-Catalyzed Hydration of Alkenes** Alkenes add water in the presence of an acid catalyst to yield alcohols (Section 8.5). The addition takes place with **Markovnikov regioselectivity**. The reaction is reversible, and the mechanism for the acid-catalyzed hydration of an alkene is simply the reverse of that for the dehydration of an alcohol (Section 7.7).



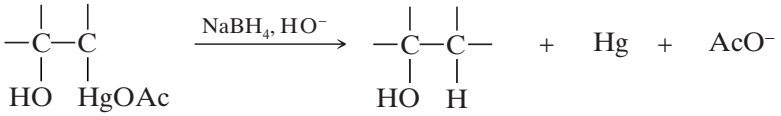
Acid-catalyzed hydration of alkenes has limited synthetic utility, however, because the carbocation intermediate may rearrange if a more stable or isoenergetic carbocation is possible by hydride or alkanide migration. Thus, a mixture of isomeric alcohol products may result.

2. **Oxymercuration–Demercuration** Alkenes react with mercuric acetate in a mixture of water and tetrahydrofuran (THF) to produce (hydroxyalkyl)mercury compounds. These can be reduced to alcohols with sodium borohydride and water (Section 8.5).

Oxymercuration



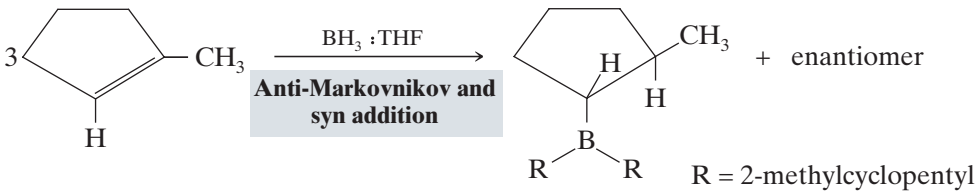
Demercuration



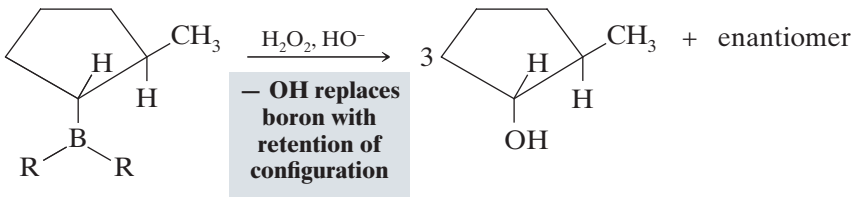
In the oxymercuration step, water and mercuric acetate add to the double bond; in the demercuration step, sodium borohydride reduces the acetoxymercury group and replaces it with hydrogen. The net addition of H— and —OH takes place with **Markovnikov regioselectivity** and **generally takes place without the complication of rearrangements**, as sometimes occurs with acid-catalyzed hydration of alkenes. The overall alkene hydration is not stereoselective because even though the oxymercuration step occurs with anti addition, the demercuration step is not stereoselective (radicals are thought to be involved), and hence a mixture of syn and anti products results.

3. **Hydroboration–Oxidation** An alkene reacts with BH_3:THF or diborane to produce an alkylborane. Oxidation and hydrolysis of the alkylborane with hydrogen peroxide and base yield an alcohol (Section 8.6).

Hydroboration



Oxidation



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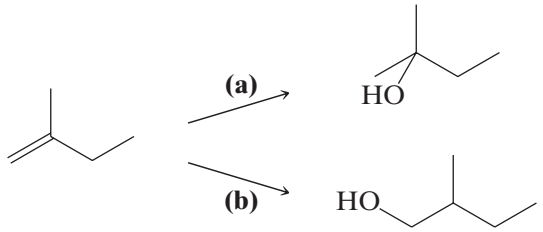
In the first step, boron and hydrogen undergo syn addition to the alkene; in the second step, treatment with hydrogen peroxide and base replaces the boron with —OH with retention of configuration. The net addition of —H and —OH occurs with **anti-Markovnikov regioselectivity** and **syn stereoselectivity.** Hydroboration–oxidation, therefore, serves as a useful regiochemical complement to oxymercuration–demercuration.

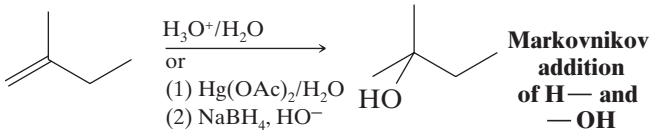
Solved Problem 10.3

What conditions would you use for each reaction?

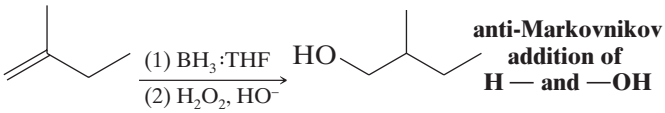


Answer

We recognize that synthesis by path (a) would require a Markovnikov addition of water to the alkene. So, we could use either acid-catalyzed hydration or oxymercuration–demercuration.

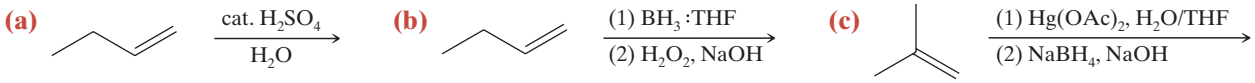


Synthesis by path (b) requires an anti-Markovnikov addition, so we would choose hydroboration–oxidation.



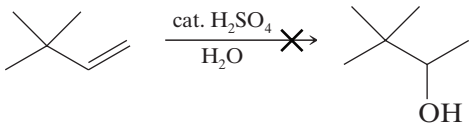
Practice Problem 10.3

Predict the major products of the following reactions:



Practice Problem 10.4

The following reaction does not produce the product shown.



(a) Predict the major product from the conditions shown above, and write a detailed mechanism for its formation.

(b) What reaction conditions would you use to successfully synthesize the product shown above (3,3-dimethyl-2-butanol).

10.4 | REACTIONS OF ALCOHOLS

The reactions of alcohols have mainly to do with the following:

- The oxygen atom of the hydroxyl group is nucleophilic and weakly basic.
- The hydrogen atom of the hydroxyl group is weakly acidic.
- The hydroxyl group can be converted to a leaving group so as to allow substitution or elimination reactions.

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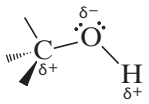
Our understanding of the reactions of alcohols will be aided by an initial examination of the electron distribution in the alcohol functional group and of how this distribution affects its reactivity. The oxygen atom of an alcohol polarizes both the C—O bond and the O—H bond of an alcohol:

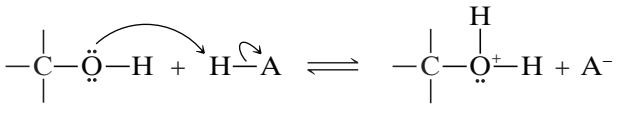


The C—O and O—H bonds of an alcohol are polarized

Polarization of the O—H bond makes the hydrogen partially positive and explains why alcohols are weak acids (Section 10.5). Polarization of the C—O bond makes the carbon atom partially positive, and if it were not for the fact that HO^- is a strong base and, therefore, a very poor leaving group, this carbon would be susceptible to nucleophilic attack.

The electron pairs on the oxygen atom make it both ***basic*** and ***nucleophilic***. In the presence of strong acids, alcohols act as bases and accept protons in the following way:

Protonation of an alcohol



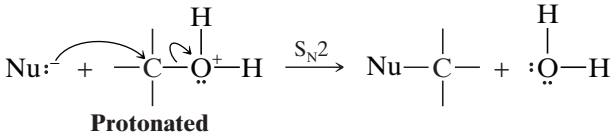
Alcohol **Strong acid** **Protonated alcohol**

- Protonation of the alcohol converts a poor leaving group (HO^-) into a good one (H_2O).

Protonation also makes the carbon atom even more positive (because $-\overset{+}{O}H_2$ is more electron withdrawing than —OH) and, therefore, even more susceptible to nucleophilic attack.

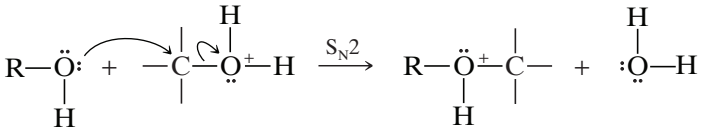
- Once the alcohol is protonated substitution reactions become possible (S_N2 or S_N1, depending on the class of alcohol, Section 10.7).

The protonated hydroxyl group is a good leaving group (H_2O)



Protonated alcohol

Because alcohols are nucleophiles, they, too, can react with protonated alcohols. This, as we shall see in Section 10.10A, is an important step in one synthesis of ethers:



Protonated ether

At a high enough temperature and in the absence of a good nucleophile, protonated alcohols are capable of undergoing E1 or E2 reactions. This is what happens in alcohol dehydrations (Section 7.7).

Alcohols also react with PBr_3 and $SOCl_2$ to yield alkyl bromides and alkyl chlorides. These reactions, as we shall see in Section 10.8, are initiated by the alcohol using its unshared electron pairs to act as a nucleophile.

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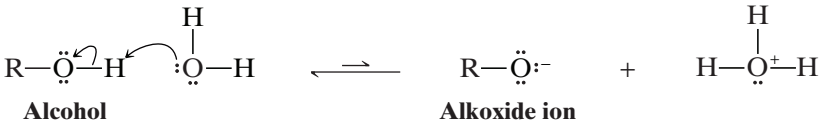
10.5 | ALCOHOLS AS ACIDS

- Alcohols have acidities similar to that of water.

Methanol is a slightly stronger acid than water (pK_a = 15.7) but most alcohols are somewhat weaker acids. Values of pK_a for several alcohols are listed in Table 10.1.

Table 10.1 pK_a Values for Some Weak Acids

Acid	pK_a
CH_3OH	15.5
H_2O	15.74
CH_3CH_2OH	15.9
$(CH_3)_3COH$	18.0



(If R is bulky, there is less stabilization of the alkoxide by solvation and greater destabilization due to inductive effects. Consequently, the equilibrium lies even further toward the alcohol.)

- Sterically hindered alcohols such as *tert*-butyl alcohol are less acidic, and hence their conjugate bases more basic, than unhindered alcohols such as ethanol or methanol.

One reason for this difference in acidity has to do with the effect of solvation. With an unhindered alcohol, water molecules can easily surround, solvate, and hence stabilize the alkoxide anion that would form by loss of the alcohol proton to a base. As a consequence of this stabilization, formation of the alcohol's conjugate base is easier, and therefore its acidity is increased. If the R group of the alcohol is bulky, solvation of the alkoxide anion is hindered. Stabilization of the conjugate base is not as effective, and consequently the hindered alcohol is a weaker acid. Another reason that hindered alcohols are less acidic has to do with the inductive electron-donating effect of alkyl groups. The alkyl groups of a hindered alcohol donate electron density, making formation of an alkoxide anion more difficult than with a less hindered alcohol.

- All alcohols are much stronger acids than terminal alkynes, and they are very much stronger acids than hydrogen, ammonia, and alkanes (see Table 3.1).

Helpful Hint: Any factor that stabilizes the conjugate base of an acid increases its acidity.

Relative Acidity

Water and alcohols are the strongest acids in this series.

$$H_2O > ROH > RC{\equiv}CH > H_2 > NH_3 > RH$$

Sodium and potassium alkoxides can be prepared by treating alcohols with sodium or potassium metal or with the metal hydride (Section 6.15B). Because most alcohols are weaker acids than water, most alkoxide ions are stronger bases than the hydroxide ion.

- Conjugate bases of compounds with higher pK_a values than an alcohol will deprotonate an alcohol.

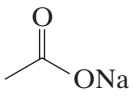
Relative Basicity

$$R^- > H_2N^- > H^- > RC{\equiv}C^- > RO^- > HO^-$$

Hydroxide is the weakest base in this series.

Practice Problem 10.5

Write equations for the acid–base reactions that would occur (if any) if ethanol were added to solutions of each of the following compounds. In each reaction, label the stronger acid, the stronger base, and so forth (consult Table 3.1).

(a) $NaNH_2$ **(b)** $H{-}{\equiv}{:}^-Na^+$ **(c)**  **(d)** NaOH

Sodium and potassium alkoxides are often used as bases in organic syntheses (Section 6.15B). We use alkoxides, such as ethoxide and *tert*-butoxide, when we carry out reactions that require stronger bases than hydroxide ion but do

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not require exceptionally powerful bases, such as the amide ion or the anion of an alkane. We also use alkoxide ions when, for reasons of solubility, we need to carry out a reaction in an alcohol solvent rather than in water.

10.6 | CONVERSION OF ALCOHOLS INTO ALKYL HALIDES

In this and several following sections we will be concerned with reactions that involve substitution of the alcohol hydroxyl group.

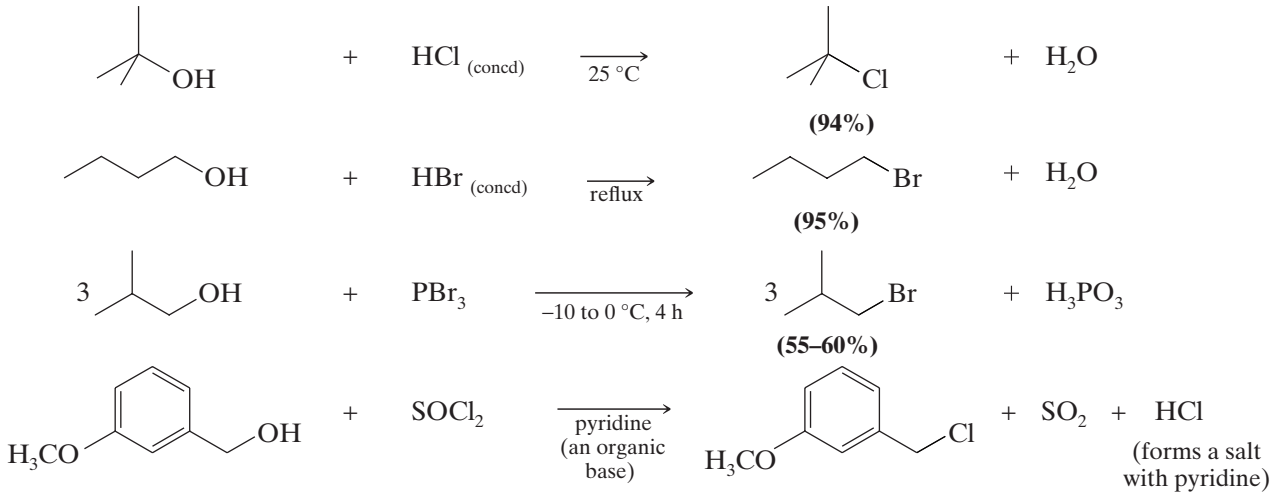
- A hydroxyl group is such a poor leaving group (it would depart as hydroxide) that a common theme of these reactions will be conversion of the hydroxyl to a group that can depart as a weak base.

These processes begin by reaction of the alcohol oxygen as a base or nucleophile, after which the modified oxygen group undergoes substitution. First, we shall consider reactions that convert alcohols to alkyl halides.

The most commonly used reagents for conversion of alcohols to alkyl halides are the following:

- Hydrogen halides (HCl, HBr, HI)
- Phosphorus tribromide (PBr_3)
- Thionyl chloride ($SOCl_2$)

Examples of the use of these reagents are the following. All of these reactions result in cleavage of the C—O bond of the alcohol. In each case, the hydroxyl group is first converted to a suitable leaving group. We will see how this is accomplished when we study each type of reaction.



10.7 | ALKYL HALIDES FROM THE REACTION OF ALCOHOLS WITH HYDROGEN HALIDES

When alcohols react with a hydrogen halide, a substitution takes place producing an alkyl halide and water:

$$R{-}OH + HX \longrightarrow R{-}X + H_2O$$

- The order of reactivity of alcohols is $3° > 2° > 1° <$ methyl.
- The order of reactivity of the hydrogen halides is HI > HBr > HCl (HF is generally unreactive).

The reaction is *acid catalyzed*. Alcohols react with the strongly acidic hydrogen halides HCl, HBr, and HI, but they do not react with nonacidic NaCl, NaBr, or NaI. Primary and secondary alcohols can be converted to alkyl chlorides and bromides by allowing them to react with a mixture of a sodium halide and sulfuric acid:

$$ROH + NaX \xrightarrow{H_2SO_4} RX + NaHSO_4 + H_2O$$

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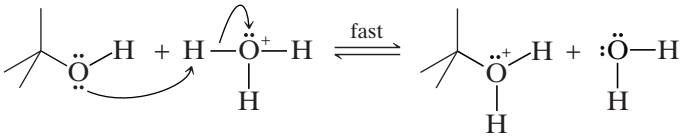
10.7A Mechanisms of the Reactions of Alcohols with HX

- Secondary, tertiary, allylic, and benzylic alcohols appear to react by a mechanism that involves the formation of a carbocation.

We again illustrate this mechanism with the reaction of *tert*-butyl alcohol and aqueous hydrochloric acid (H_3O^+, Cl^-).

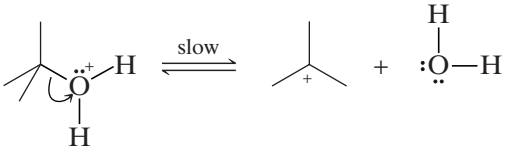
The first two steps in this S_N1 substitution mechanism are the same as in the mechanism for the dehydration of an alcohol (Section 7.7).

Step 1



The alcohol accepts a proton.

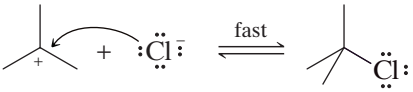
Step 2



The protonated hydroxyl group departs as a leaving group to form a carbocation and water.

In step 3 the mechanisms for the dehydration of an alcohol and the formation of an alkyl halide differ. In dehydration reactions the carbocation loses a proton in an E1 reaction to form an alkene. In the formation of an alkyl halide, the carbocation reacts with a nucleophile (a halide ion) in an S_N1 reaction.

Step 3



A halide anion reacts with the carbocation.

How can we account for S_N1 substitution in this case versus elimination in others?

When we dehydrate alcohols, we usually carry out the reaction in concentrated sulfuric acid and at high temperature. The hydrogen sulfate (HSO_4^-) present after protonation of the alcohol is a weak nucleophile, and at high temperature the highly reactive carbocation forms a more stable species by losing a proton and becoming an alkene. Furthermore, the alkene is usually volatile and distills from the reaction mixture as it is formed, thus drawing the equilibrium toward alkene formation. The net result is *an E1 reaction*.

In the reverse reaction, that is, the hydration of an alkene (Section 8.5), the carbocation *does* react with a nucleophile. It reacts with water. Alkene hydrations are carried out in dilute sulfuric acid, where the water concentration is high. In some instances, too, carbocations may react with HSO_4^- ions or with sulfuric acid, itself. When they do, they form alkyl hydrogen sulfates ($R—OSO_2OH$).

When we convert an alcohol to an alkyl halide, we carry out the reaction in the presence of acid and *in the presence of halide ions*, and not at elevated temperature. Halide ions are good nucleophiles (they are much stronger nucleophiles than water), and since halide ions are present in high concentration, most of the carbocations react with an electron pair of a halide ion to form a more stable species, the alkyl halide product. The overall result is an S_N1 reaction.

These two reactions, dehydration and the formation of an alkyl halide, also furnish another example of the competition between nucleophilic substitution and elimination (see Section 6.18). Very often, in conversions of alcohols to alkyl halides, we find that the reaction is accompanied by the formation of some alkene (i.e., by elimination). The free energies of activation for these two reactions of carbocations are not very different from one another. Thus, not all of the carbocations become stable products by reacting with nucleophiles; some lose a β proton to form an alkene.

Primary Alcohols

Not all acid-catalyzed conversions of alcohols to alkyl halides proceed through the formation of carbocations.

- Primary alcohols and methanol react to form alkyl halides under acidic conditions by an S_N2 mechanism.

In these reactions the function of the acid is to produce *a protonated alcohol*. The halide ion then displaces a molecule of water (a good leaving group) from carbon; this produces an alkyl halide:

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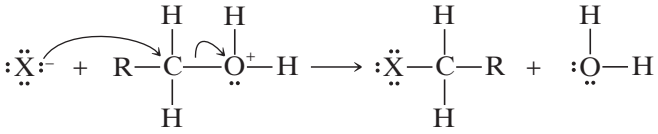
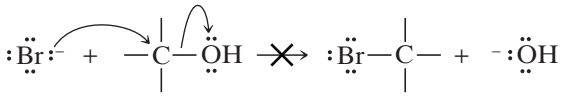


(Protonated 1° alcohol or methanol) (A good leaving group)

Acid Is Required Although halide ions (particularly iodide and bromide ions) are strong nucleophiles, they are not strong enough to carry out substitution reactions with alcohols themselves.

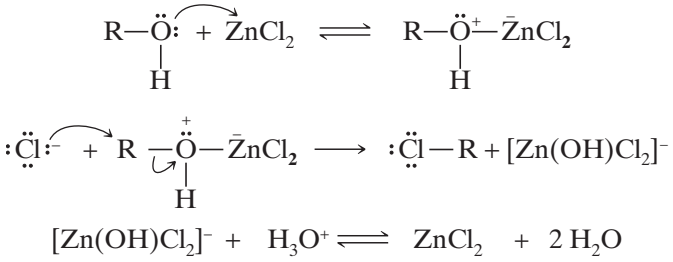
- Reactions like the following do not occur because the leaving group would have to be a strongly basic hydroxide ion:



We can see now why the reactions of alcohols with hydrogen halides are acid-promoted.

- Acid protonates the alcohol hydroxyl group, making it a good leaving group.

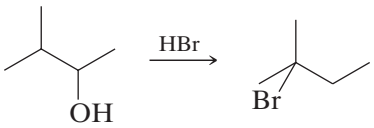
Because the chloride ion is a weaker nucleophile than bromide or iodide ions, hydrogen chloride does not react with primary or secondary alcohols unless zinc chloride or some similar Lewis acid is added to the reaction mixture as well. Zinc chloride, a good Lewis acid, forms a complex with the alcohol through association with an unshared pair of electrons on the oxygen atom. This enhances the hydroxyl group's leaving potential sufficiently that chloride can displace it.



- As we might expect, many reactions of alcohols with hydrogen halides, particularly those in which carbocations are formed, *are accompanied by rearrangements*.

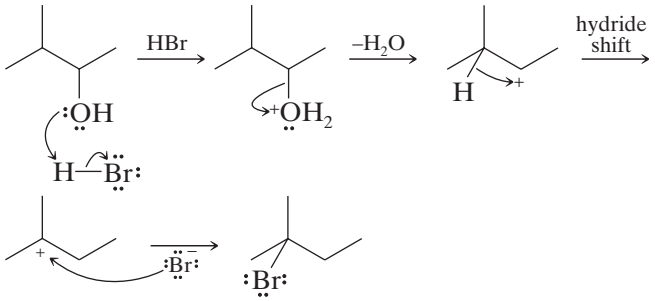
Solved Problem 10.4

Treating 3-methyl-2-butanol (see the following reaction) yields 2-bromo-2-methylbutane as the sole product. Propose a mechanism that explains the course of the reaction.



Answer

The reaction must involve a rearrangement by a hydride shift from the initially formed carbocation.



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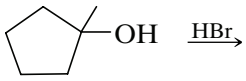
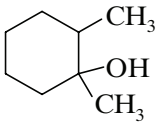
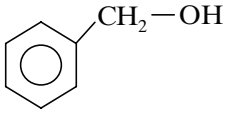
Solved Problem 10.5

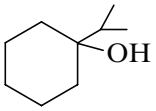
Give the major product for each of the following reactions.

(a) $CH_3-CH_2-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_3 \xrightarrow{HBr}$

(b)  $\xrightarrow{HBr}$

(c)  $\xrightarrow{HBr}$

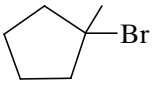
(d)  $\xrightarrow{HBr}$

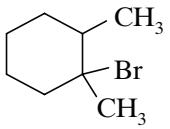
(e)  $\xrightarrow{HI}$

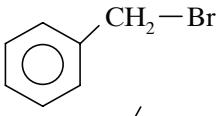
Answer

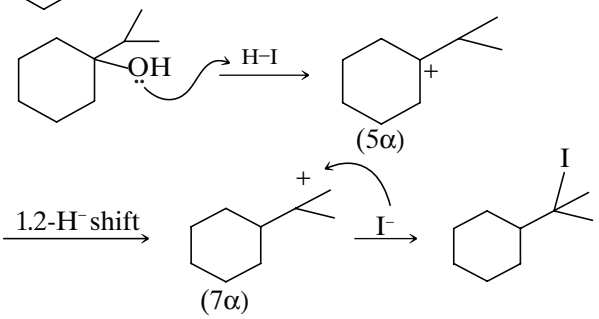
The major products formed in the given reactions are as follows:

(a) $CH_3-CH_2-\underset{\displaystyle Br}{\underset{|}{CH}}-CH_3$

(b) 

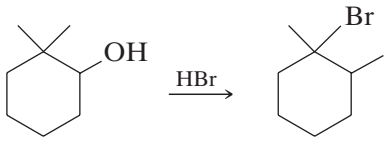
(c) 

(d) 

(e) 

Practice Problem 10.6

Write a detailed mechanism for the following reaction.



Practice Problem 10.7

(a) What factor explains the observation that tertiary alcohols react with HX faster than secondary alcohols? **(b)** What factor explains the observation that methanol reacts with HX faster than a primary alcohol?

Since rearrangements can occur when some alcohols are treated with hydrogen halides, how can we successfully convert a secondary alcohol to an alkyl halide without rearrangement? The answer to this question comes in the next section, where we discuss the use of reagents such as thionyl chloride ($SOCl_2$) and phosphorus tribromide (PBr_3).

10.8 | ALKYL HALIDES FROM THE REACTION OF ALCOHOLS WITH PBr_3 OR $SOCl_2$

Primary and secondary alcohols react with phosphorus tribromide to yield alkyl bromides.

$$3\ R\text{-}OH\ (1^\circ \text{ or } 2^\circ) + PBr_3 \longrightarrow 3\ R-Br + H_3PO_3$$

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- The reaction of an alcohol with PBr_3 does not involve the formation of a carbocation and *usually occurs without rearrangement* of the carbon skeleton (especially if the temperature is kept below 0 °C).
- Phosphorus tribromide is often preferred as a reagent for the transformation of an alcohol to the corresponding alkyl bromide.

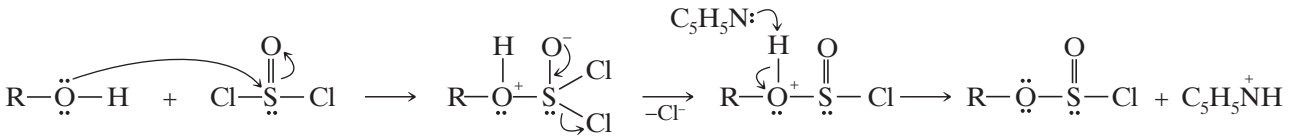
The mechanism for the reaction involves sequential replacement of the bromine atom in PBr_3 by three molecules of the alcohol to form a trialkylphosphite, $P(OR)_3$, and three molecules of HBr.

$$ROH + PBr_3 \longrightarrow P(OR)_3 + 3\ HBr$$

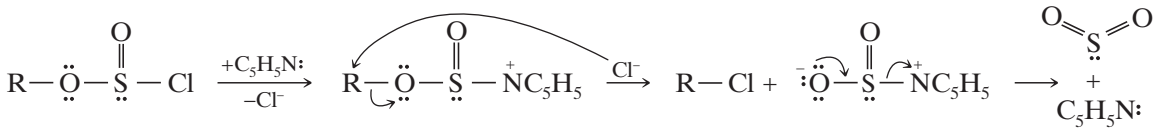
The trialkylphosphite goes on to react with three molecules of HBr to form three molecules of the alkyl bromide and a molecule of phosphonic acid.

$$P(OR)_3 + 3\ HBr \longrightarrow 3\ RBr + H_3PO_3$$

Thionyl chloride ($SOCl_2$) converts primary and secondary alcohols to alkyl chlorides. Pyridine (C_5H_5N) is often included to promote the reaction. The alcohol substrate attacks thionyl chloride as shown below, releasing a chloride anion and losing its proton to a molecule of pyridine. The result is an alkylchlorosulfite.



The alkylchlorosulfite intermediate then reacts rapidly with another molecule of pyridine, in the same fashion as the original alcohol, to give a pyridinium alkylsulfite intermediate, with release of the second chloride anion. A chloride anion then attacks the substrate carbon, displacing the sulfite leaving group, which in turn decomposes to release gaseous SO_2 and pyridine.



The following reactions show the commonly used methods to convert an alcohol into an alkyl halide.

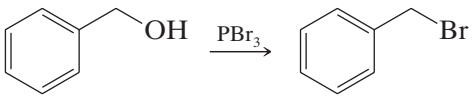
1. $R{-}OH + HI \xrightarrow[\Delta]{} R{-}I$
2. $R{-}OH + HBr \xrightarrow[\Delta]{} R{-}Br$
3. $R{-}OH + HCl \xrightarrow[\Delta]{ZnCl_2} R{-}Cl$
4. $R{-}OH + PCl_5 \longrightarrow R{-}Cl$
5. $R{-}OH + PCl_3 \xrightarrow{Pyridine} R{-}Cl$
6. $R{-}OH + SOCl_2 \xrightarrow[Pyridine]{} R{-}Cl + SO_2 + HCl$ (Darzen process)
7. $R{-}OH \xrightarrow{PBr_3} R{-}Br$

Solved Problem 10.6

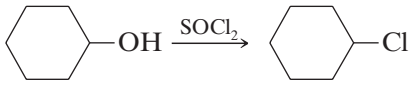
Starting with alcohols, outline a synthesis of each of the following: **(a)** benzyl bromide, **(b)** cyclohexyl chloride, and **(c)** butyl bromide.

Answers

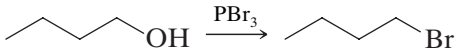
(a)



(b)



(c)



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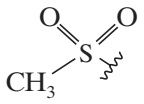
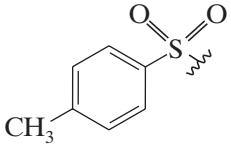
10.9 | TOSYLATES, MESYLATES, AND TRIFLATES: LEAVING GROUP DERIVATIVES OF ALCOHOLS

The hydroxyl group of an alcohol can be converted to a good leaving group by conversion to a **sulfonate ester** derivative. The most common sulfonate esters used for this purpose are methanesulfonate esters ("**mesylates**"), *p*-toluenesulfonate esters ("**tosylates**"), and trifluoromethanesulfonates ("**triflates**").



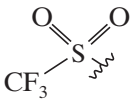
or $MeSO_2$—
or Ms—

The mesyl group



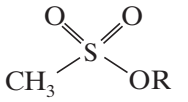
or Ts—

The tosyl group



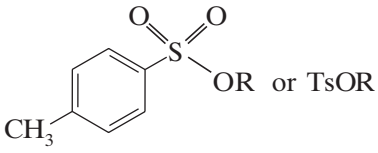
or CF_3SO_2—
or Tf—

The trifyl group



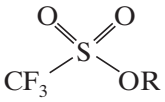
or $MeSO_3R$
or MsOR

An alkyl mesylate



or TsOR

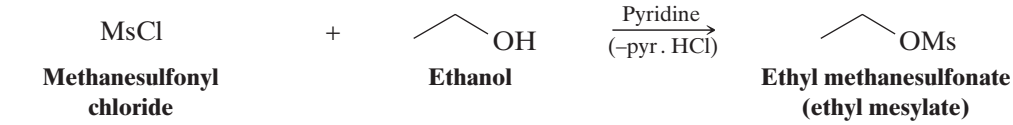
An alkyl tosylate



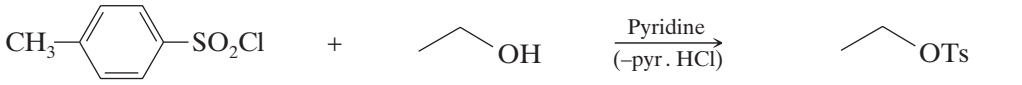
or CF_3SO_3R
or TfOR

An alkyl triflate

The desired sulfonate ester is usually prepared by reaction of the alcohol in pyridine with the appropriate sulfonyl chloride, that is, methanesulfonyl chloride (mesyl chloride) for a mesylate, *p*-toluenesulfonyl chloride (tosyl chloride) for a tosylate, or trifluoromethanesulfonyl chloride [or trifluoromethanesulfonic anhydride (triflic anhydride)] for a triflate. Pyridine (C_5H_5N, pyr) serves as the solvent and to neutralize the HCl formed. Ethanol, for example, reacts with methanesulfonyl chloride to form ethyl methanesulfonate and with *p*-toluenesulfonyl chloride to form ethyl *p*-toluenesulfonate:



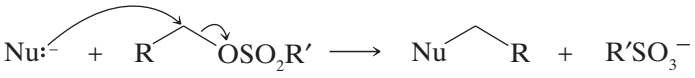
Methanesulfonyl chloride + **Ethanol** → **Ethyl methanesulfonate (ethyl mesylate)**



***p*-Toluenesulfonyl chloride (TsCl)** + **Ethanol** → **Ethyl *p*-toluenesulfonate (ethyl tosylate)**

It is important to note that formation of the sulfonate ester does not affect the stereochemistry of the alcohol carbon, because the C—O bond is not involved in this step. Thus, if the alcohol carbon is a chirality center, no change in configuration occurs on making the sulfonate ester—the reaction proceeds with **retention of configuration.** On reaction of the sulfonate ester with a nucleophile, the usual parameters of nucleophilic substitution reactions become involved.

Substrates for Nucleophilic Substitution Mesylates, tosylates, and triflates, because they are good leaving groups, are frequently used as substrates for nucleophilic substitution reactions. They are good leaving groups because the sulfonate anions they become when they depart are very weak bases. The triflate anion is the weakest base in this series, and is thus the best leaving group among them.



An alkyl sulfonate (tosylate, mesylate, etc.) → **A sulfonate ion (a very weak base– a good leaving group)**

- To carry out a nucleophilic substitution on an alcohol, we first convert the alcohol to an alkyl sulfonate and then, in a second reaction, allow it to react with a nucleophile.
- If the mechanism is S_N2, as shown in the second reaction of the following example, **inversion of configuration** takes place at the carbon that originally bore the alcohol hydroxyl group:

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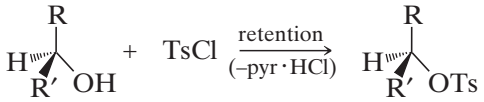
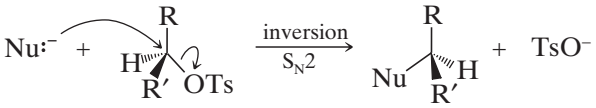
Step 1

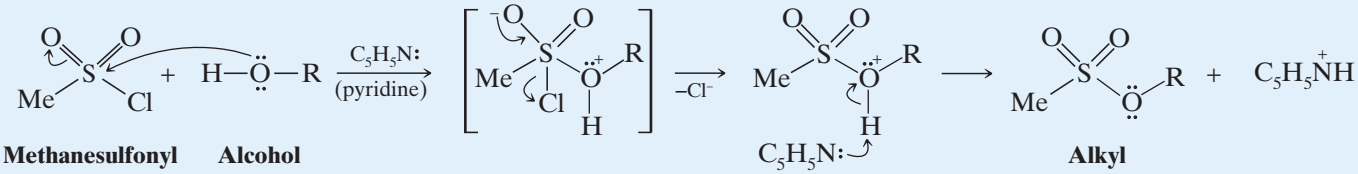


Step 2



The fact that the C—O bond of the alcohol does not break during formation of the sulfonate ester is accounted for by the following mechanism. Methanesulfonyl chloride is used in the example.

A MECHANISM FOR THE REACTION — Conversion of an Alcohol into a Mesylate (an Alkyl Methanesulfonate)



Methanesulfonyl chloride **Alcohol**

The alcohol oxygen attacks the sulfur atom of the sulfonyl chloride.

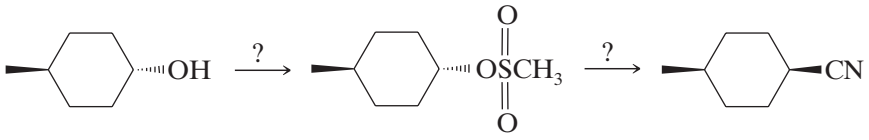
The intermediate loses a chloride ion.

Loss of a proton leads to the product.

Alkyl methanesulfonate

Solved Problem 10.7

Supply the missing reagents.



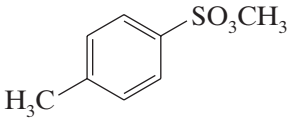
Answer

The overall transformation over two steps involves replacing an alcohol hydroxyl group by a cyano group with inversion of configuration. To accomplish this, we need to convert the alcohol hydroxyl to a good leaving group in the first step, which we do by making it a methanesulfonate ester (a mesylate) using methanesulfonyl chloride in pyridine. The second step is an S_N2 substitution of the methanesulfonate (mesyl) group, which we do using potassium or sodium cyanide in a polar aprotic solvent such as dimethylformamide (DMF).

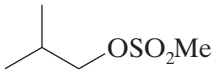
Practice Problem 10.8

Show how you would prepare the following compounds from the appropriate sulfonyl chlorides.

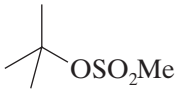
(a)



(b)



(c)



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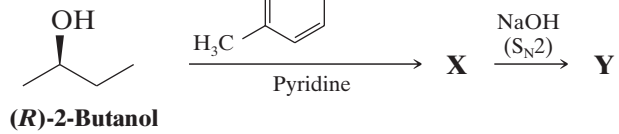
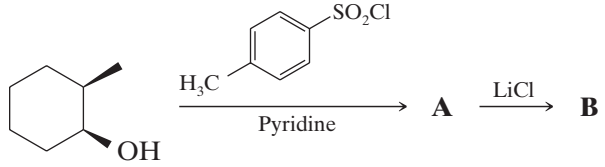
Practice Problem 10.9

Write structures for products **X**, **Y**, **A**, and **B**, showing stereochemistry.

(a)



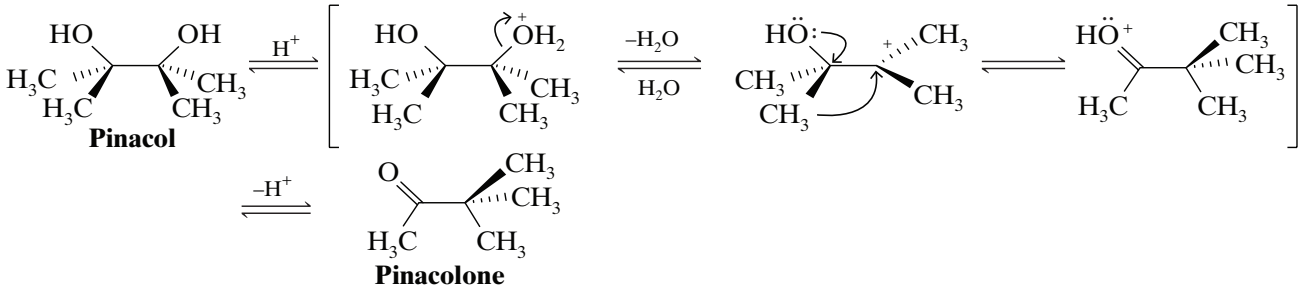
(b)



10.10 | REARRANGEMENTS

10.10A Pinacol Rearrangement

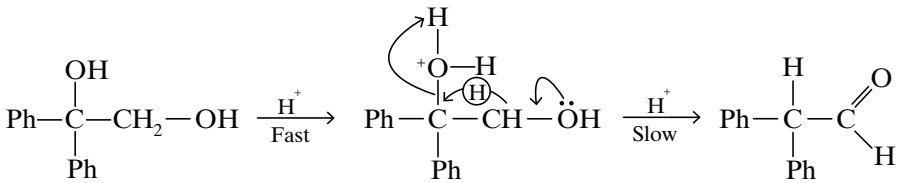
A defining example of pinacol rearrangement is shown in the following sequence of reactions. A pinacol itself is produced by reduction of acetone with magnesium, probably via a ketyl intermediate. Since the diol is symmetrical, protonation and loss of water takes place with equal probability at either of the hydroxyl groups. The resulting tertiary carbocation is relatively stable; and it reverts back to pinacol by reaction in the presence of isotopically labeled water. A 1,2-methyl shift generates an even more stable carbocation in which the charge is delocalized through heteroatom resonance. This new cation is simply the conjugate acid of the ketone pinacolone, which is the product of repeated rearrangements catalyzed by proton transfer. Each step in this rearrangement is potentially reversible, as shown by the acid catalyzed dehydration of pinacolone (and pinacol) to 2,3-dimethyl-1,3-butadiene under vigorous conditions.



The various factors that are important in the study of a pinacol rearrangement include the following:

1. The hydroxyl group that is lost as water or the intermediate carbocation that is more stable.
2. The inherent shifting tendency (i.e., migratory aptitude) of different substituent groups.
3. The influence of steric hindrance and other strain factors on the rearrangement.
4. Whether epoxides are formed as intermediates in the pinacol rearrangement.
5. Whether product stability governs the outcome of competing rearrangements.
6. Whether the reaction conditions (i.e., type of acid, concentration, solvent and temperature) influence the path of the rearrangement.

A few examples are given below to show the general nature of this transformation, and to illustrate the effect of some of the above factors.



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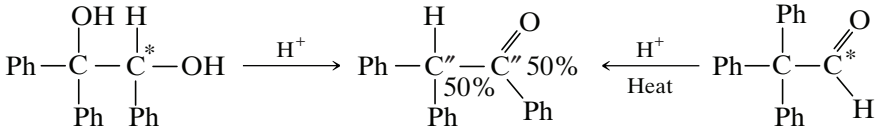
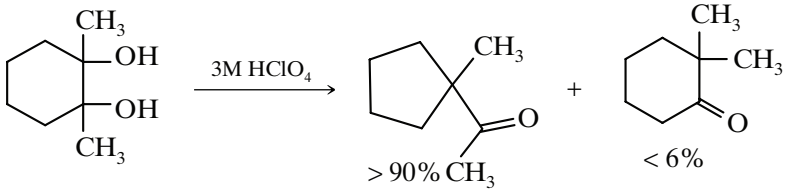
The above example predicts kinetic versus thermodynamic product control. Under mild acid condition, the diol rearranges rapidly to an aldehyde via a 1,2-H shift to the initially formed diphenyl tertiary carbocation. More vigorous acid treatment of the diol or the aldehyde generates the more stable phenyl ketone (a conjugated system of the phenyl and carbonyl groups).



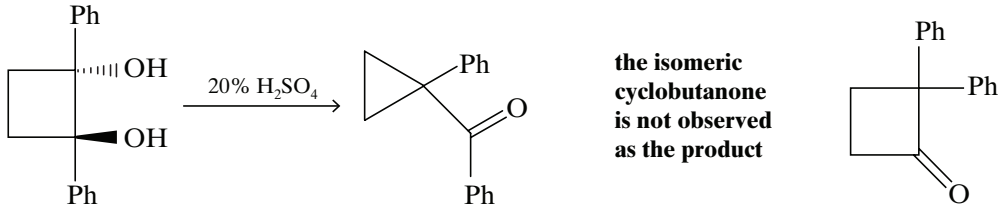
Here, rate of racemization = Rate of rearrangement
The isotopic label C* is scrambled as C″

The above is an example of a similar reacting system, which provides additional information from stereochemical and isotopic labeling viewpoints. Loss of water from the tertiary carbinol site, followed by a reversible 1,2-hydride shift, generates a conjugate acid of the ketone product. At short reaction times, racemization of the recovered diol starting material takes place at the same rate as that of rearrangement. A corresponding phenyl shift to the initially formed tertiary carbocation generates the aldehyde conjugate acid; and the aldehyde itself isomerizes to the same rearranged ketone under the conditions of the rearrangement. An isotopic carbon label (C*) in either the diol or aldehyde is scrambled (C″) in the course of these reactions, thus indicating an epoxide intermediate.

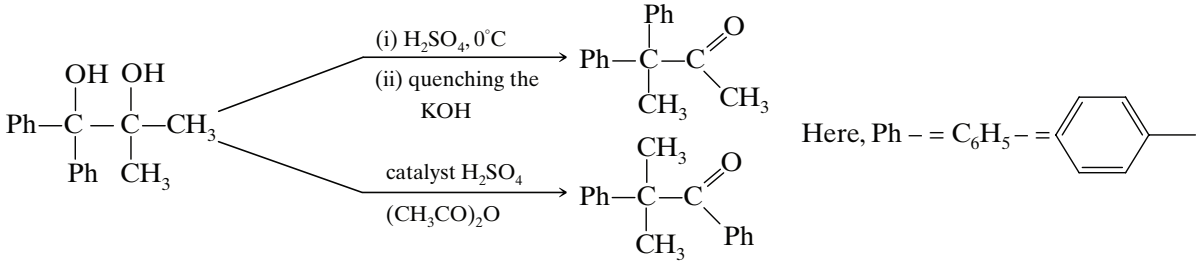


Both *cis* and *trans* isomers are interconverted

In this reaction, either the *cis* or *trans* diol may be used as a reactant. These isomers are rapidly interconvertible under the rearrangement conditions, indicating that the initial water loss is reversible; this is confirmed by isotopic oxygen exchange. The preference for a methylene group shift to a methyl group shift may reflect inherent migratory aptitudes, or possible group configurations in the tertiary carbocation intermediate. In the conformation shown above, both methyl and methylene groups may shift, or an epoxide ring may be formed reversibly. An alternative chair-like conformation with an equatorial methyl group should be more stable; however, it would not be suitable for a methyl shift. The predominant ring contraction is, therefore, understandable.



This is an unusual case where a strained ring contracts to an even smaller ring. Phenyl groups generally have a high migratory aptitude, so the failure to obtain 2,2-diphenylcyclobutanone as a product might seem surprising. However, the carbocation resulting from a phenyl shift would be just as strained as its precursor. In contrast, the shift of a methylene group of the ring generates an unstrained cation stabilized by phenyl and oxygen substituents. Conjugative stabilization of the phenyl ketone and absence of sp^2 hybridized carbon atoms in the small ring may also contribute to the stability of the resultant product.



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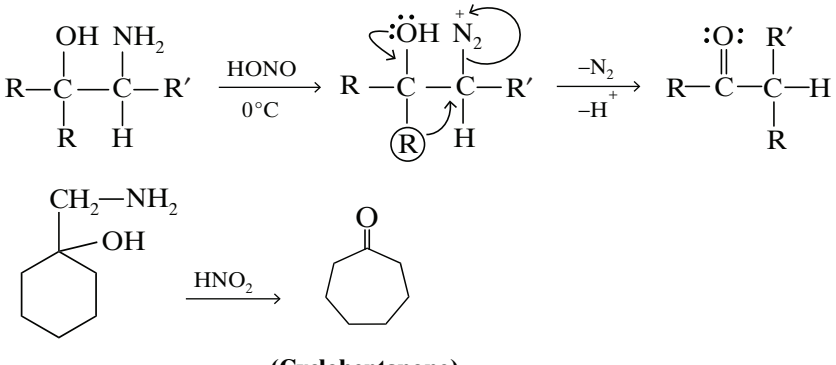
This reaction clearly shows the influence of reaction conditions on product composition, but explaining the manner in which different conditions perturb the outcome is quite challenging. Treatment with cold sulfuric acid should produce the more stable diphenyl tertiary carbocation, and a methyl group shift would then lead to the observed product. A Lewis acid in acetic anhydride, on the other hand, may selectively acetylate the less hindered dimethyl carbinol. In this case, the acetate becomes the favored leaving group (presumably coordinated with acid), followed by a 1,2-phenyl shift. It is reported that a symmetrically substituted isomeric diol rearranges exclusively by a methyl shift, but the configuration of the starting material was not stated (two diastereomers are possible). Due to the influence of other factors (previously mentioned), it has not been possible to determine an unambiguous migratory order for substituents in the pinacol rearrangement. However, some general trends are discernable. Benzopinacol, $(C_6H_5)_2C(OH)C(OH)(C_6H_5)_2$, undergoes rapid rearrangement to $(C_6H_5)_3CCOC_6H_5$ under much milder conditions than required for pinacol. It is often the case that phenyl or other aromatic substituents adjacent to a carbocation being formed will facilitate that ionization during their migration to the cationic site. In non-aromatic compounds of the type $(CH_3)_2C(OH)C(OH)RCH_3$, migration of R increases in the order $R = CH_3 < R = C_2H_5 << R = (CH_3)_3C$. Since the shifting alkyl group must carry a part of the overall positive charge, alkyl substitution should have a stabilizing influence on the rearrangement of the transition state. Finally, fluorine substitution, as in $C_6H_5(CF_3)C(OH)C(OH)(CF_3)C_6H_5$ renders the diol unreactive under acid catalyzed rearrangement conditions. Here, the powerful.

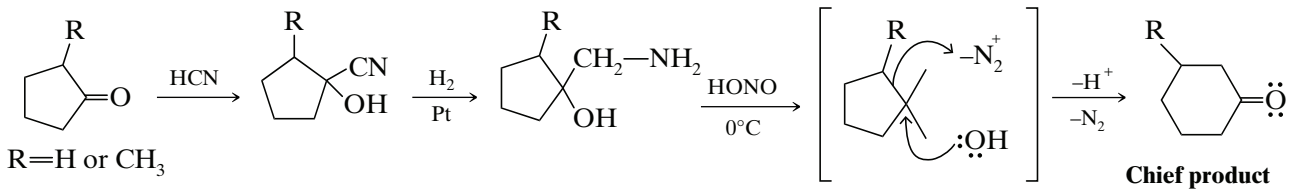
10.10B Tiffeneau–Demjanov Rearrangement

The pinacol rearrangement presented a problem as it was difficult to determine the initial site of the carbocation formation. This uncertainty was removed by *nitrous acid deamination* of the corresponding primary amino alcohols, as shown in the following reaction. As this reaction is normally carried out under very mild conditions, the possibility of the initial rearrangement getting obscured by subsequent contributions is reduced considerably.



(Cycloheptanone)

The Tiffeneau–Demjanov rearrangement is often used to transform a cyclic ketone into a homolog that is one ring size larger. Such an application, which proceeds via a *cyanohydrin intermediate*, is shown in the first example below.



R=H or CH_3

Chief product

Cyclic ketones have two α-carbon atoms, each of which may shift to the nascent primary carbocation. If R = H in the above case these two groups are identical and on shifting give the same product. However, if $R = CH_3$, the secondary alkyl group shifts preferentially, the main product being 3-methylcyclohexanone; 2-methyl isomer is the minor product here. The second reaction given below is informative because it shows that the chiral secondary butyl group moves with retention of configuration.

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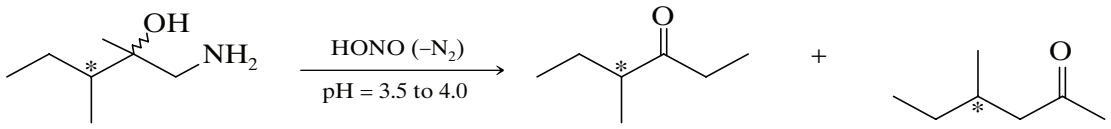
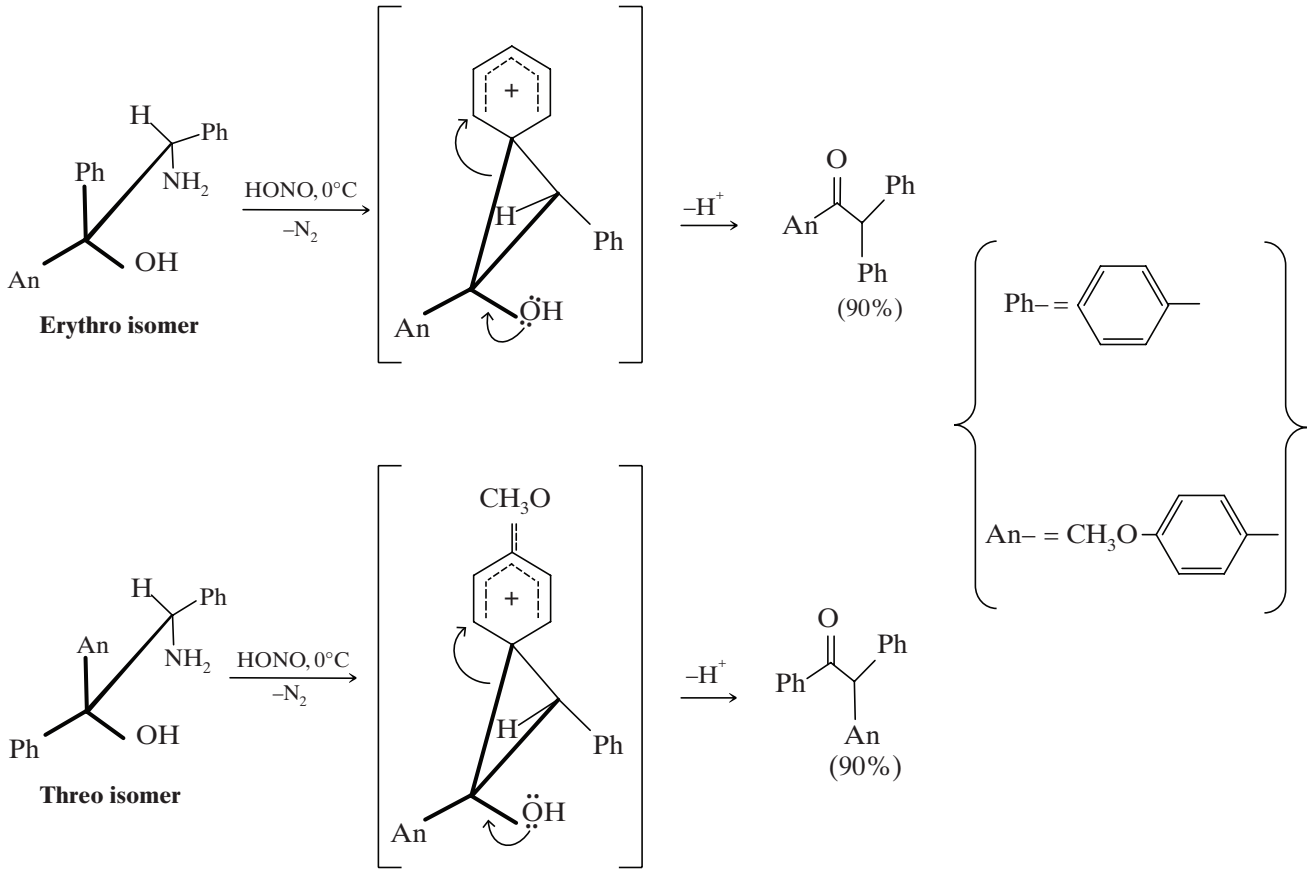


(3R)-1-amino-2,3-dimethyl-2-pentanol (mixture of diastereomers) | **(4R)-4-methyl-3-hexanone (1,2-methyl shift)** | **4-methyl-2-hexanone (1,2-sec-butyl shift, 87% R)**

The third example illustrates the importance of substrate configuration during rearrangement. The initial stage of an aryl group shift to an adjacent carbocation site may be viewed as an intramolecular *electrophilic substitution* of the Friedel-Crafts type of reaction. The aryl ring approach from the side opposite to the departing nitrogen of the diazonium ion generates a *phenonium ion* intermediate (shown in brackets), the structure of which is similar to a *benzenonium ion*.



Erythro isomer

The third example illustrates the importance of substrate configuration during rearrangement. The initial stage of an aryl group shift to an adjacent carbocation site may be viewed as an intramolecular *electrophilic substitution* of the Friedel-Crafts type of reaction. The aryl ring approach from the side opposite to the departing nitrogen of the diazonium ion generates a *phenonium ion* intermediate (shown in brackets), the structure of which is similar to a *benzenonium ion*.

10.11 | SYNTHESIS OF ETHERS

10.11A Ethers by Intermolecular Dehydration of Alcohols

Two alcohol molecules can form an ether by loss of water through an acid-catalyzed substitution reaction.

$$R-OH + HO-R \xrightarrow[-H_2O]{HA} R-O-R$$

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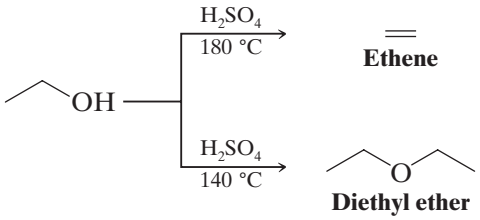
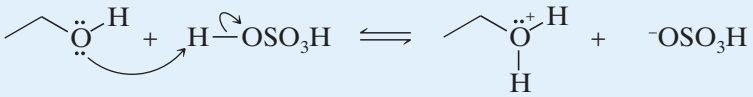
This reaction competes with the formation of alkenes by acid-catalyzed alcohol dehydration (Sections 7.7 and 7.8). Intermolecular dehydration of alcohols usually takes place at lower temperature than dehydration to an alkene, and dehydration to the ether can be aided by distilling the ether as it is formed. For example, diethyl ether is made commercially by dehydration of ethanol. Diethyl ether is the predominant product at 140 °C; ethene is the predominant product at 180 °C.



The formation of the ether occurs by an S_N2 mechanism with one molecule of the alcohol acting as the nucleophile and another protonated molecule of the alcohol acting as the substrate (see Section 10.4).

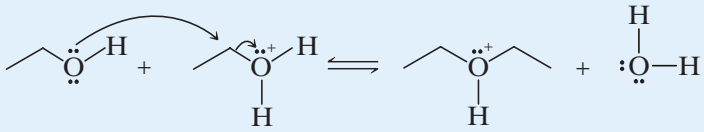
A MECHANISM FOR THE REACTION — Intermolecular Dehydration of Alcohols to Form an Ether

Step 1



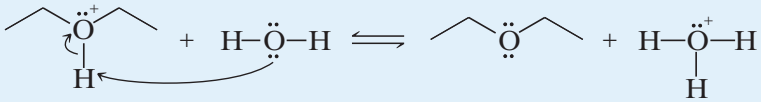
This is an acid–base reaction in which the alcohol accepts a proton from the sulfuric acid.

Step 2



Another molecule of the alcohol acts as a nucleophile and attacks the protonated alcohol in an S_N2 reaction.

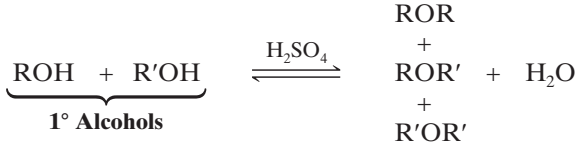
Step 3



Another acid–base reaction converts the protonated ether to an ether by transferring a proton to a molecule of water (or to another molecule of the alcohol).

Complications of Intermolecular Dehydration The method of synthesizing ethers by intermolecular dehydration has some important limitations.

- Attempts to synthesize ethers by intermolecular dehydration of secondary alcohols are usually unsuccessful because alkenes form too easily.
- Attempts to make ethers with tertiary alkyl groups lead predominantly to alkenes.
- Intermolecular dehydration is not useful for the preparation of unsymmetrical ethers from primary alcohols because the reaction leads to a mixture of products:



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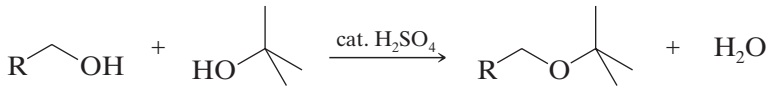
Practice Problem 10.10

An exception to what we have just said has to do with syntheses of unsymmetrical ethers in which one alkyl group is a *tert*-butyl group and the other group is primary. For example, this synthesis can be accomplished by adding *tert*-butyl alcohol to a mixture of the primary alcohol and H_2SO_4 at room temperature.



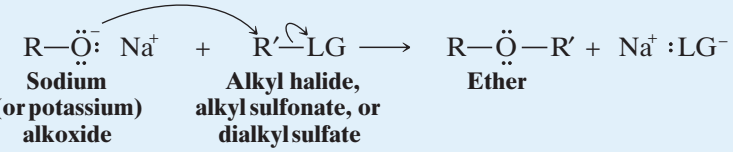
Give a likely mechanism for this reaction and explain why it is successful.

10.11B The Williamson Ether Synthesis

An important route to unsymmetrical ethers is a nucleophilic substitution reaction known as the **Williamson ether synthesis**.

- The Williamson ether synthesis consists of an S_N2 reaction of a sodium alkoxide with an alkyl halide, alkyl sulfonate, or alkyl sulfate.

A MECHANISM FOR THE REACTION — The Williamson Ether Synthesis

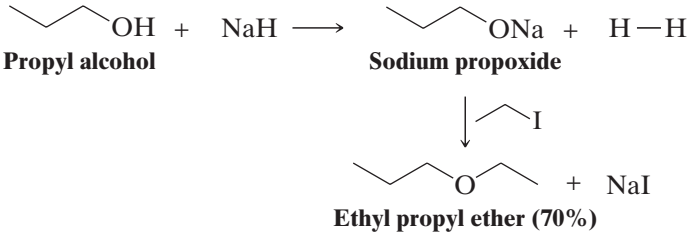


Sodium (or potassium) alkoxide — **Alkyl halide, alkyl sulfonate, or dialkyl sulfate** — **Ether**

The alkoxide ion reacts with the substrate in an S_N2 reaction, with the resulting formation of an ether. The substrate must be unhindered and bear a good leaving group. Typical substrates are 1° or 2° alkyl halides, alkyl sulfonates, and dialkyl sulfates:

$$-LG = -\ddot{Br}:,\quad -\ddot{I}:,\quad -OSO_2R'',\ \text{or}\ -OSO_2OR''$$

The following reaction is a specific example of the Williamson ether synthesis. The sodium alkoxide can be prepared by allowing an alcohol to react with NaH:



Propyl alcohol — **Sodium propoxide**

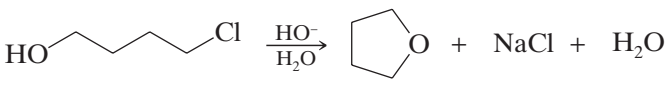
Ethyl propyl ether (70%)

The usual limitations of S_N2 reactions apply here.

- Best results are obtained when the alkyl halide, sulfonate, or sulfate is primary (or methyl). **If the substrate is tertiary, elimination is the exclusive result**. Substitution is also favored over elimination at lower temperatures.

Solved Problem 10.8

The cyclic ether tetrahydrofuran (THF) can be synthesized by treating 4-chloro-1-butanol with aqueous sodium hydroxide (see below). Propose a mechanism for this reaction.



Tetrahydrofuran

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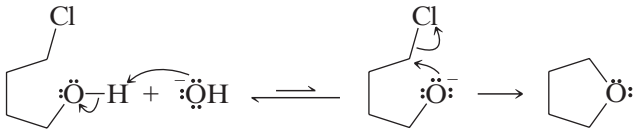
Answer

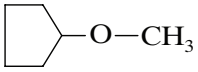
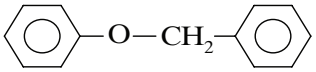
Removal of a proton from the hydroxyl group of 4-chloro-1-butanol gives an alkoxide ion that can then react with itself in an intramolecular S_N2 reaction to form a ring.



Even though treatment of the alcohol with hydroxide does not favor a large equilibrium concentration of the alkoxide, the alkoxide anions that are present react rapidly by the intramolecular S_N2 reaction. As alkoxide anions are consumed by the substitution reaction, their equilibrium concentration is replenished by deprotonation of additional alcohol molecules, and the reaction is drawn to completion.

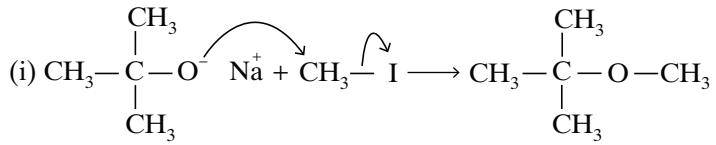
Solved Problem 10.9

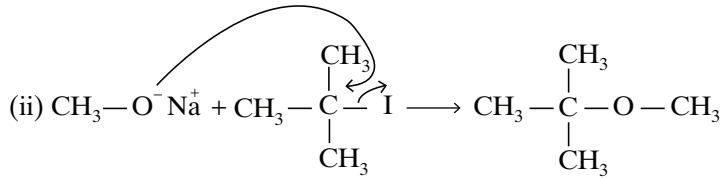
Prepare the following ethers by Williamson's ether synthesis

(a) $CH_3-O-C(CH_3)_2-CH_3$ **(b)**  **(c)** 

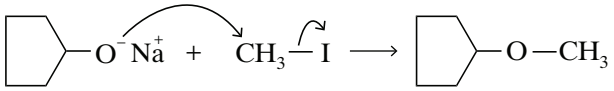
Answer

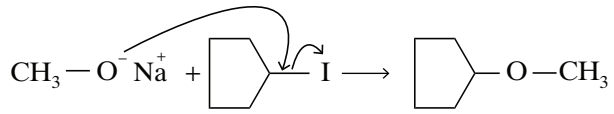
There are two approaches for preparing each of the above-mentioned ethers by Williamson's ether synthesis. These are provided below:

(a) (i) 

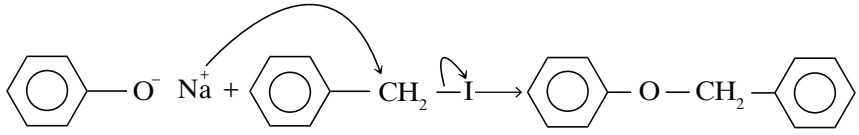
(ii) 

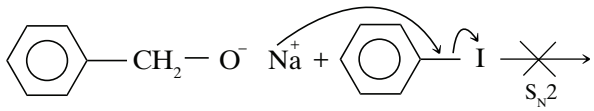
Out of the two approaches, (i) is more favorable.

(b) (i) 

(ii) 

The approach (i) is more favorable because CH_3-I is more reactive toward S_N2 reaction (due to less steric hindrance).

(c) (i) 

(ii) 

Only approach (i) works because aryl halide will not undergo S_N2 reaction since it is resonance stabilized.

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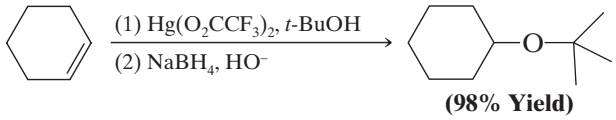
10.11C Synthesis of Ethers by Alkoxymercuration–Demercuration

Alkoxymercuration–demercuration is another method for synthesizing ethers.

- The reaction of an alkene with an alcohol in the presence of a mercury salt such as mercuric acetate or trifluoroacetate leads to an alkoxymercury intermediate, which on reaction with sodium borohydride yields an ether.

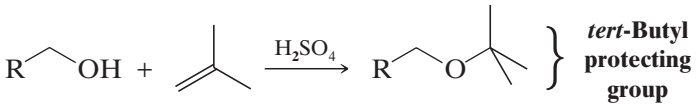
When the alcohol reactant is also the solvent, the method is called solvomercuration–demercuration. This method directly parallels hydration by oxymercuration–demercuration (Section 8.5):



(98% Yield)

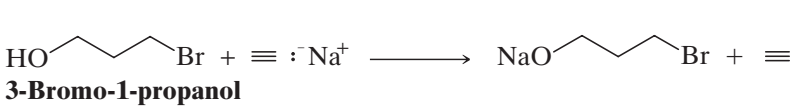
10.11D *tert*-Butyl Ethers by Alkylation of Alcohols: Protecting Groups

Primary alcohols can be converted to *tert*-butyl ethers by dissolving them in a strong acid such as sulfuric acid and then adding isobutylene to the mixture. (This procedure minimizes dimerization and polymerization of the isobutylene.)



- A *tert*-butyl ether can be used to "protect" the hydroxyl group of a primary alcohol while another reaction is carried out on some other part of the molecule.
- A *tert*-butyl **protecting group** can be removed easily by treating the ether with dilute aqueous acid.

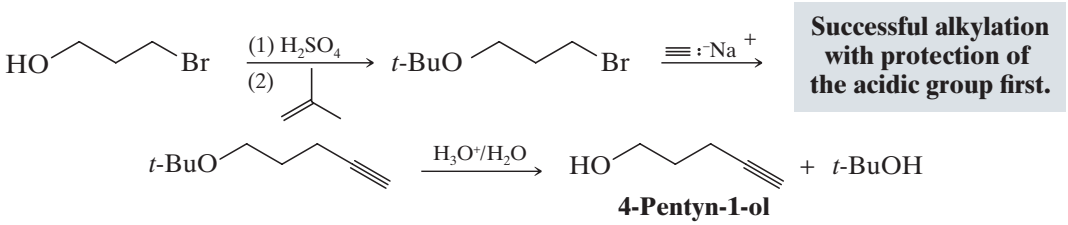
Suppose, for example, we wanted to prepare 4-pentyn-1-ol from 3-bromo-1-propanol and sodium acetylide. If we allow them to react directly, the strongly basic sodium acetylide will react first with the hydroxyl group, making the alkylation unsuccessful:



3-Bromo-1-propanol

Unsuccessful alkylation due to competing acid–base reaction.

However, if we protect the —OH group first, the synthesis becomes feasible:



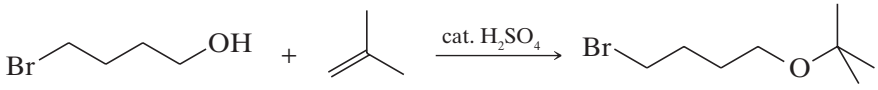
4-Pentyn-1-ol

Successful alkylation with protection of the acidic group first.

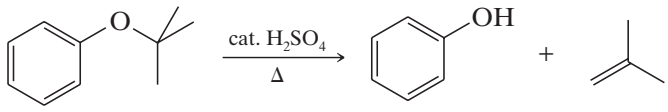
Practice Problem 10.11

Propose mechanisms for the following reactions.

(a)



(b)



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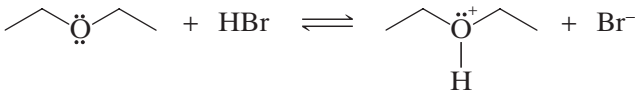
10.12 | REACTIONS OF ETHERS

Dialkyl ethers react with very few reagents other than acids. The only reactive sites that molecules of a dialkyl ether present to another reactive substance are the C—H bonds of the alkyl groups and the —Ö:— group of the ether linkage. Ethers resist attack by nucleophiles (why?) and by bases. This lack of reactivity coupled with the ability of ethers to solvate cations (by donating an electron pair from their oxygen atom) makes ethers especially useful as solvents for many reactions.

Ethers are like alkanes in that they undergo halogenation reactions (Chapter 9), but these reactions are of little synthetic importance. They also undergo slow autoxidation to form explosive peroxides (see Section 9.3D).

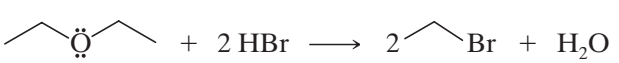
The oxygen of the ether linkage makes ethers weakly basic. Ethers can react with proton donors to form **oxonium salts**:



An oxonium salt

10.12A Cleavage of Ethers

Heating dialkyl ethers with very strong acids (HI, HBr, and H_2SO_4) causes them to undergo reactions in which the carbon–oxygen bond breaks. Diethyl ether, for example, reacts with hot concentrated hydrobromic acid to give two molecular equivalents of bromoethane:

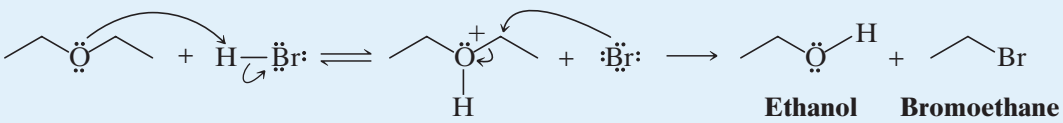


Cleavage of an ether

The mechanism for this reaction begins with formation of an oxonium cation. Then, an S_N2 reaction with a bromide ion acting as the nucleophile produces ethanol and bromoethane. Excess HBr reacts with the ethanol produced to form the second molar equivalent of bromoethane.

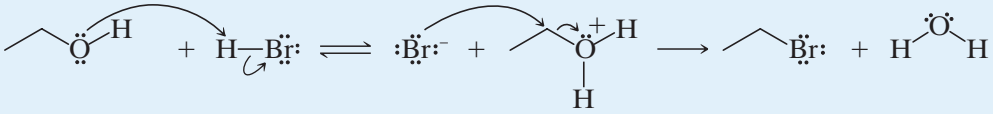
A MECHANISM FOR THE REACTION — Ether Cleavage by Strong Acids

Step 1



Ethanol **Bromoethane**

Step 2 **In step 2 the ethanol (just formed) reacts with HBr (present in excess) to form a second molar equivalent of bromoethane**



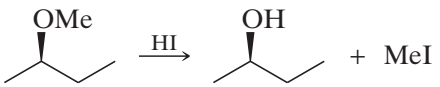
Practice Problem 10.12

When an ether is treated with *cold* concentrated HI, cleavage occurs as follows:

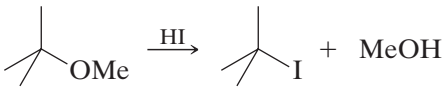


When mixed ethers are used, the alcohol and alkyl iodide that form depend on the nature of the alkyl groups. Use mechanisms to explain the following observations:

(a)



(b)



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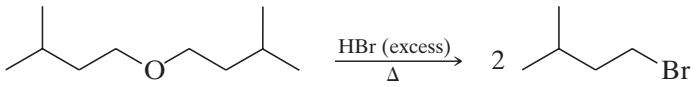
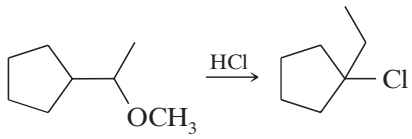
Practice Problem 10.13

Write a detailed mechanism for the following reaction.



Practice Problem 10.14

Provide a mechanism for the following reaction.

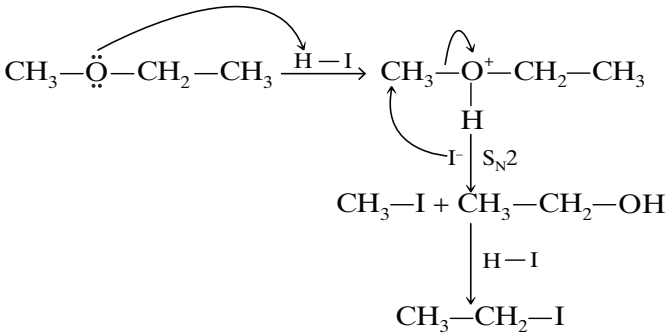


Solved Problem 10.10

Explain why methyl ethyl ether forms both methyliodide and ethyliodide on being heated with excess of HI?

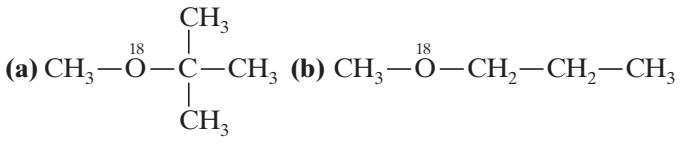
Answer

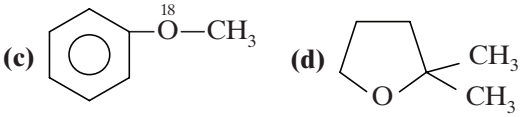
The formation of both methyl- and ethyl iodide can be explained as follows:



Solved Problem 10.11

Give the major products obtained on heating each of the following ethers with one equivalent of HI.



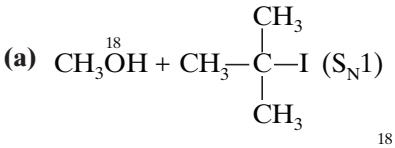


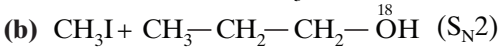
(e) $CH_3—CH_2—O—CH_2—Ph$

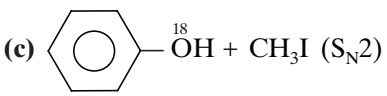
(f) $CH_3—CH_2—O—CH_2—CH_3$

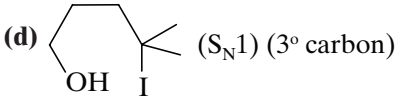
Answer

The major products formed in the reactions with above ethers are as follows:









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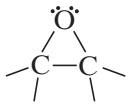
(e) $Ph-CH_2-I + CH_3-CH_2-OH$
[S_N1 (due to the formation of benzyl carbocation)]

(f) $CH_3-CH_2-I + CH_3-CH_2-OH$

10.13 | EPOXIDES

Epoxides are cyclic ethers with three-membered rings. In IUPAC nomenclature epoxides are called **oxiranes**. The simplest epoxide has the common name ethylene oxide:



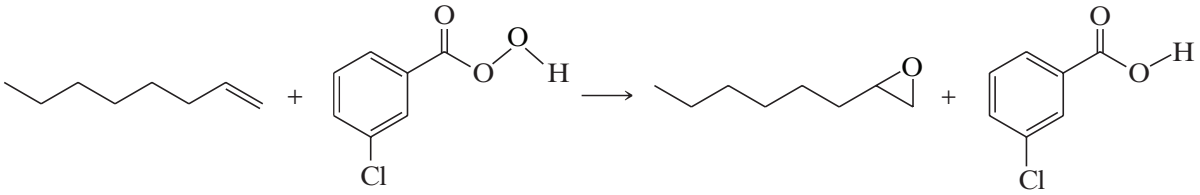
An epoxide



IUPAC name: oxirane
Common name: ethylene oxide

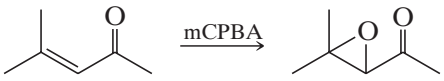
10.13A Synthesis of Epoxides: Epoxidation

Epoxides can be synthesized by the reaction of an alkene with an organic **peroxy acid** (RCO_3H—sometimes called simply a **peracid**), a process that is called **epoxidation**. *meta*-Chloroperoxybenzoic acid (mCPBA) is one peroxy acid reagent commonly used for epoxidation. The following reaction is an example.



1-Octene **mCPBA** **(81%)** ***meta*-Chlorobenzoic acid**

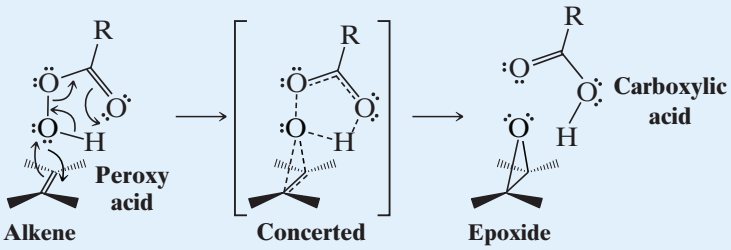
meta-Chlorobenzoic acid is a by-product of the reaction. Often it is not written in the chemical equation, as the following example illustrates.



(77%)

As the first example illustrates, the peroxy acid transfers an oxygen atom to the alkene. The following mechanism has been proposed.

A MECHANISM FOR THE REACTION — Alkene Epoxidation



The peroxy acid transfers an oxygen atom to the alkene in a cyclic, single-step mechanism. The result is the syn addition of the oxygen to the alkene, with the formation of an epoxide and a carboxylic acid.

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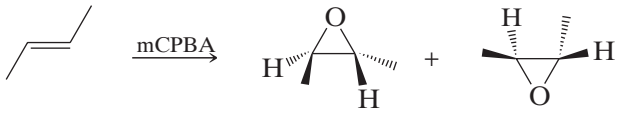
10.13B Stereochemistry of Epoxidation

- The reaction of alkenes with peroxy acids is, of necessity, a **syn** addition, and it is **stereospecific**. Furthermore, the oxygen atom can add to either face of the alkene.

For example, *trans*-2-butene yields racemic *trans*-2,3-dimethyloxirane, because addition of oxygen to each face of the alkene generates an enantiomer. *cis*-2-Butene, on the other hand, yields only *cis*-2,3-dimethyloxirane, no matter which face of the alkene accepts the oxygen atom, due to the plane of symmetry in both the reactant and the product. If additional chirality centers are present in a substrate, then diastereomers would result.



***cis*-2-Butene** ***cis*-2,3-Dimethyloxirane (a meso compound)**



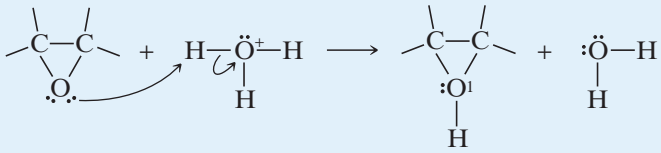
***trans*-2-Butene** **Enantiomeric *trans*-2,3-dimethyloxiranes**

10.14 | REACTIONS OF EPOXIDES

- The highly strained three-membered ring of epoxides makes them much more reactive toward nucleophilic substitution than other ethers.

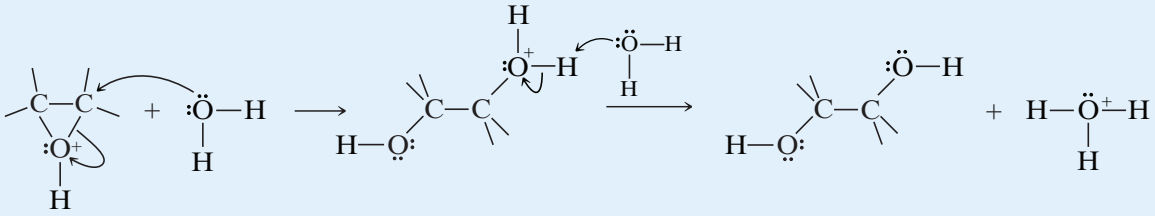
Acid catalysis assists epoxide ring opening by providing a better leaving group (an alcohol) at the carbon atom undergoing nucleophilic attack. This catalysis is especially important if the nucleophile is a weak nucleophile such as water or an alcohol. An example is the acid-catalyzed hydrolysis of an epoxide.

A MECHANISM FOR THE REACTION — Acid-Catalyzed Ring Opening of an Epoxide



Epoxide **Protonated epoxide**

The acid reacts with the epoxide to produce a protonated epoxide.



Protonated epoxide **Weak nucleophile** **Protonated 1,2-diol** **1,2-Diol**

The protonated epoxide reacts with the weak nucleophile (water) to form a protonated 1,2-diol, which then transfers a proton to a molecule of water to form the 1,2-diol and a hydronium ion.

Epoxides can also undergo base-catalyzed ring opening. Such reactions do not occur with other ethers, but they are possible with epoxides (because of ring strain), provided that the attacking nucleophile is also a strong base such as an alkoxide ion or hydroxide ion.

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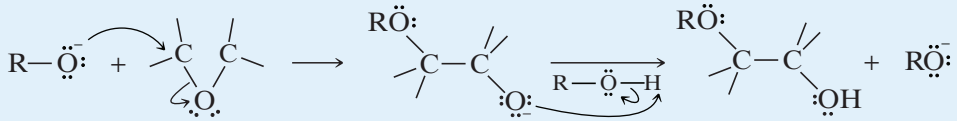
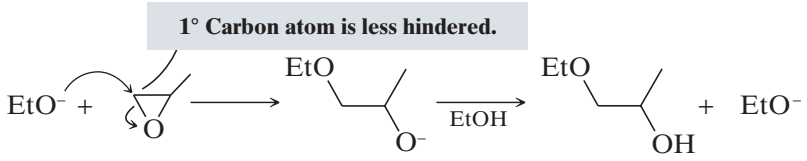
A MECHANISM FOR THE REACTION — Base-Catalyzed Ring Opening of an Epoxide



A strong nucleophile such as an alkoxide ion or a hydroxide ion is able to open the strained epoxide ring in a direct S_N2 reaction.

- **Base-catalyzed ring opening** of an unsymmetrical epoxide occurs primarily by attack of the nucleophile ***at the less substituted carbon atom***.

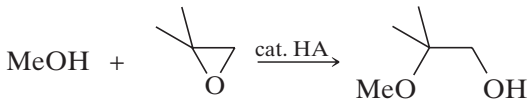
For example, methyloxirane reacts with an alkoxide ion mainly at its primary carbon atom:



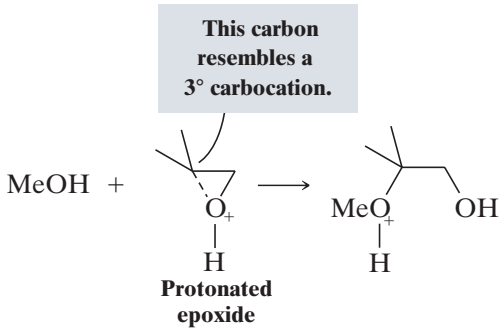
This is just what we should expect: the reaction is, after all, an S_N2 reaction, and, as we learned earlier (Section 6.13A), primary substrates react more rapidly in S_N2 reactions because they are less sterically hindered.

- **Acid-catalyzed ring opening** of an unsymmetrical epoxide occurs primarily by attack of the nucleophile ***at the more substituted carbon atom***.

For example,



The reason: bonding in the protonated epoxide (see the following reaction) is unsymmetrical, with the more highly substituted carbon atom bearing a considerable positive charge; the reaction is S_N1 like. The nucleophile, therefore, attacks this carbon atom even though it is more highly substituted:



The more highly substituted carbon atom bears a greater positive charge because it resembles a more stable tertiary carbocation. [Notice how this reaction (and its explanation) resembles that given for halohydrin formation from unsymmetrical alkenes in Section 8.13 and attack on mercurinium ions.]

Formation of arene oxide and its rearrangement into phenol: Arene oxide is formed when enzyme P_{450} reacts with benzene and the product rearranges into phenol in presence of acid.

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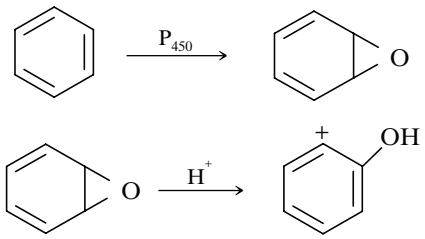
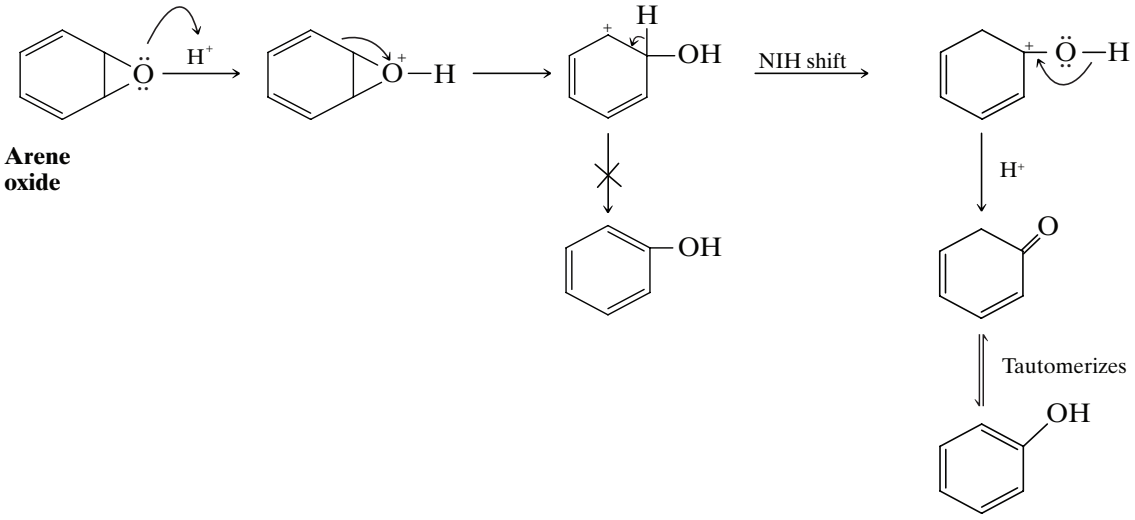
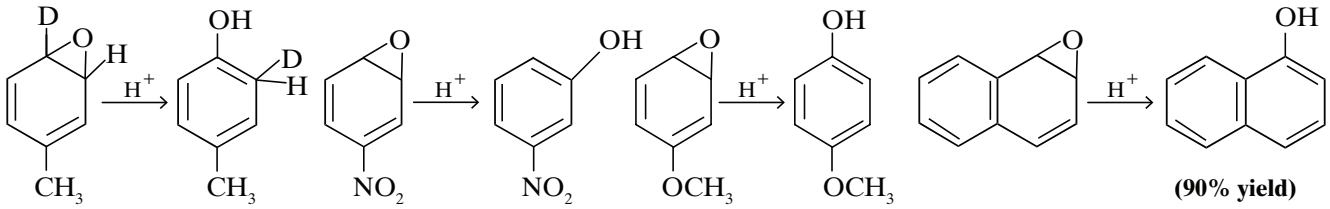


The mechanism of arene oxide–phenol rearrangement is explained as follows:



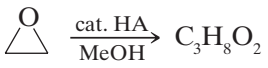
Here, NIH – National Institute of Health Shift

In all the reactions of arene oxide rearrangement, first the carbocation is stabilized which then leads to the final products. For example,

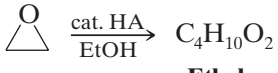


Practice Problem 10.15

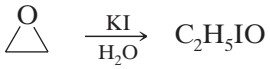
Propose structures for each of the following products derived from oxirane (ethylene oxide):

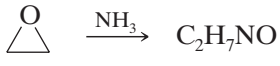
(a) 

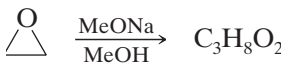
Methyl Cellosolve

(b) 

Ethyl Cellosolve

(c) 

(d) 

(e) 

Practice Problem 10.16

Provide a mechanistic explanation for the following observation.

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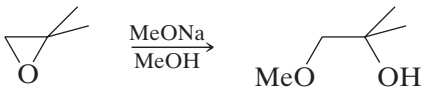
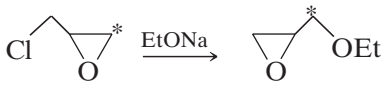


Practice Problem 10.17

When sodium ethoxide reacts with 1-(chloromethyl)oxirane (also called epichlorohydrin), labeled with ^{14}C as shown by the asterisk in **I**, the major product is **II**. Provide a mechanistic explanation for this result.

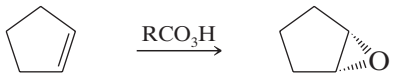


I **II**

1-(Chloromethyl)oxirane (epichlorohydrin)

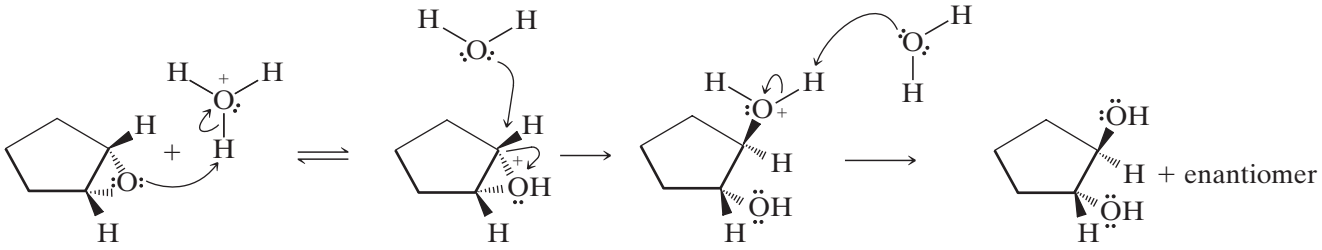
10.15 | ANTI 1,2-DIHYDROXYLATION OF ALKENES VIA EPOXIDES

Epoxidation of cyclopentene with a peroxycarboxylic acid produces 1,2-epoxycyclopentane:



Cyclopentene **1,2-Epoxycyclopentane**

Acid-catalyzed hydrolysis of 1,2-epoxycyclopentane, shown below, yields a trans diol, *trans*-1,2-cyclopentanediol. Water acting as a nucleophile attacks the protonated epoxide from the side opposite the epoxide group. The carbon atom being attacked undergoes an inversion of configuration. We show here only one carbon atom being attacked. Attack at the other carbon atom of this symmetrical system is equally likely and produces the enantiomeric form of *trans*-1,2-cyclopentanediol:



***trans*-1,2-Cyclopentanediol**

Epoxidation followed by acid-catalyzed hydrolysis gives us, therefore, a method for **anti 1,2-dihydroxylation** of a double bond (as opposed to syn 1,2-dihydroxylation, Section 8.15). The stereochemistry of this technique parallels closely the stereochemistry of the bromination of cyclopentene given earlier (Section 8.13).

Practice Problem 10.18

Outline a mechanism similar to the one just given that shows how the enantiomeric form of *trans*-1,2-cyclopentanediol is produced.

10.16 | CROWN ETHERS

Crown ethers are compounds having structures like that of 18-crown-6, below. 18-Crown-6 is a cyclic oligomer of ethylene glycol. Crown ethers are named as *x*-crown-*y*, where *x* is the total number of atoms in the ring and *y* is the number of oxygen atoms. A key property of crown ethers is that they are able to bind cations, as shown below for 18-crown-6 and a potassium ion.

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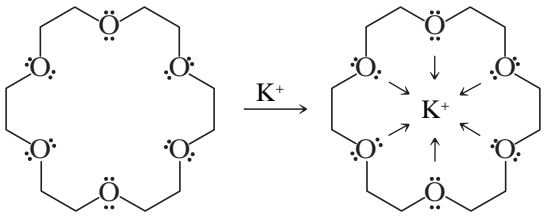
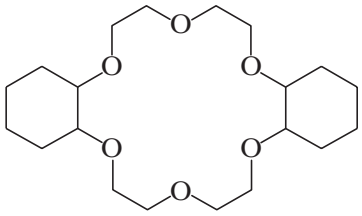


18-Crown-6

Crown ethers render many salts soluble in nonpolar solvents. For this reason they are called **phase transfer catalysts**. When a crown ether coordinates with a metal cation it masks the ion with a hydrocarbon-like exterior. 18-Crown-6 coordinates very effectively with potassium ions because the cavity size is correct and because the six oxygen atoms are ideally situated to donate their electron pairs to the central ion in a Lewis acid–base complex.

- The relationship between a crown ether and the ion it binds is called a **host–guest relationship**.

Salts such as KF, KCN, and potassium acetate can be transferred into aprotic solvents using catalytic amounts of 18-crown-6. Use of a crown ether with a nonpolar solvent can be very favorable for an S_N2 reaction because the nucleophile (such as F^-, CN^-, or acetate from the compounds just listed) is unencumbered by solvent in an aprotic solvent, while at the same time the cation is prevented by the crown ether from associating with the nucleophile. Dicyclohexano-18-crown-6 is another example of a phase transfer catalyst. It is even more soluble in nonpolar solvents than 18-crown-6 due to its additional hydrocarbon groups. Phase transfer catalysts can also be used for reactions such as oxidations. (There are phase transfer catalysts that are not crown ethers, as well.)



Dicyclohexano-18-crown-6

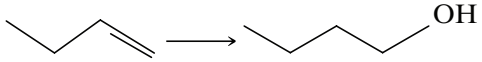
Practice Problem 10.19

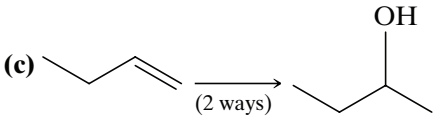
Write structures for **(a)** 15-crown-5 and **(b)** 12-crown-4.

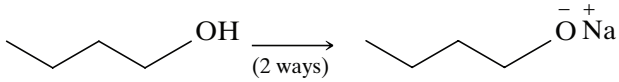
Solved Problem 10.12

Suggest reagents for the following transformations

(a) $CH_3I \longrightarrow CH_3OH$

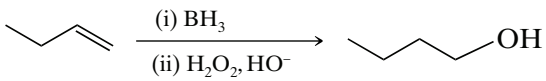
(b) 

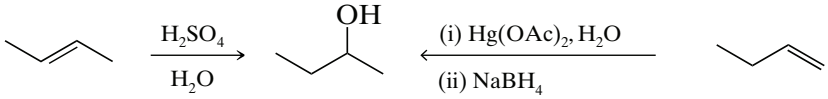
(c) 

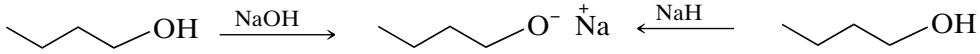
(d) 

Answer

(a) $CH_3I \xrightarrow{NaOH} CH_3OH$

(b) 

(c) 

(d) 

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Solved Problem 10.13

Choose the best synthetic route to $(CH_3)_3COCH_3$ amongst the following:

(a) React $(CH_3)_3COH$ with KOH, then add CH_3I.

(b) React $(CH_3)_3COH$ with NaOH, then add CH_3I.

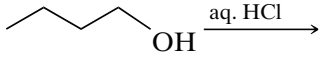
(c) React CH_3OH with KOH, then add $(CH_3)_3Cl$.

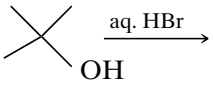
Answer

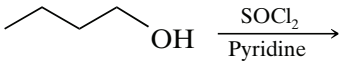
The best synthetic route to $(CH_3)_3COCH_3$ is route **(a)**. In route **(b)**, there is difference in the basicity of hydroxide and *t*-butoxide, and the conjugate base of $(CH_3)_3COH$ is not sufficiently large to affect complete deprotonation of the alcohol. When CH_3I is added to the reaction mixture, there will be two alkoxides (hydroxide and *t*-butoxide) competing for the reaction. In route **(c)**, reaction of CH_3O— (a strong base) with a tertiary alkyl halide will give E_2, not S_N2, products.

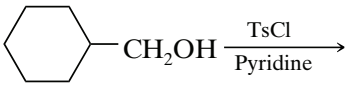
Solved Problem 10.14

Give the products of each of the following reaction.

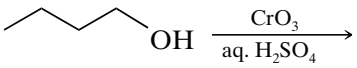
(a) 

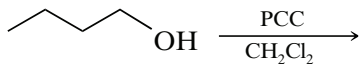
(b) 

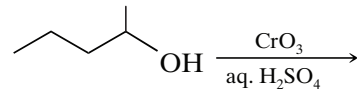
(c) 

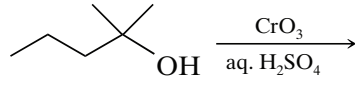
(d) 

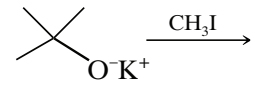
(e) Product of reaction (d) $\xrightarrow[DMF]{NaCN}$

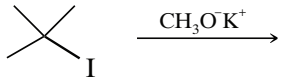
(f) 

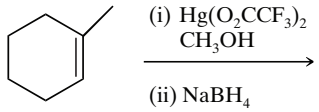
(g) 

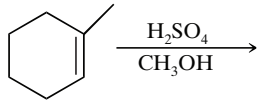
(h) 

(i) 

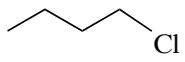
(j) 

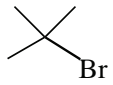
(k) 

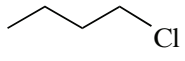
(l) 

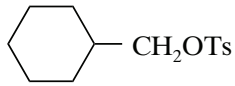
(m) 

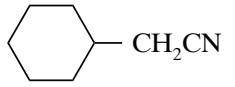
Answer

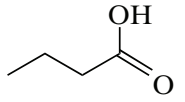
(a) 

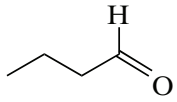
(b) 

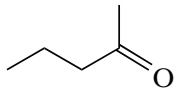
(c) 

(d) 

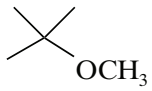
(e) 

(f) 

(g) 

(h) 

(i) No reaction (or possible dehydration)

(j) 

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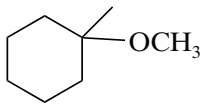
(l, m) 

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Solved Problem 10.15

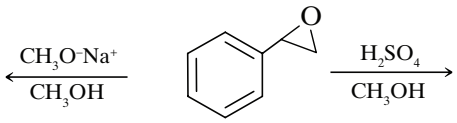
Why does ethylene oxide react readily with nucleophiles such as ammonia, whereas THF is inert to nucleophilic attack by ammonia?

Answer

The carbon–oxygen bond of a generic ether R—O—R is inert to nucleophilic attack because an alkoxide (RO—) is a poor leaving group. Therefore, we expect THF to be inert to nucleophilic attack. An epoxide has significant ring strain (about 27 kcal mol^{-1}). Breaking of C—O bond relieves this ring strain. This release of ring strain lowers the transition state energy so as to overcome the poor leaving group ability of RO—, so that the C—O bond of an epoxide can be cleaved by a strong nucleophile.

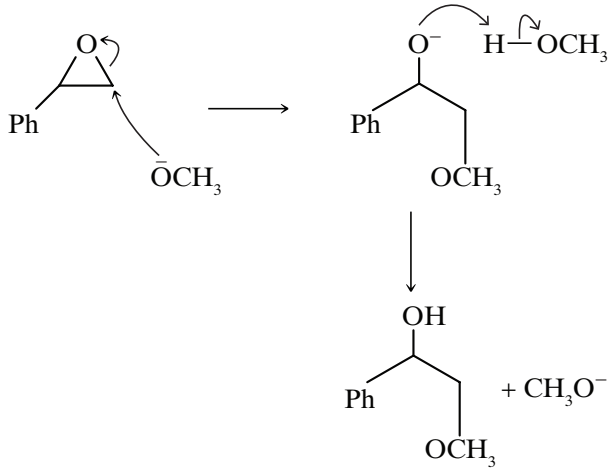
Solved Problem 10.16

Give the products and mechanism for each of the following reactions. Explain why nucleophilic attack on the epoxide occurs at different sites in the two reactions.

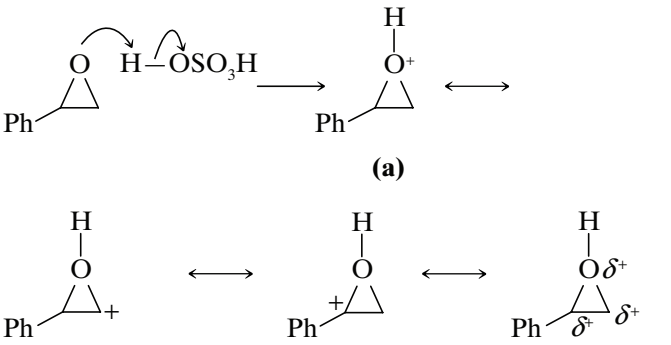


Answer

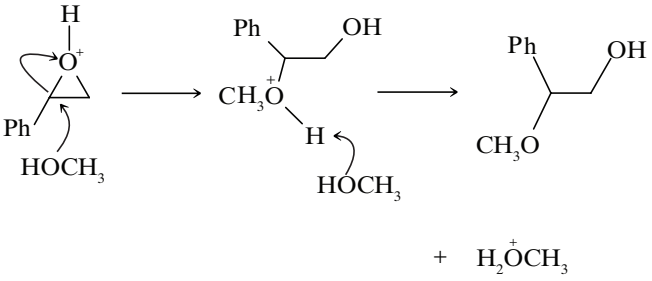
Attack by a strong nucleophile such as CH_3O^- (methoxide ion) on an epoxide occurs at the least hindered carbon, similar to an S_N2 reaction. Since methoxide is regenerated in the last step, this mechanism suggests that only a catalytic amount of CH_3O^- is required.



Attack by a weak nucleophile such as methanol (CH_3OH) can occur only when the epoxide has been protonated so that a better leaving group is formed. Under these conditions, the epoxide C–O bonds are weakened because the leaving group has been improved. The protonated epoxide can be viewed as a resonance hybrid of the following structures:



A weak nucleophile attacks the resonance hybrid carbon with the largest δ^+ charge. The magnitude of the δ^+ is determined by the relative importance of the resonance contributors. Resonance contributor **(a)** is the most important because all the atoms have a full octet. Contributor **(b)** is a secondary carbocation with benzene ring resonance whereas contributor **(c)** is a primary carbocation, so contributor **(b)** is more important than **(c)**. These relative contributions in the resonance hybrid reveal that the benzylic carbon has more $\delta+$ than the primary carbon, so the nucleophile attacks at the benzylic carbon. (The same reasoning applies to any three-membered ring with two carbons and a third atom bearing a positive charge, such as a protonated epoxide, a halonium ion or a mercurinium ion.)



Since the proton source is regenerated in the last step, this mechanism suggests that only a catalytic amount of acid is needed.

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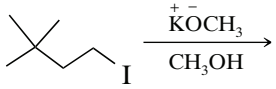
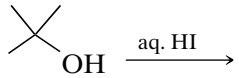
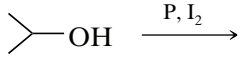
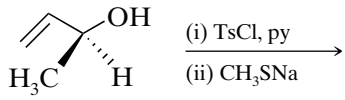
Solved Problem 10.17

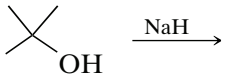
Provide the organic product(s) of the following reactions. Pay careful attention to stereochemistry. If more than one product is formed, indicate which product (if any) is the major product. If no reaction occurs, write "NR".

(a) 

(b) 

(c) 

(d) 

(e) 

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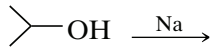
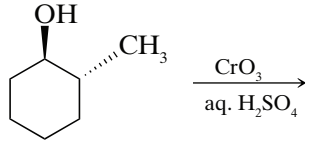
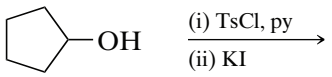
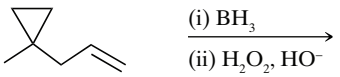
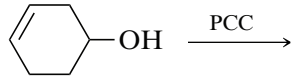
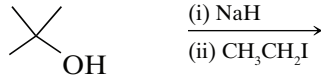
(g) 

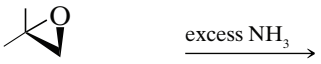
(h) 

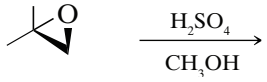
(i) 

(j) 

(k) 

(l) 

(m) 

(n) 

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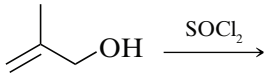
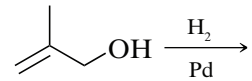
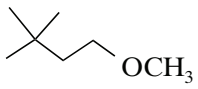
(p) 

(q) 

(r) 

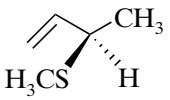
(s) 

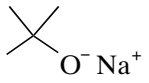
Answer

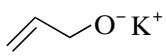
(a) 

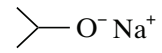
(b) 

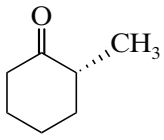
(c) 

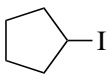
(d) 

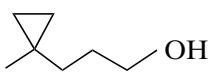
(e) 

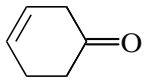
(f) 

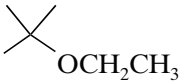
(g) 

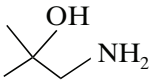
(h) 

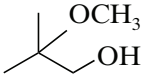
(i) 

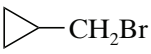
(j) 

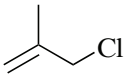
(k) 

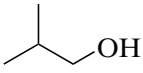
(l) 

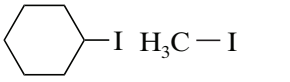
(m) 

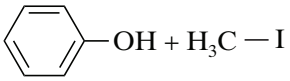
(n) 

(o) 

(p) 

(q) 

(r) 

(s) 

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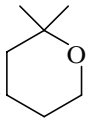
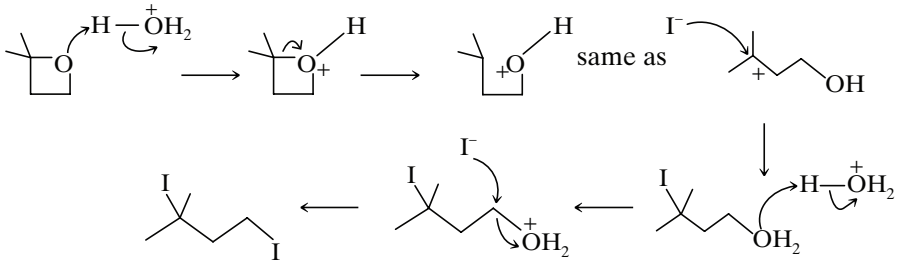
Solved Problem 10.18

Consider the reaction of  and  with aqueous HI.

(a) Give the mechanism and product of the faster reaction. **(b)** Explain your choice of the faster reaction.

Answer

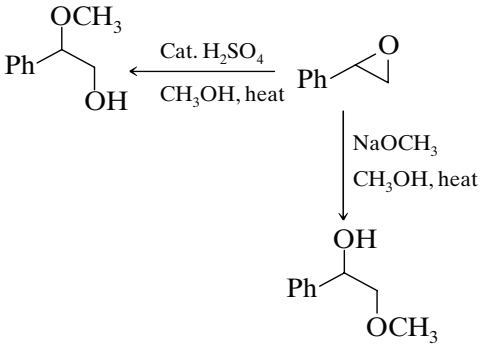
(a)



Several variations of this mechanism are acceptable, as long as they make chemical sense and lead to the same diiodide. **(b)** A significant difference between these two reactants is the presence of a ring strain in the four-membered ring ether (called an oxetane). This ring strain is absent in the six-membered ring ether (called a tetrahydropyran). Relief of this ring strain would make the oxetane cleavage reaction faster than the tetrahydropyran cleavage reaction.

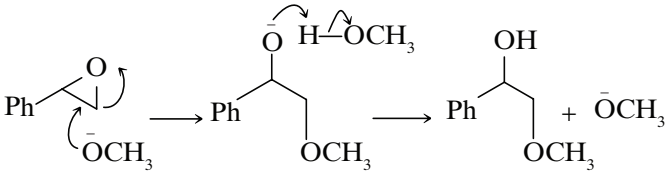
Solved Problem 10.19

Explain why the following reactions give different products:

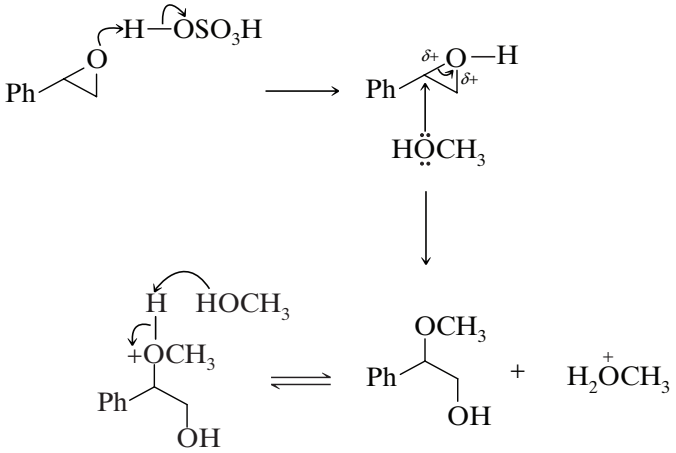


Answer

When reacting with strong nucleophiles, epoxides react via an S_N2 mechanism. Attack occurs at the least hindered carbon atom.



When reacting with weak nucleophiles under acidic conditions, epoxides react via an S_N1 type mechanism. Since the nucleophile is weak, it attacks the carbon with the largest amount of $\delta+$ charge, regardless of steric hindrance. This large amount of charge resides where it is most stable; in this case, on the more substituted carbon. Additional charge stabilization results from resonance with the benzene ring.



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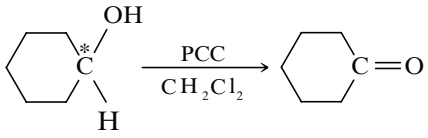
Solved Problem 10.20

Define oxidation and reduction from an organic perspective, and give specific examples.

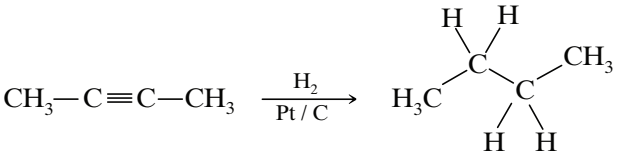
Answer

Oxidation: A carbon atom is oxidized when there is an increase in the number of bonds between that carbon and the atoms that are more electronegative than carbon, usually oxygen. For example, the indicated carbon atom is oxidized because the number of bonds between carbon and oxygen is increased from one to two.



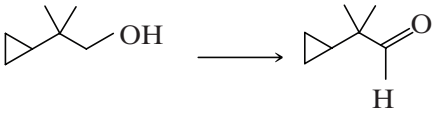
[*– This carbon is oxidized]

Reduction: A carbon atom is reduced when there is an increase in the number of bonds between that carbon and the atoms that are less electronegative than carbon, usually hydrogen. For example, the indicated carbon atoms are reduced because the number of bonds between carbon and hydrogen is increased from zero to two.

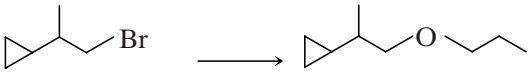


Solved Problem 10.21

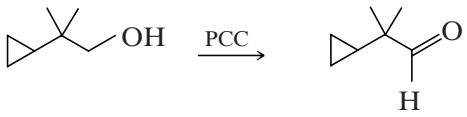
Write the best reagents above each reaction arrow. If the transformation cannot be achieved in a single step by any reagents, write "NR".

(a) 

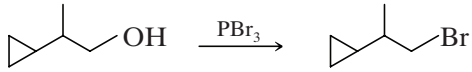
(b) 

(c) 

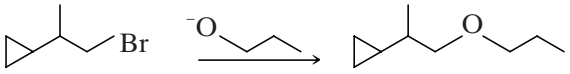
Answer

(a) 

Acidic Cr^{6+} reagents convert primary alcohols into carboxylic acids.

(b) 

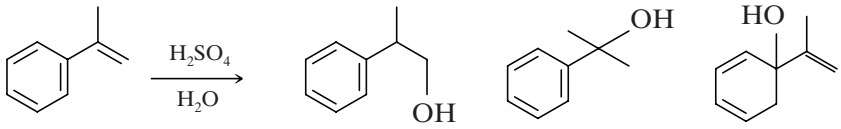
Aqueous HBr may react involving a carbocation mechanism, thus allowing undesirable rearrangements.

(c) 

Williamson ether synthesis

Solved Problem 10.22

Consider the following reaction:



(a) **(b)** **(c)**

(a) Provide a complete mechanism for the formation of the major product.

(b) Briefly explain the choice of major product.

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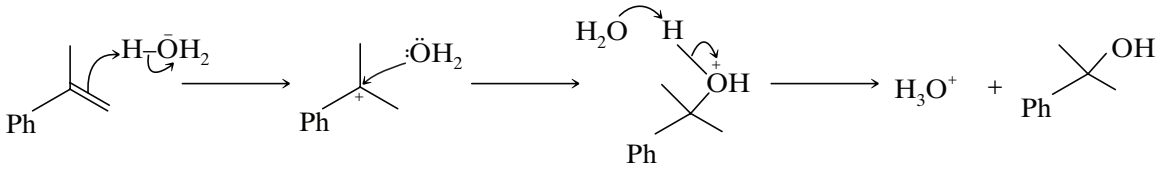
Answer

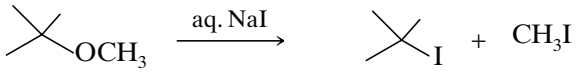
(a)



(b) Initial reaction of the alkene with H_3O^+ can form two carbocations. The more stable benzylic tertiary carbocation (shown in the above mechanism) is formed in preference to the less stable primary carbocation. This is the rate determining step, and thus controls the product distribution. Formation of the more stable carbocation is the mechanistic basis for Markovnikov's rule.

Solved Problem 10.23

Briefly explain why the following reaction does not occur.



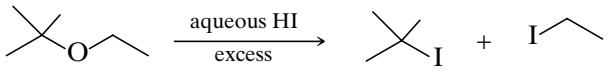
Answer

By itself, $(CH_3)_3CO^-$ is not a good enough leaving group to allow iodide to attack the methyl carbon in an S_N2 fashion. Protonation of the oxygen converts the leaving group to methanol (CH_3OH), which is good enough to leave when iodide attacks.

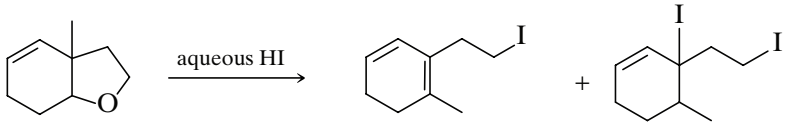
Solved Problem 10.24

Give the mechanisms of the following reactions

(a)

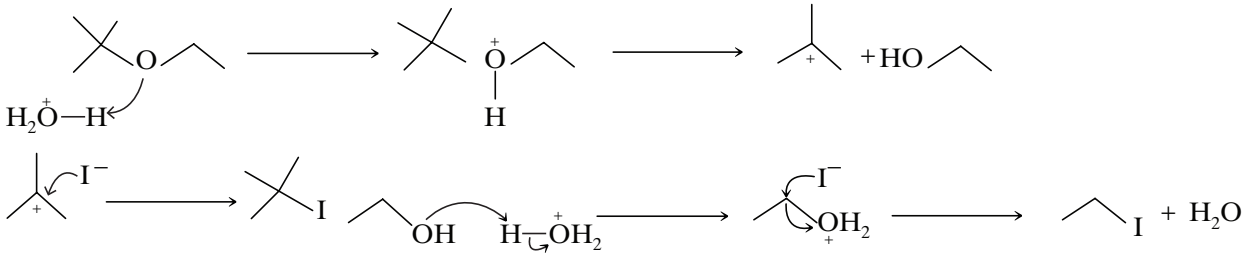


(b)



Answer

(a)



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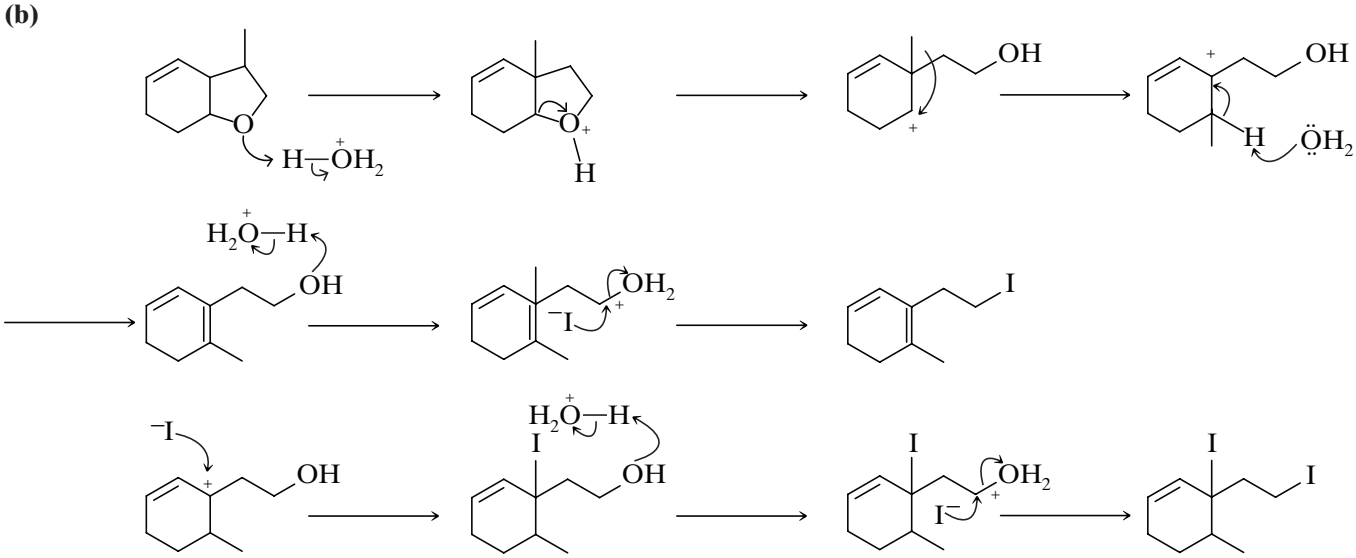
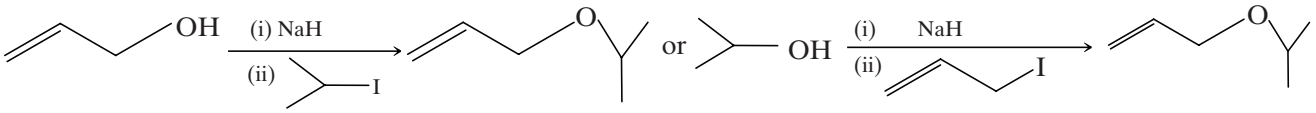
(b)



Solved Problem 10.25

Which of the following two routes to allyl isopropyl ether is more efficient? Explain.



Answer

The reaction of NaH with an alcohol (ROH) yields an alkoxide (RO–). Alkoxides are generally strong bases. If an alkoxide is reacted with a methyl or primary alkyl halide, S_N2 substitution can proceed in good yield. If the alkyl halide is secondary or tertiary, then elimination predominates. In this example, the second reaction (primary alkyl iodide) will give the better ratio of substitution versus elimination products.

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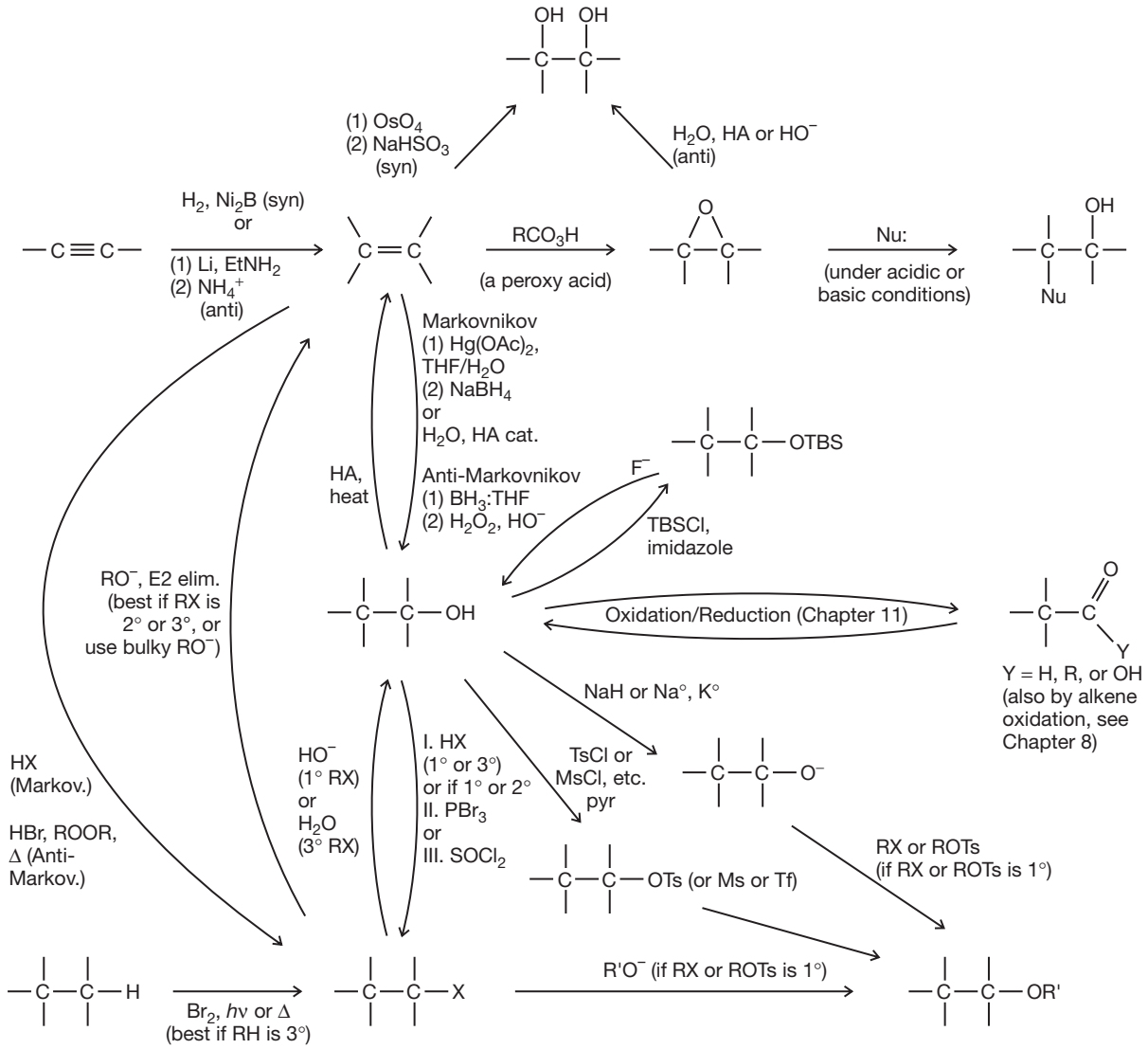
SUMMARY AND REVIEW TOOLS

Some Synthetic Connections of Alkenes, Alkynes, Alcohols, Alkyl Halides, and Ethers



- Alkynes to alkenes
- Alkenes and alcohols
- Alcohols and alkyl halides
- Alkenes and alkyl halides
- Alcohols and ethers
- Alkenes, epoxides, and 1,2-diols
- Alkanes to alkyl halides
- Alcohol silyl protecting group
- Alcohols to carbonyl compounds

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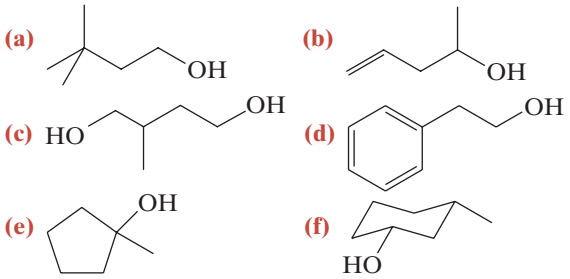
REVIEW PROBLEMS

Nomenclature

10.20 Give an IUPAC substitutive name for each of the following alcohols:

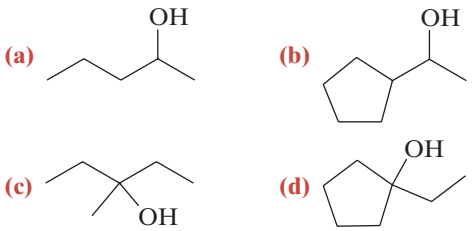


10.21 Write structural formulas for each of the following:

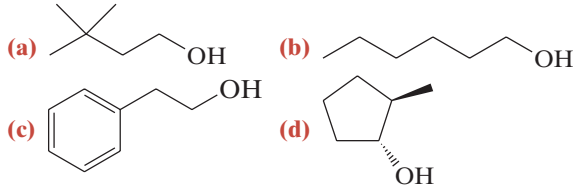
(a) *Z*-But-2-en-1-ol
(b) *R*-Butane-1,2,4-triol
(c) (1*R*,2*R*)-Cyclopentane-1,2-diol
(d) 1-Ethylcyclobutanol
(e) 2-Chlorohex-3-yn-1-ol
(f) Tetrahydrofuran
(g) 2-Ethoxypentane
(h) Ethyl phenyl ether
(i) Diisopropyl ether
(j) 2-Ethoxyethanol

Reactions and Synthesis

10.22 Provide the alkene needed to synthesize each of the following by oxymercuration–demercuration.



10.23 Provide the alkene needed to synthesize each of the following by hydroboration–oxidation.



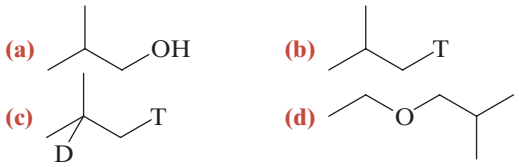
10.24 Starting with each of the following, outline a practical synthesis of 1-butanol:

(a) 1-Butene **(b)** 1-Chlorobutane
(c) 2-Chlorobutane **(d)** 1-Butyne

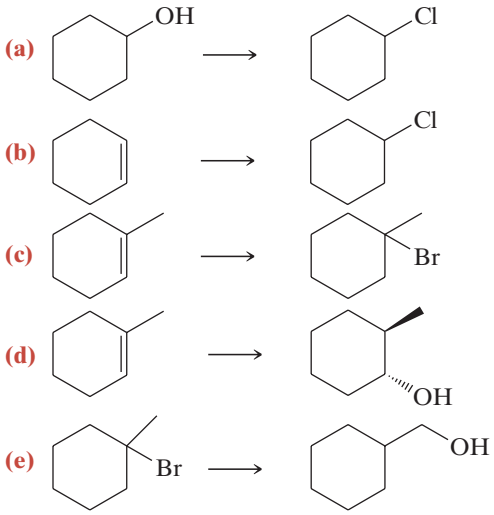
10.25 Show how you might prepare 2-bromobutane from

(a) 2-Butanol **(b)** 1-Butanol
(c) 1-Butene **(d)** 1-Butyne

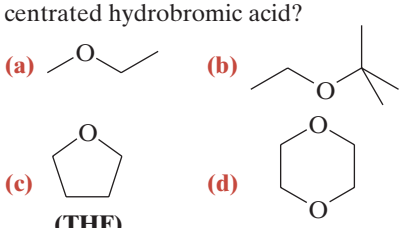
10.26 Starting with 2-methylpropene (isobutylene) and using any other needed reagents, outline a synthesis of each of the following (T = tritium, D = deuterium):



10.27 Show how you might carry out the following transformations:



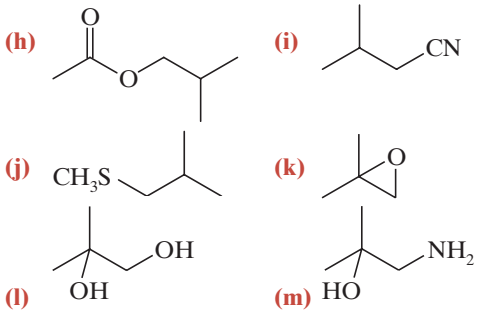
10.28 What compounds would you expect to be formed when each of the following ethers is refluxed with excess concentrated hydrobromic acid?



(THF) **(1,4-dioxane)**

10.29 Starting with isobutane, show how each of the following could be synthesized. (You need not repeat the synthesis of a compound prepared in an earlier part of this problem.)

(a) *tert*-Butyl bromide
(b) 2-Methylpropene
(c) Isobutyl bromide
(d) Isobutyl iodide
(e) Isobutyl alcohol (two ways)
(f) *tert*-Butyl bromide
(g) Isobutyl methyl ether



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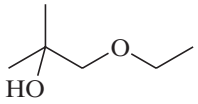
(n) 

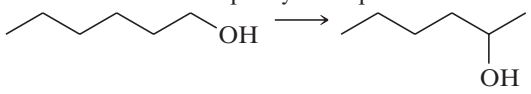
10.30 Outlined below is a synthesis of the gypsy moth sex attractant disparlure (a pheromone). Give the structure of disparlure and intermediates **A–D**.

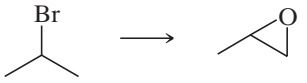
$$HC\equiv CNa \xrightarrow[\text{liq. } NH_3]{\text{1-bromo-5-methylhexane}} A\ (C_9H_{16}) \xrightarrow[\text{liq. } NH_3]{NaNH_2}$$

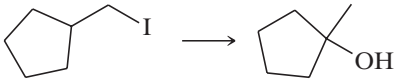
$$B\ (C_9H_{15}Na) \xrightarrow{\text{1-bromodecane}} C\ (C_{19}H_{36}) \xrightarrow[Ni_2B(P\text{-}2)]{H_2}$$

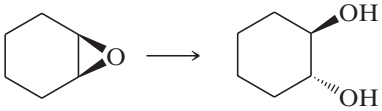
$$D\ (C_{19}H_{38}) \xrightarrow{mCPBA} \textbf{Disparlure}\ (C_{19}H_{38}O)$$

10.31 Provide the reagents necessary for the following syntheses. More than one step may be required.

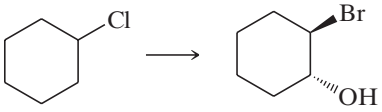
(a) 

(b) 

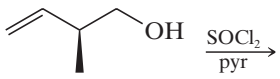
(c) 

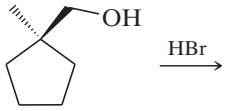
(d) 

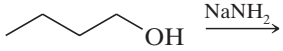
(e) 

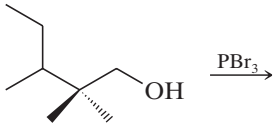
(f) 

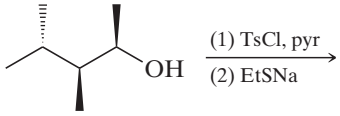
10.32 Predict the major product from each of the following reactions.

(a) 

(b) 

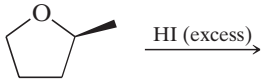
(c) 

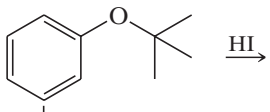
(d) 

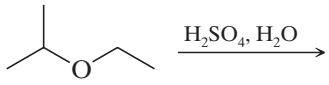
(e) 

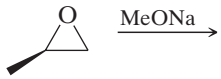
(f) 

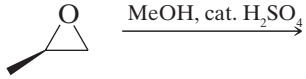
10.33 Predict the products from each of the following reactions.

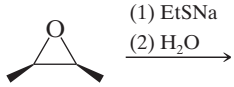
(a) 

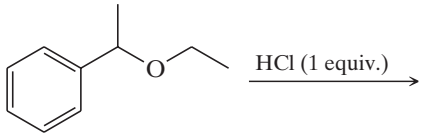
(b) 

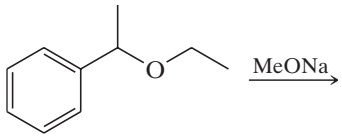
(c) 

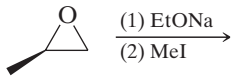
(d) 

(e) 

(f) 

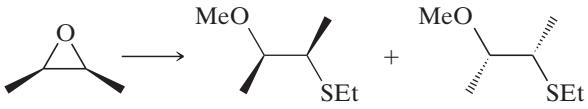
(g) 

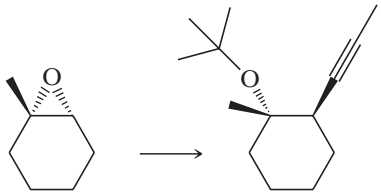
(h) 

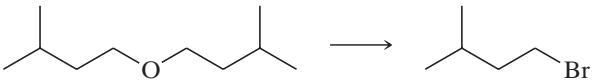
(i) 

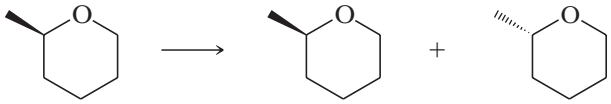
(j) 

10.34 Provide the reagents necessary to accomplish the following syntheses.

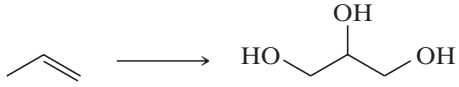
(a) 

(b) 

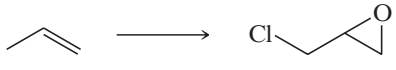
(c) 

(d) 

10.35 Provide reagents that would accomplish the follwing syntheses.

(a) 

Glycerol

(b) 

Epichlorohydrin

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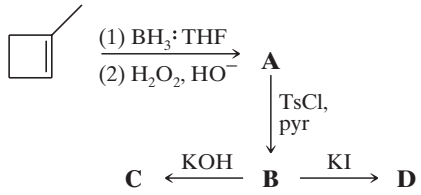
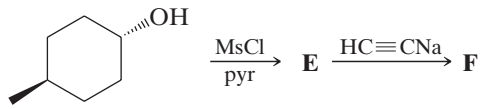
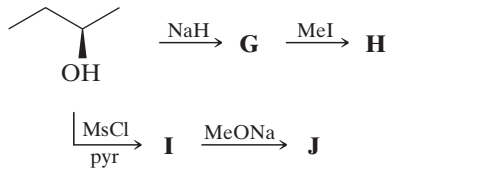
10.36 Write structures for compounds **A–J** showing stereochemistry where appropriate.

(a) 

What is the stereochemical relationship between **A** and **C**?

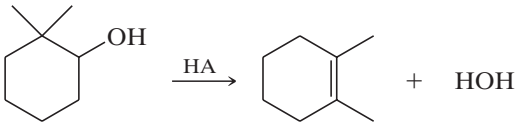
(b) 

(c) 

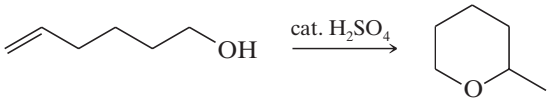
What is the stereochemical relationship between **H** and **J**?

Mechanisms

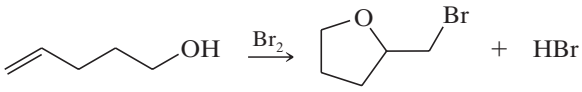
10.37 Write a mechanism that accounts for the following reaction:



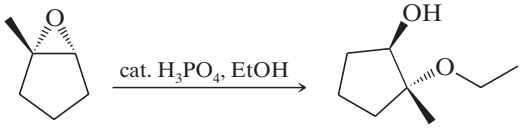
10.38 Propose a reasonable mechanism for the following reaction.



10.39 Propose a reasonable mechanism for the following reaction.

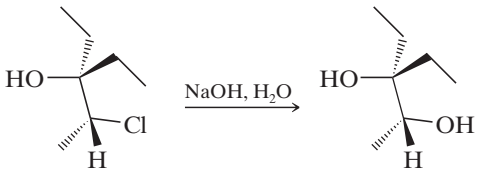


10.40 Propose a reasonable mechanism for the following reaction.

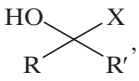


10.41 Vicinal halo alcohols (halohydrins) can be synthesized by treating epoxides with HX. **(a)** Show how you would use this method to synthesize 2-chlorocyclopentanol from cyclopentene. **(b)** Would you expect the product to be *cis*-2-chlorocyclopentanol or *trans*-2-chlorocyclopentanol; that is, would you expect a net syn addition or a net anti addition of —Cl and —OH? Explain.

10.42 Base-catalyzed hydrolysis of the 1,2-chlorohydrin **1** is found to give a chiral glycol **2** with retention of configuration. Propose a reasonable mechanism that would account for this transformation. Include all formal charges and arrows showing the movement of electrons.



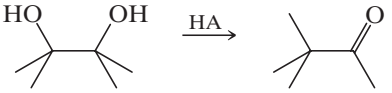
1 **2**

10.43 Compounds of the type 

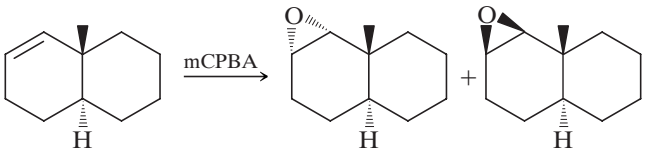
, called α-haloalcohols, are unstable and cannot be isolated.

Propose a mechanistic explanation for why this is so.

10.44 While simple alcohols yield alkenes on reaction with dehydrating acids, diols form carbonyl compounds. Rationalize mechanistically the outcome of the following reaction:



10.45 When the bicyclic alkene **I**, a *trans*-decalin derivative, reacts with a peroxy acid, **II** is the major product. What factor favors the formation of **II** in preference to **III**? (You may find it helpful to build a handheld molecular model.)



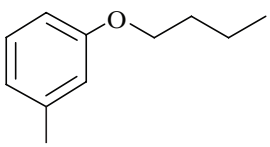
I **II (major)** **III (minor)**

10.46 Use Newman projection formulas for ethylene glycol (1,2-ethanediol) and butane to explain why the gauche conformer of ethylene glycol is expected to contribute more to its ensemble of conformers than would the gauche conformer of butane to its respective set of conformers.

ADDITIONAL OBJECTIVE QUESTIONS

Single Correct Choice Type

1. Which of the following synthetic routes may be employed to prepare the following aryl ether?



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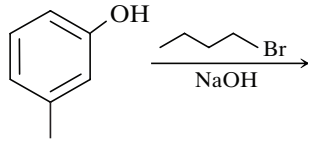
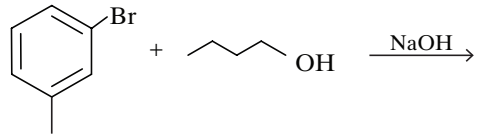
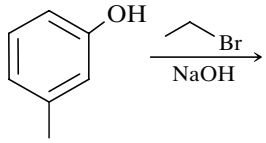
(a) 

(b) 

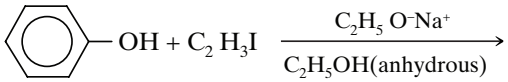
(c) 

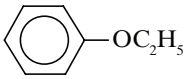
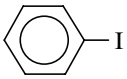
(d) Both (a) and (b) will work

2. The reaction products of
(a) $C_6H_5OH + CH_3I$ **(b)** $C_6H_5I + CH_3OH$
(c) $C_6H_5CH_3 + HOI$ **(d)** $C_6H_6 + CH_3OI$

3. The best combination for the preparation of ether by Williamson's synthesis are
(a) $(CH_3)_3CBr$ and CH_3ONa
(b) $(CH_3)_3CBr$ and CH_3OH
(c) CH_3Br and $(CH_3)_3CONa$
(d) CH_3Br and $(CH_3)_3COH$

4. The product of the following reactions is

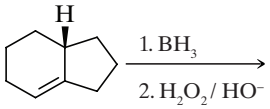


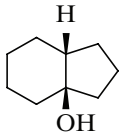
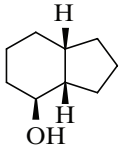
(a)  **(b)** 

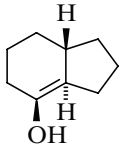
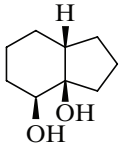
(c) $C_6H_5OC_6H_5$ **(d)** $C_2H_5OC_2H_5$

5. When alkyl halide is heated with dry Ag_2O, it produces
(a) ester. **(b)** ether. **(c)** ketone. **(d)** alcohol.

6. Choose the major product of the following reaction

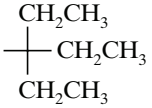
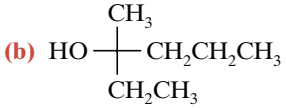


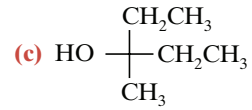
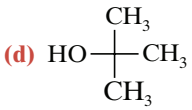
(a)  **(b)** 

(c)  **(d)** 

7. The product of the following reaction is

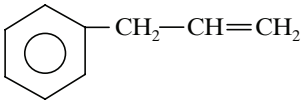
CH_3MgBr (excess) + Ethyl ester →

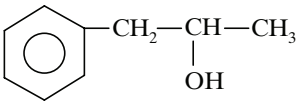
(a)  **(b)** 

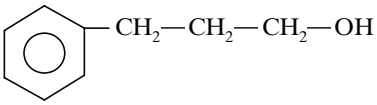
(c)  **(d)** 

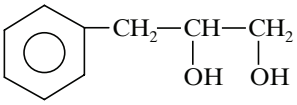
8. Mixed ether is also known as
(a) symmetric ethers. **(b)** unsymmetric ethers.
(c) dialkyl ethers. **(d)** oxane.

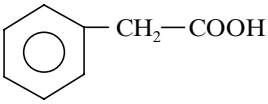
9. The following compound on mercuration-demercuration produces the major product



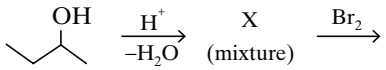
(a) 

(b) 

(c) 

(d) 

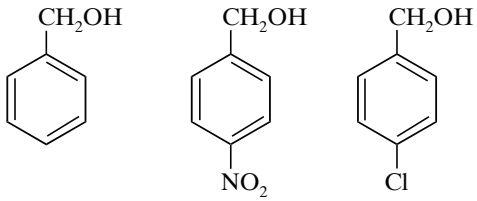
10. The following reaction gives five compounds of molecular formula $C_4H_8Br_2$.



The number of compounds in X will be
(a) 2 **(b)** 3 **(c)** 4 **(d)** 5

11. Which set of reagents is used for the purpose of adding water to an alkene in a Markovnikov addition without rearrangement?
(a) BH_3, THF followed by H_2O_2, NaOH
(b) H_2O, H_2SO_4
(c) Br_2, H_2O
(d) $Hg(O_2CCH_3)_2$, H_2O followed by $NaBH_4$, NaOH

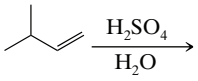
12. Mark the correct increasing order of reactivity of the following compounds with HBr/HCl.



(i) **(ii)** **(iii)**

(a) (i) < (ii) < (iii) **(b)** (ii) < (i) < (iii)
(c) (ii) < (iii) < (i) **(d)** (iii) < (ii) < (i)

13. What is the major product of the following reaction?



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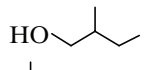
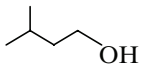
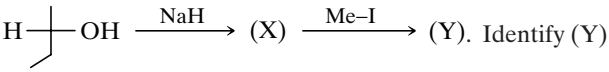
(a)  (b) 

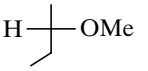
(c)  (d) 

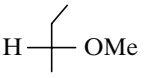
14. When phenyl magnesium bromide reacts with *tert*-butanol, which of the following product is formed?

(a) *tert*-Butyl methyl ether **(b)** Benzene

(c) *tert*-Butyl benzene **(d)** Phenol

15.  Identify (Y)

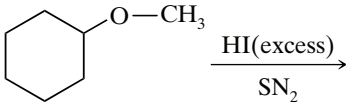
(a)  (b)

(c)  **(d)** None of these

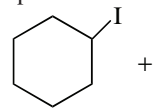
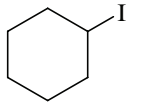
16. Cyclohexene is best prepared from cyclohexanol by which of the following?

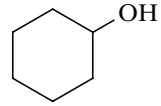
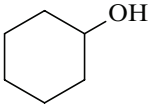
(a) Conc. H_3PO_4 **(b)** Conc. HCl/$ZnCl_2$

(c) Conc. HCl **(d)** Conc. HBr

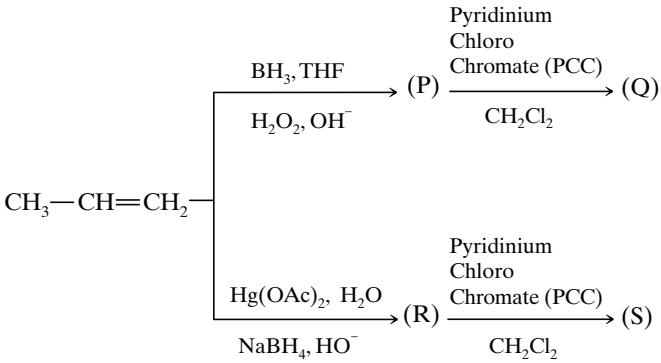
17. 

Final product will be

(a)  + CH_3OH (c)  + CH_3I

(b)  + CH_4 (d)  + CH_3I

18.



Relationship between products **(Q)** and **(S)** is

(a) positional isomer. **(b)** chain isomer.

(c) stereoisomer. **(d)** functional isomer.

19. Incorrect statement regarding Williamson ether synthesis is

(a) less hindered halide is used in this reaction.

(b) less hindered alkoxide ion is used in this reaction.

(c) mechanism of reaction will be S_N2.

(d) more hindered halide is used in this reaction.

20. Which of the given compound do not undergo acid catalyzed hydrolysis?

(a) Ph—O—Ph **(b)** Ph—O—CH=CH_2

(c) Ph—O—CH_2—Ph **(d)** CH_3—O—CH_2CH_3

21. Williamson synthesis of ether is an example of

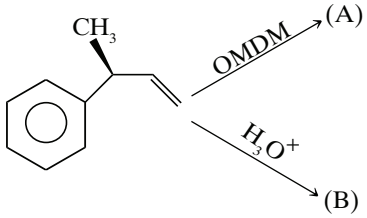
(a) nucleophilic addition.

(b) electrophilic addition.

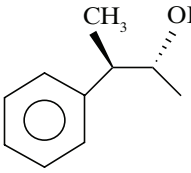
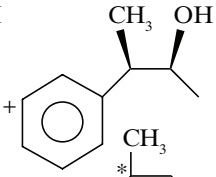
(c) electrophilic substitution.

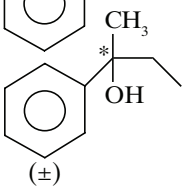
(d) nucleophilic substitution.

22. Predict the major products (A) and (B).

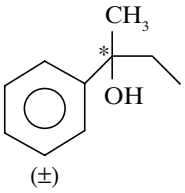


(OMDM is oxymercuration-demercuration)

(a) A =  + 

B = 

(±)

(b) A = 

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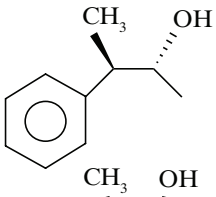
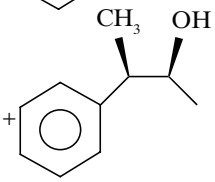
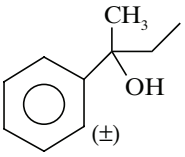
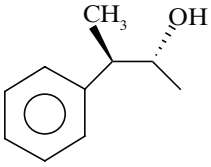
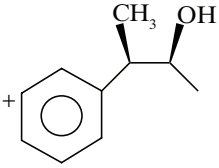
B = 



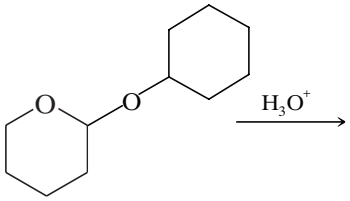
(c) A = B = 

(±)

(d) A = B = 



23. The product of following reaction is



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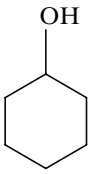
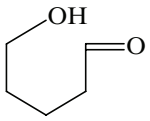
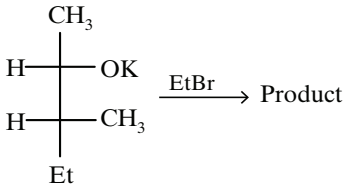
(a) 

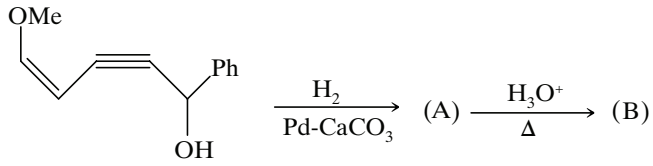
(b) 

(c) Both (a) and (b) (d) No reaction

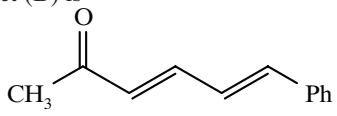
24. 

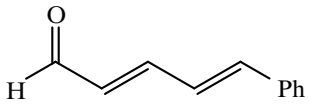
Correct stereochemical relationship between reactant and product will be

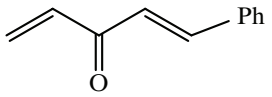
(a) enantiomer. (b) diastereomer.
(c) structural isomer. (d) none of these.

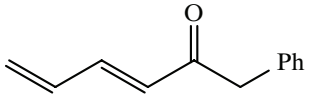
25. 

Product (B) is

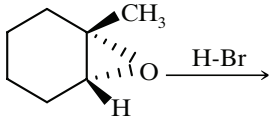
(a) 

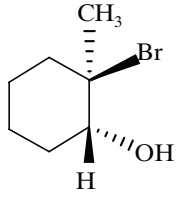
(b) 

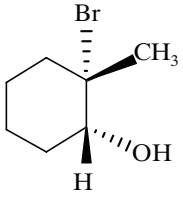
(c) 

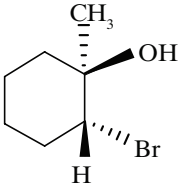
(d) 

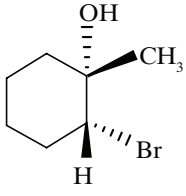
26. Choose the major product of the following reaction.



(a) 

(b) 

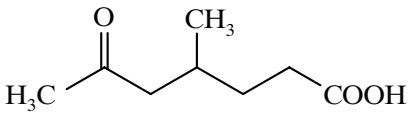
(c) 

(d) 

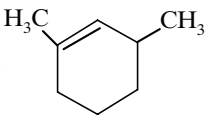
Linked Comprehension Type

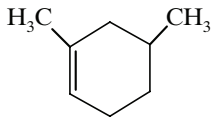
Paragraph for Questions 1 to 4

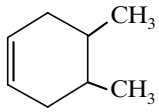
Compound A of formula $C_8H_{14}O$, reacts with $LiAlH_4$ to yield two isomeric products B and C, both in equal yield. Heating either B or C with conc. H_2SO_4 produces D with formula C_8H_{14}. Ozonolysis of D produces a keto aldehyde after Zn/H_2O treatment. Oxidation of this keto aldehyde with aq. Cr (VI) produces

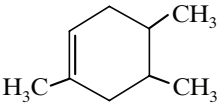


1. The structure of D is

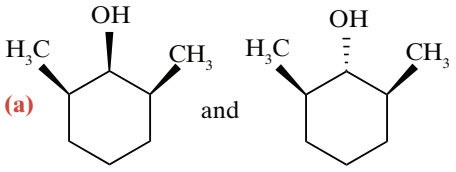
(a) 

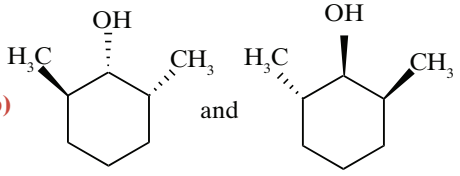
(b) 

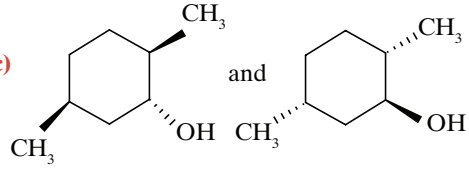
(c) 

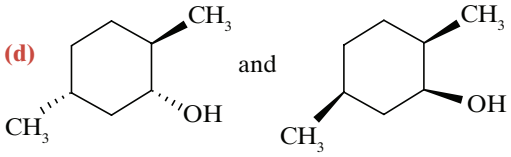
(d) 

2. The structures of B and C are

(a) 

(b) 

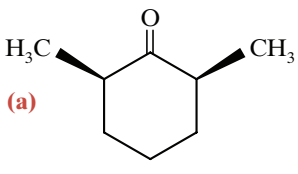
(c) 

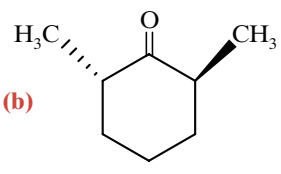
(d) 

3. The compounds B and C are

(a) enantiomers (b) meso compound
(c) diastereomers (d) constitutional isomers.

4. The structure of A is

(a) 

(b) 

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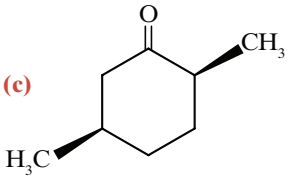
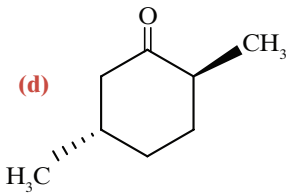
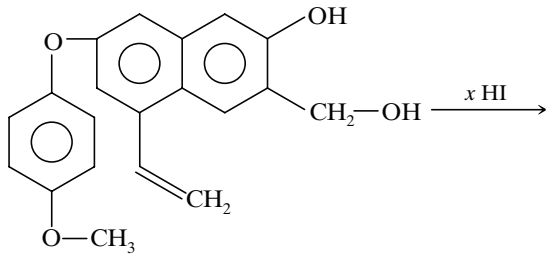
(c) 

(d) 

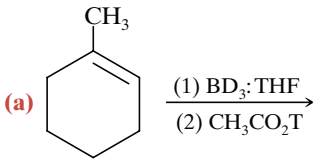
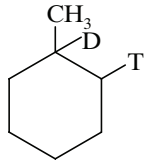
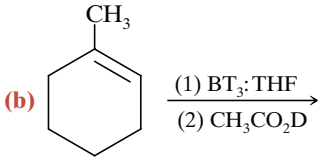
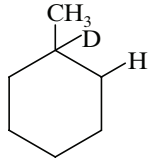
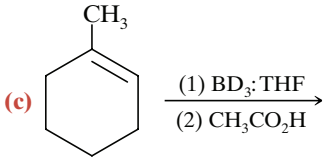
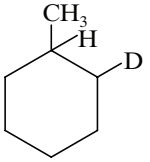
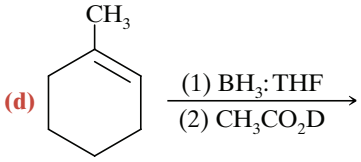
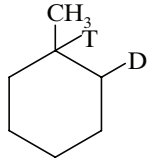
Integer Type

1. In the following reaction value of x is



Matrix Match Type

1.

Column I Reaction	Column II Product
(a) 	(p) 
(b) 	(q) 
(c) 	(r) 
(d) 	(q) 

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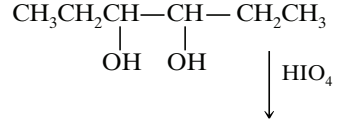
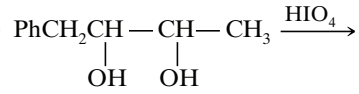
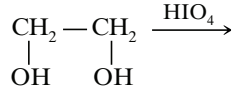
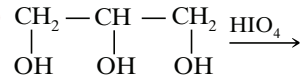
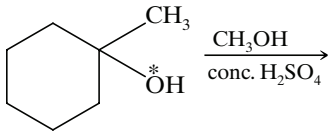
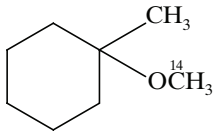
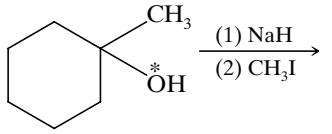
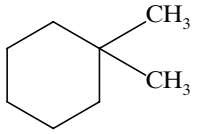
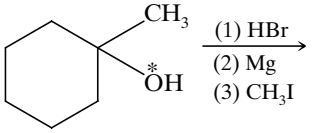
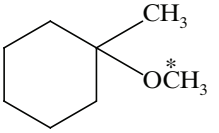
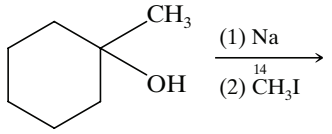
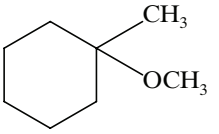
(a) 	(p) $2H_2C=O + HCOOH$
(b) 	(q) $2CH_3CH_2CH=O$
(c) 	(r) $2H_2C=O$
(d) 	(s) $PhCH_2CH=O + CH_3CH=O$

3.

Column I Reaction	Column II Product
(a) 	(p) 
(b) 	(q) 
(c) 	(r) 
(d) 	(s) 

ANSWER KEY

Single Correct Choice Type

1. (a) 2. (a) 3. (c) 4. (a)

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5. (b) **6.** (b) **7.** (d) **8.** (b)
9. (a) **10.** (b) **11.** (d) **12.** (c)
13. (b) **14.** (b) **15.** (a) **16.** (a)
17. (c) **18.** (d) **19.** (d) **20.** (a)
21. (d) **22.** (a) **23.** (c) **24.** (d)
25. (b) **26.** (a)

Linked Comprehension Type

1. (b) **2.** (a) **3.** (c) **4.** (a)

Integer Type

1. (3)

Matrix Match Type

1. a→(p); b→(s); c→(q); d→(r)
2. a→(q); b→(s); c→(r); d→(p)
3. a→(s); b→(r); c→(q); d→(p)

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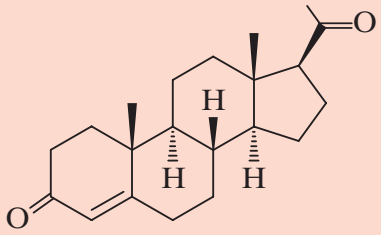
11

Alcohols from Carbonyl Compounds

Oxidation–Reduction and Organometallic Compounds



Progesterone

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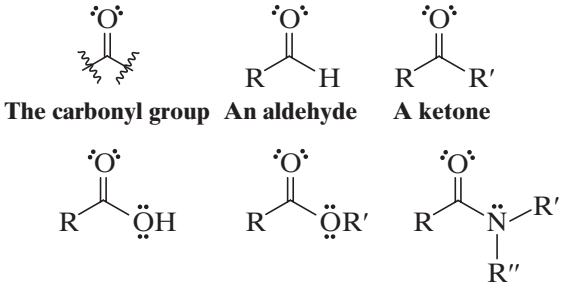
11.1 | Structure of the Carbonyl Group
11.2 | Oxidation–Reduction Reactions in Organic Chemistry
11.3 | Alcohols by Reduction of Carbonyl Compounds
11.4 | Oxidation of Alcohols
11.5 | Organometallic Compounds
11.6 | Preparation of Organolithium and Organomagnesium Compounds
11.7 | Reactions of Organolithium and Organomagnesium Compounds
11.8 | Alcohols from Grignard Reagents
11.9 | Lithium Dialkylcuprates: The Corey–Posner, Whitesides–House Synthesis

11.1 | STRUCTURE OF THE CARBONYL GROUP

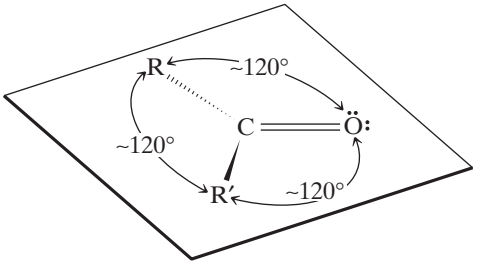
Carbonyl compounds are a broad group of compounds that includes aldehydes, ketones, carboxylic acids, esters, and amides.



The carbonyl group **An aldehyde** **A ketone**

A carboxylic acid **An ester** **An amide**

The carbonyl carbon atom is sp^2 hybridized; thus, it and the three atoms attached to it lie in the same plane. The bond angles between the three attached atoms are what we would expect of a trigonal planar structure; they are approximately 120°:



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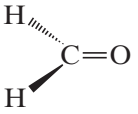
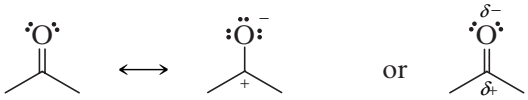
The carbon–oxygen double bond consists of two electrons in a σ bond and two electrons in a π bond. The π bond is formed by overlap of the carbon p orbital with a p orbital from the oxygen atom. The electron pair in the π bond occupies both lobes (above and below the plane of the σ bonds).



Formaldehyde

- The more electronegative oxygen atom strongly attracts the electrons of both the σ bond and the π bond, causing the carbonyl group to be highly polarized; the carbon atom bears a substantial positive charge and the oxygen atom bears a substantial negative charge.

Polarization of the π bond can be represented by the following resonance structures for the carbonyl group:



Resonance structures for the carbonyl group **Hybrid**

Evidence for the polarity of the carbon–oxygen bond can be found in the rather large dipole moments associated with carbonyl compounds.

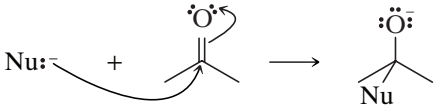


Formaldehyde $\mu = 2.27$ D **Acetone** $\mu = 2.88$ D

11.1A Reactions of Carbonyl Compounds with Nucleophiles

One of the most important reactions of carbonyl compounds is **nucleophilic addition to the carbonyl group**. The carbonyl group is susceptible to nucleophilic attack because, as we have just seen, the carbonyl carbon bears a partial positive charge.

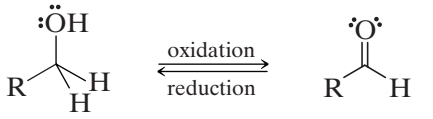
- When a nucleophile adds to the carbonyl group, it uses an electron pair to form a bond to the carbonyl carbon atom and an electron pair from the carbon–oxygen double bond shifts out to the oxygen:



As the reaction takes place, the carbon atom undergoes a change from trigonal planar geometry and sp^2 hybridization to tetrahedral geometry and sp^3 hybridization.

- Two important nucleophiles that add to carbonyl compounds are **hydride ions** from compounds such as $NaBH_4$ or $LiAlH_4$ and **carbanions** from compounds such as RLi or RMgX (Section 11.6C).

Another related set of reactions are reactions in which alcohols and carbonyl compounds are **oxidized** and **reduced** (Sections 10.2–10.3). For example, primary alcohols can be oxidized to aldehydes, and aldehydes can be reduced to alcohols:



A primary alcohol **An aldehyde**

Let us begin by examining some general principles that apply to the oxidation and reduction of organic compounds.

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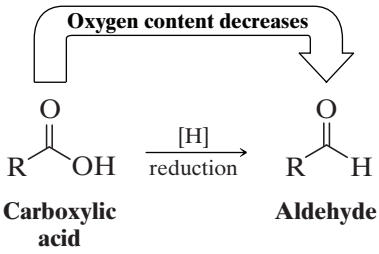
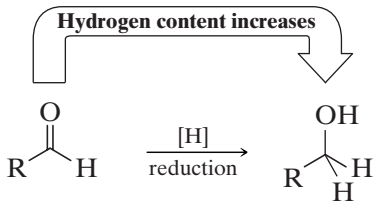
11.2 | OXIDATION–REDUCTION REACTIONS IN ORGANIC CHEMISTRY

- **Reduction** of an organic molecule usually corresponds to increasing its hydrogen content or to decreasing its oxygen content.

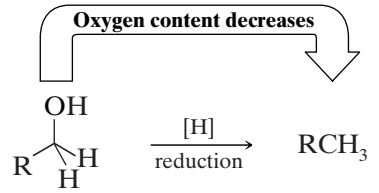
For example, converting a carboxylic acid to an aldehyde is a reduction because the oxygen content is decreased:



Converting an aldehyde to an alcohol is a reduction:



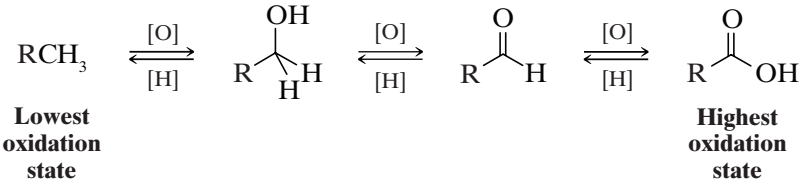
Converting an alcohol to an alkane is also a reduction:



In these examples we have used the symbol [H] to indicate that a reduction of the organic compound has taken place. We do this when we want to write a general equation without specifying what the reducing agent is.

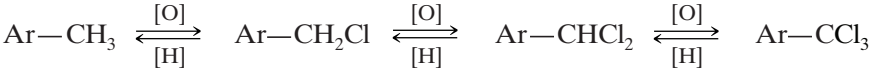
- The opposite of reduction is **oxidation**. Increasing the oxygen content of an organic molecule or decreasing its hydrogen content is an **oxidation**.

The reverse of each reaction that we have just given is an oxidation of the organic molecule, and we can summarize these oxidation–reduction reactions as shown below. We use the symbol [O] to indicate in a general way that the organic molecule has been oxidized.



- Oxidation of an organic compound may be more broadly defined as a reaction that increases its content of any element more electronegative than carbon.

For example, replacing hydrogen atoms by chlorine atoms is an oxidation:



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Of course, when an organic compound is reduced, something else—the **reducing agent**—must be oxidized. And when an organic compound is oxidized, something else—the **oxidizing agent**—is reduced. These oxidizing and reducing agents are often inorganic compounds, and in the next two sections we shall see what some of them are.

11.2A Oxidation States in Organic Chemistry

One method for assigning oxidation states in organic compounds is similar to the method we used for assigning formal charges (Section 1.10). We base the assignment on **the groups attached to the carbon (or carbons) whose oxidation state undergoes change in the reaction we are considering**. Recall that with formal charges we assumed that electrons in covalent bonds are shared equally. *When assigning oxidation states to carbon atoms we assign electrons to the more electronegative element* (see Section 1.4). For example, a bond to hydrogen (or to any atom less electronegative than carbon) makes that carbon negative by one unit (–1), and a bond to oxygen, nitrogen, or a halogen (F, Cl, and Br) makes the carbon positive by one unit (+1). A bond to another carbon does not change its oxidation state.

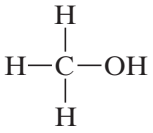
Using this method the carbon atom of methane, for example, is assigned an oxidation state of –4, and that of carbon dioxide, +4.

Solved Problem 11.1

Using the method just described, assign oxidation states to the carbon atoms of methanol (CH_3OH), formaldehyde (HCHO), and formic acid (HCO_2H) and arrange these compounds along with carbon dioxide and methane (see above) in order of increasing oxidation state.

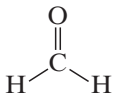
Answer

We calculate the oxidation state of each carbon based on the number of bonds it is forming to atoms more (or less) electronegative than carbon.



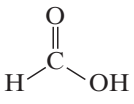
Bonds to C
3 to H = –3
1 to O = +1
Total = –2
= Oxid. state of C

Methanol



Bonds to C
2 to H = –2
2 to O = +2
Total = 0
= Oxid. state of C

Formaldehyde



Bonds to C
1 to H = –1
3 to O = +3
Total = +2
= Oxid. state of C

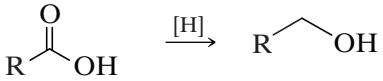
Formic acid

The order overall, based on the oxidation state of carbon in each compound, is

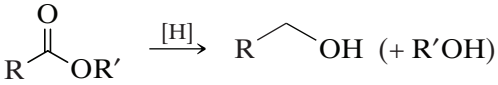
$$\underset{\text{Lowest Oxid. state of carbon}}{CH_4 = -4} < CH_3OH = -2 < HCHO = 0 < HCOOH = +2 < \underset{\text{Highest Oxid. state of carbon}}{CO_2 = +4}$$

11.3 | ALCOHOLS BY REDUCTION OF CARBONYL COMPOUNDS

Primary and secondary alcohols can be synthesized by the **reduction** of a variety of compounds that contain the carbonyl group. Several general examples are shown here:



Carboxylic acid **1° Alcohol**



Ester **1° Alcohol**

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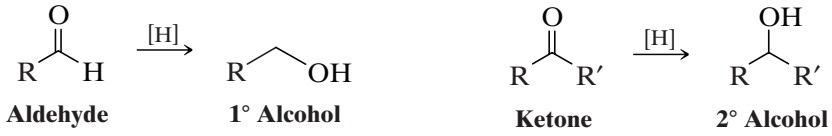
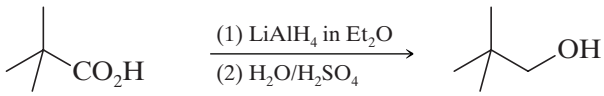


11.3A Lithium Aluminum Hydride

- Lithium aluminum hydride ($LiAlH_4$, abbreviated LAH) reduces carboxylic acids and esters to primary alcohols.

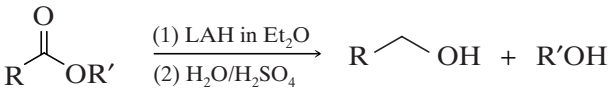
An example of lithium aluminum hydride reduction is the conversion of 2,2-dimethylpropanoic acid to 2,2-dimethylpropanol (neopentyl alcohol).



2,2-Dimethylpropanoic acid → **Neopentyl alcohol (92%)**

LAH reduction of a carboxylic acid

LAH reduction of an ester yields two alcohols, one derived from the carbonyl part of the ester group, and the other from the alkoxyl part of the ester.



LAH reduction of an ester

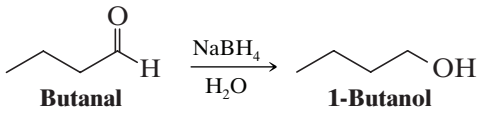
Carboxylic acids and esters are more difficult to reduce than aldehydes and ketones. LAH, however, is a strong enough **reducing agent** to accomplish this transformation. Sodium borohydride ($NaBH_4$), which we shall discuss shortly, is commonly used to reduce aldehydes and ketones, but it is not strong enough to reduce carboxylic acids and esters.

Great care must be taken when using LAH to avoid the presence of water or any other weakly acidic solvent (e.g., alcohols). **LAH reacts violently with proton donors to release hydrogen gas.** Anhydrous diethyl ether (Et_2O) is a commonly used solvent for LAH reductions. After all of the LAH has been consumed by the reduction step of the reaction, however, water and acid are added to neutralize the resulting salts and facilitate isolation of the alcohol products.

11.3B Sodium Borohydride

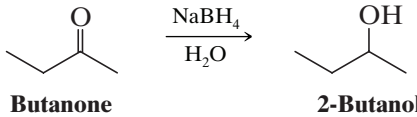
- Aldehydes and ketones are easily reduced by sodium borohydride ($NaBH_4$).

Sodium borohydride is usually preferred over LAH for the reduction of aldehydes and ketones. Sodium borohydride can be used safely and effectively in water as well as alcohol solvents, whereas special precautions are required when using LAH.



Butanal → **1-Butanol (85%)**

$NaBH_4$ reduction of an aldehyde



Butanone → **2-Butanol (87%)**

$NaBH_4$ reduction of an ketone

Aldehydes and ketones can be reduced using hydrogen and a metal catalyst, as well, and by sodium metal in an alcohol solvent.

The key step in the reduction of a carbonyl compound by either lithium aluminum hydride or sodium borohydride is the transfer of a **hydride ion** from the metal to the carbonyl carbon. In this transfer the hydride ion acts as a *nucleophile*. The mechanism for the reduction of a ketone by sodium borohydride is illustrated here.

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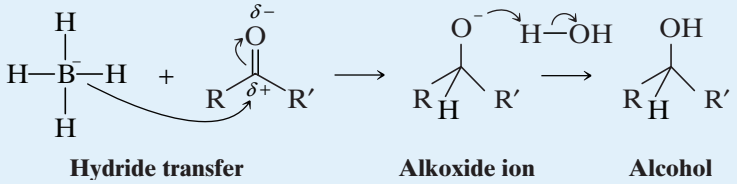
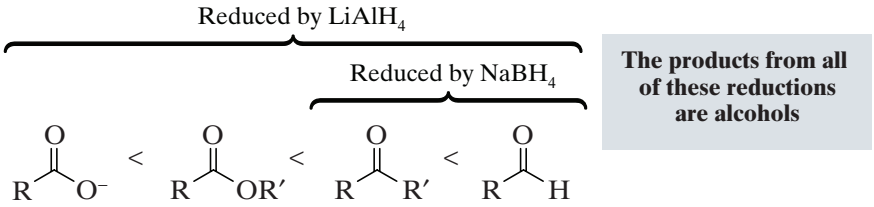
A MECHANISM FOR THE REACTION — Reduction of Aldehydes and Ketones by Hydride Transfer



These steps are repeated until all hydrogen atoms attached to boron have been transferred.

11.3C Overall Summary of $LiAlH_4$ and $NaBH_4$ Reactivity

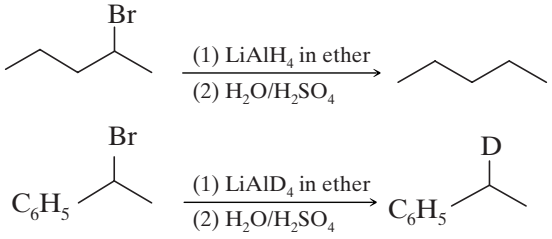
Sodium borohydride is a less powerful reducing agent than lithium aluminum hydride. Lithium aluminum hydride reduces acids, esters, aldehydes, and ketones, but sodium borohydride reduces only aldehydes and ketones:



Lithium aluminum hydride reacts violently with water, and therefore reductions with lithium aluminum hydride must be carried out in anhydrous solutions, usually in anhydrous ether. (Ethyl acetate is added cautiously after the reaction is over to decompose excess $LiAlH_4$; then water is added to decompose the aluminum complex.) Sodium borohydride reductions, by contrast, can be carried out in water or alcohol solutions.

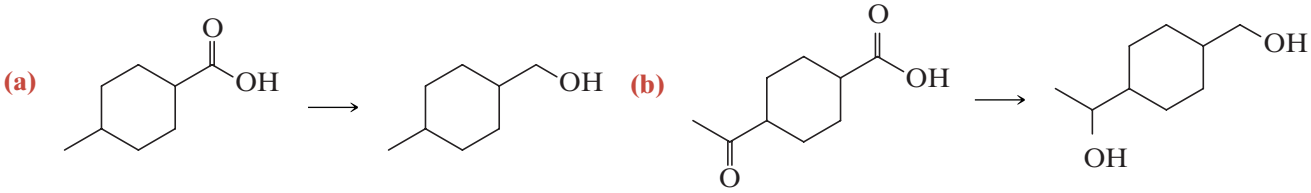
11.3D Reduction of Alkyl Halides to Hydrocarbons: RX → RH

Replacement of the halogen atom of an alkyl halide by hydrogen can be accomplished by treating the alkyl halide with lithium aluminum hydride (Section 11.3A). Because a halogen atom with a higher oxidation state is replaced by a hydrogen atom with a lower oxidation state, this reaction is a reduction. Almost all types of alkyl halides (primary, secondary, tertiary) can be reduced by $LiAlH_4$. $LiAlD_4$ can be used to replace the halogen atom with a deuterium atom.



Practice Problem 11.1

Which reducing agent, $LiAlH_4$ or $NaBH_4$, would you use to carry out the following transformations?



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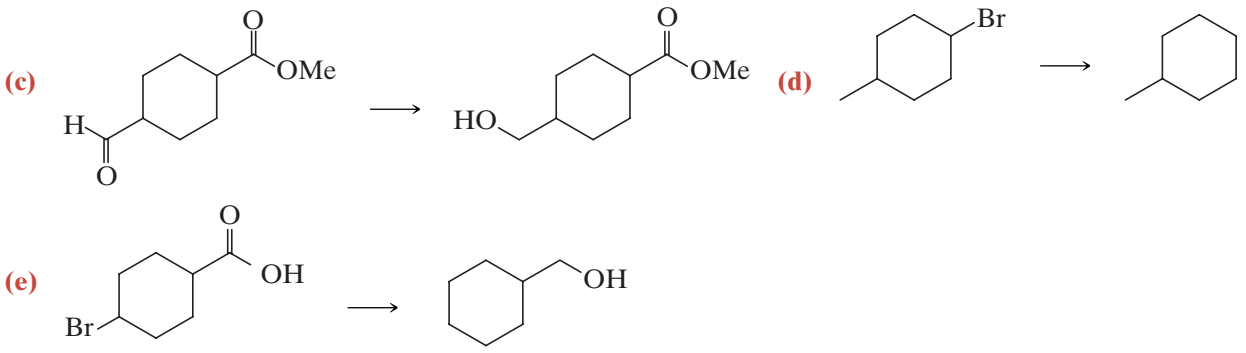
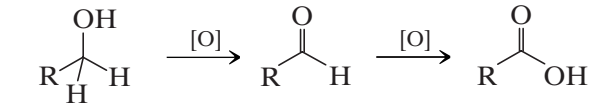


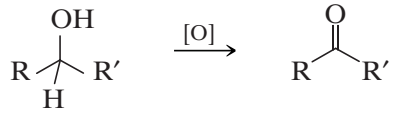
11.4 | OXIDATION OF ALCOHOLS

Primary alcohols can be oxidized to aldehydes, and aldehydes can be oxidized to carboxylic acids:



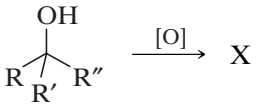
1° Alcohol **Aldehyde** **Carboxylic acid**

Secondary alcohols can be oxidized to ketones:



2° Alcohol **Ketone**

Tertiary alcohols cannot be oxidized to carbonyl compounds.



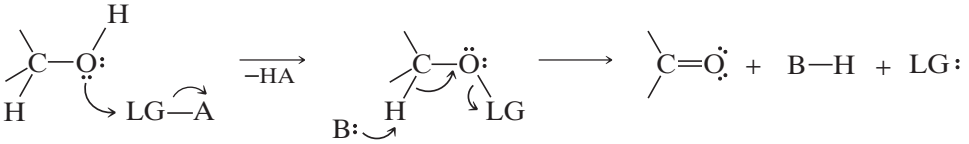
3° Alcohol

These examples have one aspect in common: when **oxidation** takes place, a hydrogen atom is lost from the alcohol or aldehyde carbon. A tertiary alcohol has no hydrogen on the alcohol carbon, and thus it cannot be oxidized in this way.

11.4A A Common Mechanistic Theme

Oxidations of primary and secondary alcohols, like those above, follow a common mechanistic path when certain reagents are used. These reagents, some of which we will discuss below, temporarily install a leaving group on the hydroxyl oxygen during the reaction. Loss of a hydrogen from the hydroxyl carbon and departure of the leaving group from the oxygen result in an elimination that forms the C=O π bond. Formation of the carbonyl double bond essentially occurs in a fashion analogous to formation of an alkene double bond by an elimination reaction. The general pathway is shown here.

Alcohol Oxidation by Elimination



A 1° or 2° alcohol reacts with a reagent that installs a leaving group (LG) on the alcohol oxygen atom.

In an elimination step, a base removes a hydrogen from the alcohol carbon, the C=O π bond forms, and the leaving group departs, resulting in the oxidized product.

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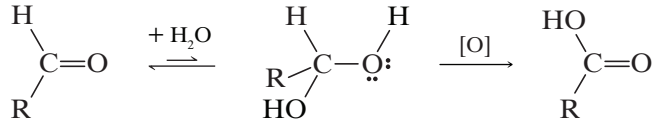
Primary and secondary alcohols have the required hydrogen atom at the alcohol carbon. They also have the hydroxyl hydrogen that is lost when the leaving group is installed, as shown above.

You might ask how an aldehyde can be oxidized by this mechanism, since an aldehyde does not contain a hydroxyl group to participate as shown above. The answer lies in whether the aldehyde reaction mixture includes water or not. In the presence of water, an aldehyde can form an aldehyde hydrate (by an **addition reaction** that we shall study in Chapter 15).



Aldehyde **Aldehyde hydrate** **Carboxylic acid**

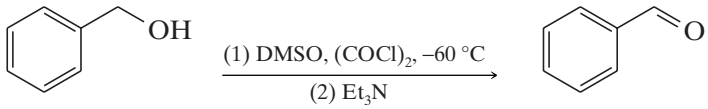
The carbon of an aldehyde hydrate has both a hydroxyl group and the hydrogen atom required for elimination; thus when water is present, an aldehyde can be oxidized by the mechanism shown above. Although the aldehyde hydrate may be present in low equilibrium concentration, those molecules in the hydrate form can be oxidized, drawing the reaction ultimately toward oxidation of all of aldehyde molecules to the corresponding carboxylic acid via LeChatelier's principle.

Aldehydes cannot be oxidized by the general mechanism above when water is absent. This fact proves to be useful when choosing conditions leading to specifically an aldehyde or a carboxylic acid from a primary alcohol.

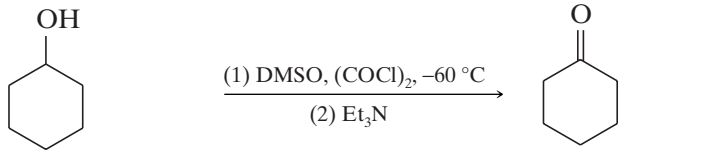
Now let us consider some specific oxidation methods that hinge on the general mechanism shown above: the Swern oxidation, and oxidations involving chromate esters.

11.4B Swern Oxidation

The Swern oxidation is broadly useful for the synthesis of aldehydes and ketones from primary and secondary alcohols, respectively. The reaction is conducted in the absence of water, thus primary alcohols form aldehydes and not carboxylic acids. Secondary alcohols are oxidized to ketones.



Swern oxidation of a 1° alcohol to an aldehyde

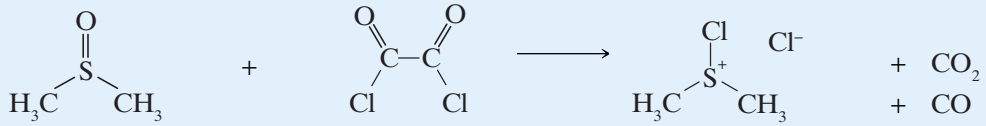


Swern oxidation of a 2° alcohol to a ketone

The reaction is carried out in sequential operations. First, oxalyl chloride (ClCOCOCl) is added to dimethyl sulfoxide (DMSO), usually at low temperature, to generate a chlorodimethylsulfonium salt (as well as CO_2, CO, and HCl by-products). The alcohol substrate is then added to the chlorodimethylsulfonium salt, during which time a dimethylsulfonium group is installed as a leaving group on the hydroxyl oxygen. Third, an amine is added as a base to promote the elimination reaction.

A MECHANISM FOR THE REACTION — The Swern Oxidation

Step 1



Dimethylsulfoxide (DMSO) **Oxalyl chloride $(COCl)_2$** **Chlorodimethylsulfonium salt**

DMSO and oxalyl chloride react to form a chlorodimethylsulfonium salt.

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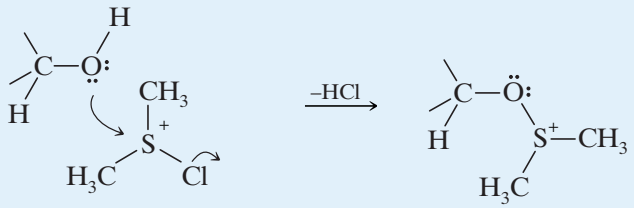
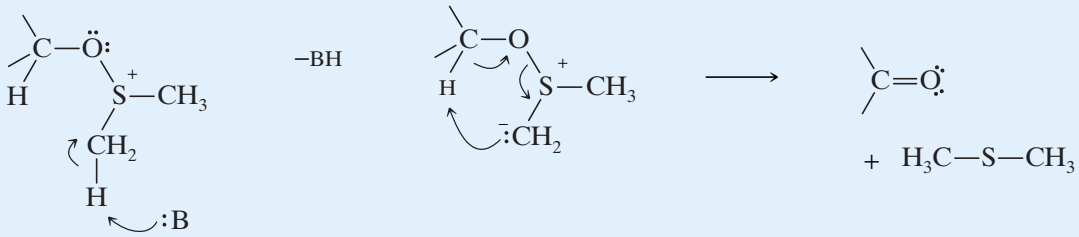
Step 2



The 1° or 2° alcohol reacts with the sulfonium salt, installing a leaving group on the alcohol oxygen atom, along with loss of the hydroxyl proton.

The oxygen now bears a leaving group that can be lost in an elimination reaction.

Step 3



A base (usually triethylamine or diisopropylamine) removes a hydrogen from a methyl group adjacent to the positively–charged sulfur.

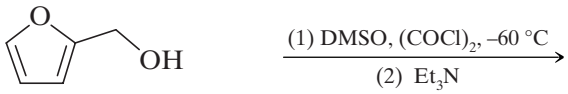
The anionic methyl group removes a proton from the alcohol carbon, forming the C=O π–bond. Dimethylsulfide departs as a leaving group, resulting in the oxidized product.

Reagents other than oxalyl chloride, including trifluoroacetic anhydride, have been used to generate various dimethylsulfonium salts for reaction with the alcohol.

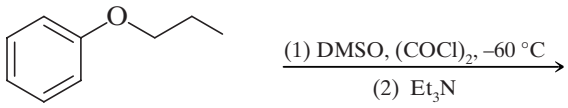
Practice Problem 11.2

What oxidation product would result from each of the following reactions?

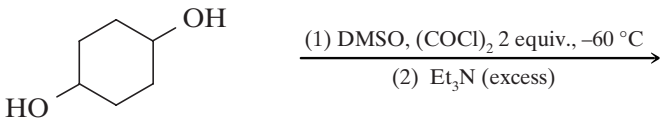
(a)



(b)



(c)



11.4C Chromic Acid (H_2CrO_4) Oxidation

Oxidations involving chromium (VI) reagents such as H_2CrO_4 are simple to carry out and have been widely used. These reactions involve formation of chromate esters, and include an elimination step similar to the general mechanisms shown in Section 10.4A. Chromium (VI) is a carcinogen and an environmental hazard, however. For this reason, methods like the Swern oxidation and others are increasingly important.

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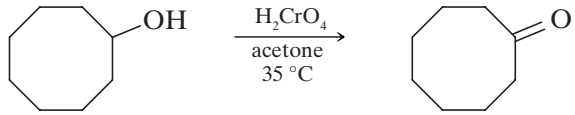
Jones reagent is one well-known source of H_2CrO_4 as the chromium (VI) oxidizing species. It can be prepared by adding CrO_3 or Na_2CrO_4 to aqueous sulfuric acid. Jones reagent is typically used by addition to solutions of an alcohol or aldehyde in acetone or acetic acid (solvents that cannot be oxidized). Primary alcohols are oxidized to carboxylic acids, via the aldehyde hydrate mentioned above. Secondary alcohols are oxidized to ketones. The following is an example of an oxidation using Jones reagent.



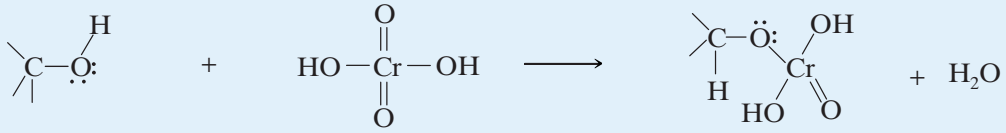
Cyclooctanol → **Cyclooctanol (92–96%)**

As mentioned earlier, the chromate oxidation mechanism first involves formation of a chromate ester with the alcohol. Then a molecule of H_2CrO_3 serves as a leaving group during the elimination step that generates the C═O bond of the carbonyl compound.

A MECHANISM FOR THE REACTION — Chromic Acid Oxidation

Formation of the Chromate Ester

Step 1

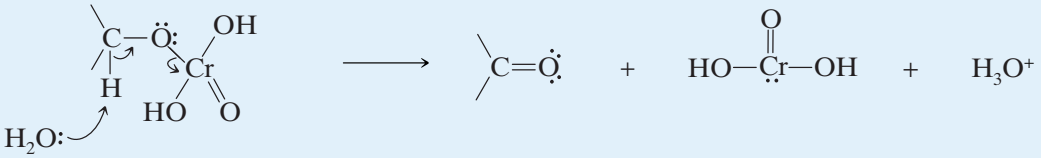


The 1° or 2° alcohol reacts with chromic acid to form a chromate ester with loss of water, installing a leaving group on the alcohol oxygen.

The oxygen now bears a leaving group that can be lost in an elimination reaction.

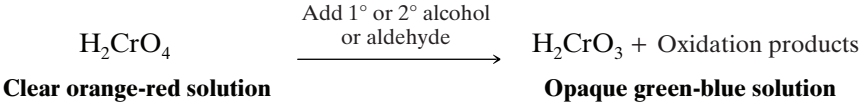
Oxidation by Elimination of H_2CrO_3

Step 2



A water molecule removes a proton from the alcohol carbon, forming the C═O π–bond. The chromium atom is reduced as H_2CrO_3 departs, resulting in the oxidized product.

Chromic acid solutions are orange-red in color, and the product mixture, containing Cr(III), is a greenish blue. Thus, reagents like Jones reagent can serve as a color-based functional group test. Primary or secondary alcohols and aldehydes are rapidly oxidized by Jones reagent, turning the solution an opaque greenish blue within a few seconds. If none of these groups are present, the solution remains orange-red until side reactions eventually change the color. This color change is the basis for the original **breathalyzer alcohol test**.



Clear orange-red solution → **Opaque green-blue solution**

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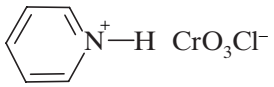
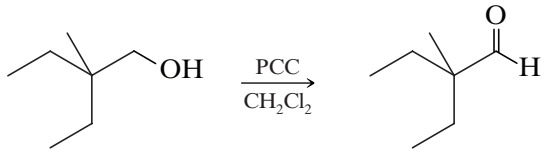
11.4D Pyridinium Chlorochromate (PCC)

Pyridinium chlorochromate (PCC) is a Cr(VI) salt formed between pyridine (C_6H_5N), HCl, and CrO_3. PCC is soluble in dichloromethane, thus it can be used under conditions that exclude water, allowing for the oxidization of primary alcohols to aldehydes because the aldehyde hydrate is not present under anhydrous conditions. Jones reagent, on the other hand, oxidizes primary alcohols to carboxylic acids because it is an aqueous reagent. The following are some general examples of PCC oxidations.

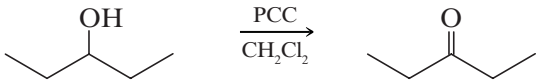


Pyridinium chlorochromate (PCC)



2-Ethyl-2-methyl-1-butanol — **2-Ethyl-2-methylbutanal**

PCC oxidation of a 1° alcohol to an aldehyde



PCC oxidation of a 2° alcohol to a ketone

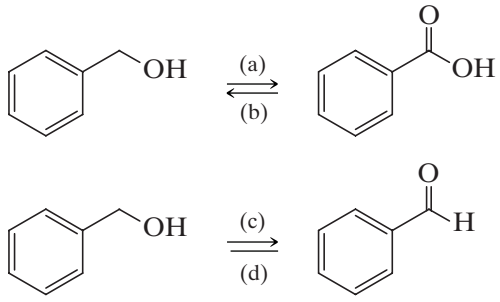
11.4E Potassium Permanganate ($KMnO_4$)

Primary alcohols and aldehydes can be oxidized by potassium permanganate ($KMnO_4$) to the corresponding carboxylic acids. Secondary alcohols can be oxidized to ketones. These reactions do not proceed by the type of mechanism described above (and we shall not discuss the mechanism here). The reaction is usually carried out in basic aqueous solution, from which MnO_2 precipitates as the oxidation takes place. After the oxidation is complete, filtration allows removal of the MnO_2 and acidification of the filtrate gives the carboxylic acid.



Solved Problem 11.2

Which reagents would you use to accomplish the following transformations?



Answer

(a) To oxidize a primary alcohol to a carboxylic acid, use (1) potassium permanganate in aqueous base, followed by (2) H_3O^+, or use chromic acid (H_2CrO_4).

(b) To reduce a carboxylic acid to a primary alcohol, use $LiAlH_4$.

(c) To oxidize a primary alcohol to an aldehyde, use the Swern oxidation or pyridinium chlorochromate (PCC).

(d) To reduce an aldehyde to a primary alcohol, use $NaBH_4$ (preferably) or $LiAlH_4$.

Practice Problem 11.3

Show how each of the following transformations could be accomplished:



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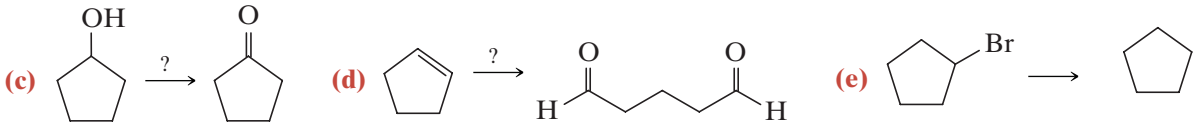
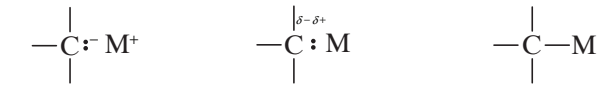


11.5 | ORGANOMETALLIC COMPOUNDS

- Compounds that contain carbon–metal bonds are called **organometallic compounds**.

The nature of the carbon–metal bond varies widely, ranging from bonds that are essentially ionic to those that are primarily covalent. Whereas the structure of the organic portion of the organometallic compound has some effect on the nature of the carbon–metal bond, the identity of the metal itself is of far greater importance. Carbon–sodium and carbon–potassium bonds are largely ionic in character; carbon–lead, carbon–tin, carbon–thallium, and carbon–mercury bonds are essentially covalent. Carbon–lithium and carbon–magnesium bonds lie between these extremes.



Primarily ionic (M = Na⁺ or K⁺) | **(M = Mg or Li)** | **Primarily covalent (M = Pb, Sn, Hg, or Tl)**

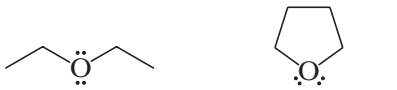
The reactivity of organometallic compounds increases with the percent ionic character of the carbon–metal bond. Alkylsodium and alkylpotassium compounds are highly reactive and are among the most powerful of bases. They react explosively with water and burst into flame when exposed to air. Organomercury and organolead compounds are much less reactive; they are often volatile and are stable in air. They are all poisonous. They are generally soluble in nonpolar solvents. Tetraethyllead, for example, was once used as an "antiknock" compound in gasoline, but because of the lead pollution it contributed to the environment it has been replaced by other antiknock agents. *tert*-Butyl methyl ether is another antiknock additive, though there are concerns about its presence in the environment, as well.

Organometallic compounds of lithium and magnesium are of great importance in organic synthesis. They are relatively stable in ether solutions, but their carbon–metal bonds have considerable ionic character. Because of this ionic nature, the carbon atom that is bonded to the metal atom of an organolithium or organomagnesium compound is a strong base and powerful nucleophile. We shall soon see reactions that illustrate both of these properties.

11.6 | PREPARATION OF ORGANOLITHIUM AND ORGANOMAGNESIUM COMPOUNDS

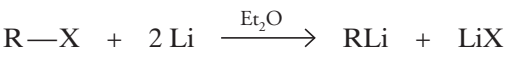
11.6A Organolithium Compounds

Organolithium compounds are often prepared by the reduction of organic halides with lithium metal. These reductions are usually carried out in ether solvents, and since organolithium compounds are strong bases, care must be taken to exclude moisture. (Why?) The ethers most commonly used as solvents are diethyl ether and tetrahydrofuran. (Tetrahydrofuran is a cyclic ether.)



Diethyl ether (Et_2O) | **Tetrahydrofuran (THF)**

- Organolithium compounds are prepared in this general way:



(or Ar—X) **(or ArLi)**

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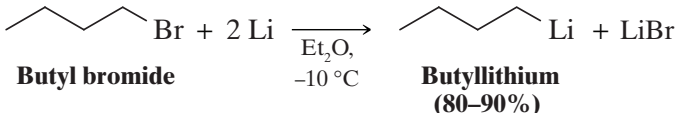
The order of reactivity of halides is RI > RBr > RCl. (Alkyl and aryl fluorides are seldom used in the preparation of organolithium compounds.)

For example, butyl bromide reacts with lithium metal in diethyl ether to give a solution of butyllithium:



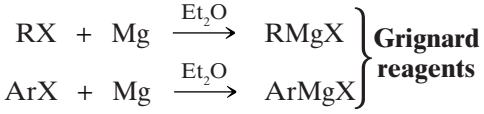
Butyl bromide — **Butyllithium (80–90%)**

Several alkyl- and aryllithium reagents are commercially available in hexane and other hydrocarbon solvents.

11.6B Grignard Reagents

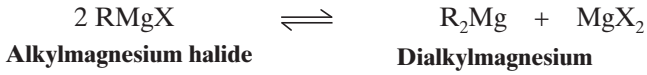
Organomagnesium halides were discovered by the French chemist Victor Grignard in 1900. Grignard received the Nobel Prize for his discovery in 1912, and organomagnesium halides are now called **Grignard reagents** in his honor. Grignard reagents have great use in organic synthesis.

- Grignard reagents are prepared by the reaction of an organic halide with magnesium metal in an anhydrous ether solvent:



The order of reactivity of halides with magnesium is also RI > RBr > RCl. Very few organomagnesium fluorides have been prepared. Aryl Grignard reagents are more easily prepared from aryl bromides and aryl iodides than from aryl chlorides, which react very sluggishly. Once prepared, a Grignard reagent is usually used directly in a subsequent reaction.

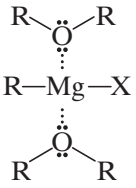
The actual structures of Grignard reagents are more complex than the general formula RMgX indicates. Experiments have established that for most Grignard reagents there is an equilibrium between an alkylmagnesium halide and a dialkylmagnesium.



Alkylmagnesium halide — **Dialkylmagnesium**

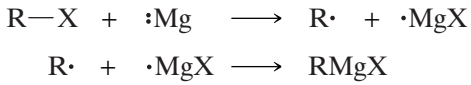
For convenience in this text, however, we shall write the formula for the Grignard reagent as though it were simply RMgX.

A Grignard reagent forms a complex with its ether solvent; the structure of the complex can be represented as follows:



Complex formation with molecules of ether is an important factor in the formation and stability of Grignard reagents.

The mechanism by which Grignard reagents form is complicated and has been a matter of debate. There seems to be general agreement that radicals are involved and that a mechanism similar to the following is likely:



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11.7 | REACTIONS OF ORGANOLITHIUM AND ORGANOMAGNESIUM COMPOUNDS

11.7A Reactions with Compounds Containing Acidic Hydrogen Atoms

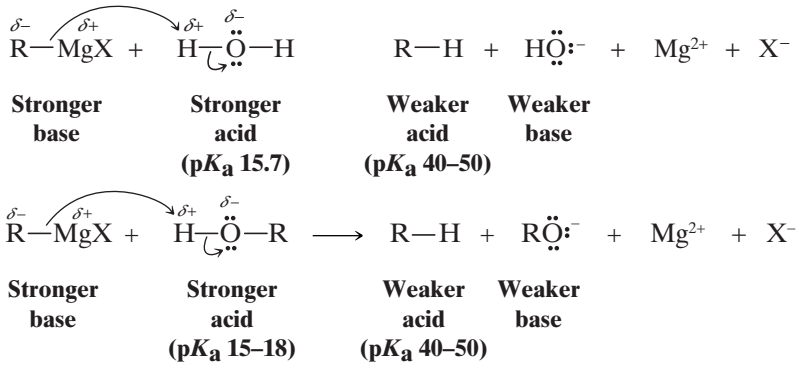
- Grignard reagents and organolithium compounds are very strong bases. They react with any compound that has a hydrogen atom attached to an electronegative atom such as oxygen, nitrogen, or sulfur.

We can understand how these reactions occur if we represent the Grignard reagent and organolithium compounds in the following ways:

$$\overset{\delta-}{R}:\overset{\delta+}{Mg}X \quad \text{and} \quad \overset{\delta-}{R}:\overset{\delta+}{Li}$$

When we do this, we can see that the reactions of Grignard reagents with water and alcohols are nothing more than acid–base reactions; they lead to the formation of the weaker conjugate acid and weaker conjugate base.

- A Grignard reagent behaves as if it contained the anion of an alkane, *as if it contained a carbanion*:

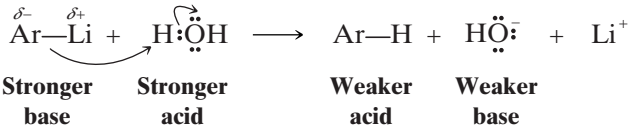


Solved Problem 11.3

Write an equation for the reaction that would take place when phenyllithium is treated with water. Designate the stronger acid and stronger base.

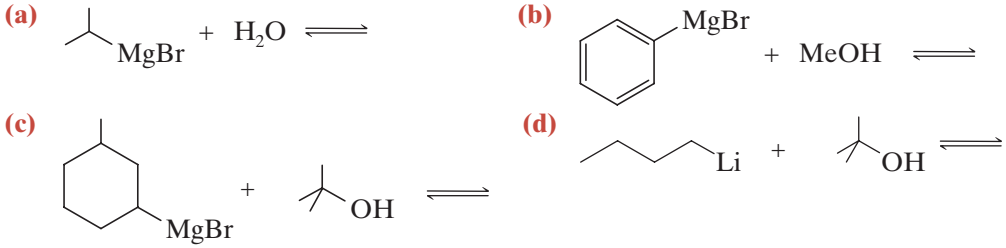
Answer

Recognizing that phenyllithium, like a Grignard reagent, acts as though it contains a carbanion, a very powerful base (pK_a = 40–50), we conclude that the following acid–base reaction would occur.



Practice Problem 11.4

Predict the products of the following acid–base reactions. Using pK_a values, indicate which side of each equilibrium reaction is favored, and label the species representing the stronger acid and stronger base in each case.



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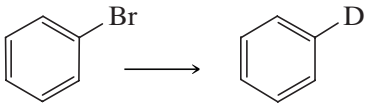
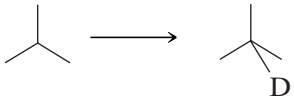
Practice Problem 11.5

Provide the reagents necessary to achieve the following transformations.

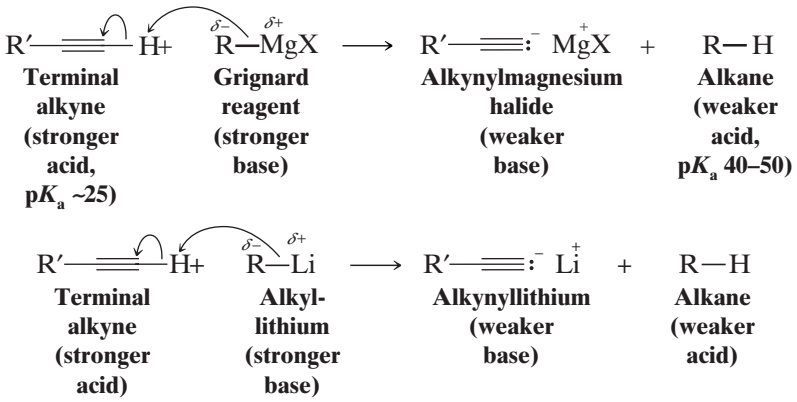
(a) 

(D = deuterium)

(b) 

Grignard reagents and organolithium compounds remove protons that are much less acidic than those of water and alcohols.

- Grignard reagents react with the terminal hydrogen atoms of 1-alkynes by an acid–base reaction, and this is a useful method for the preparation of alkynylmagnesium halides and alkynyllithiums.



The fact that these reactions go to completion is not surprising when we recall that alkanes have pK_a values of 40–50, whereas those of terminal alkynes are ~25 (Table 3.1).

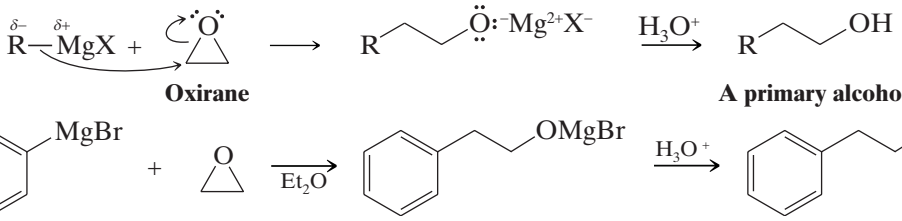
Not only are Grignard reagents strong bases, they are also *powerful nucleophiles*.

- Reactions in which Grignard reagents act as nucleophiles are by far the most important and we shall consider these next.

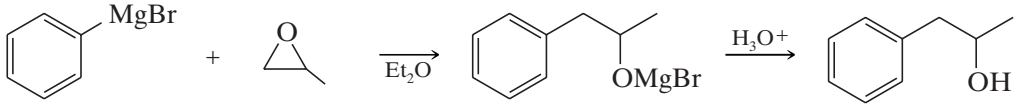
11.7B Reactions of Grignard Reagents with Epoxides (Oxiranes)

- Grignard reagents react as nucleophiles with epoxides (oxiranes), providing convenient synthesis of alcohols.

The nucleophilic alkyl group of the Grignard reagent attacks the partially positive carbon of the epoxide ring. Because it is highly strained, the ring opens, and the reaction leads to the alkoxide salt of an alcohol. Subsequent acidification produces the alcohol. (Compare this reaction with the base-catalyzed ring opening we studied in Section 10.13.) The following are examples with oxirane.



- Grignard reagents react primarily at the less-substituted ring carbon atom of a substituted epoxide.



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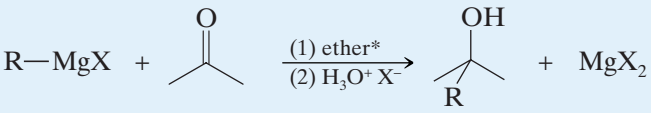
11.7C Reactions of Grignard Reagents with Carbonyl Compounds

- The most important synthetic reactions of Grignard reagents and organolithium compounds are those in which they react as nucleophiles and attack an unsaturated carbon—*especially the carbon of a carbonyl group*.

We saw in Section 11.1A that carbonyl compounds are highly susceptible to nucleophilic attack. Grignard reagents react with carbonyl compounds (aldehydes and ketones) in the following way:

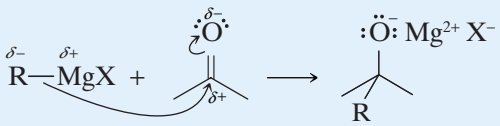
A MECHANISM FOR THE REACTION — The Grignard Reaction

Reaction



Mechanism

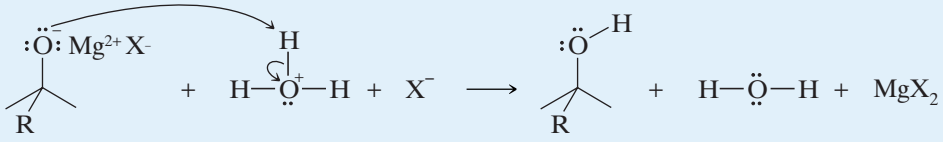
Step 1



Grignard reagent | **Carbonyl compound** | **Halomagnesium alkoxide**

The strongly nucleophilic Grignard reagent uses its electron pair to form a bond to the carbon atom. One electron pair of the carbonyl group shifts out to the oxygen. This reaction is a nucleophilic addition to the carbonyl group, and it results in the formation of an alkoxide ion associated with Mg^{2+} and X^-.

Step 2



Halomagnesium alkoxide | **Alcohol**

In the second step, the addition of aqueous HX causes protonation of the alkoxide ion; this leads to the formation of the alcohol and MgX_2.

*By writing "(1) ether" over the arrow and "(2) H_3O^+ X^-" under the arrow, we mean that in the first laboratory step the Grignard reagent and the carbonyl compound are allowed to react in an ether solvent. Then in a second step, after the reaction of the Grignard reagent and the carbonyl compound is over, we add aqueous acid (e.g., dilute HX) to convert the salt of the alcohol (ROMgX) to the alcohol itself. If the alcohol is tertiary, it will be susceptible to acid-catalyzed dehydration. In this case, a solution of NH_4Cl in water is often used because it is acidic enough to convert ROMgX to ROH while not allowing acid-catalyzed reactions of the resulting tertiary alcohol.

11.8 | ALCOHOLS FROM GRIGNARD REAGENTS

Grignard additions to carbonyl compounds are especially useful because they can be used to prepare primary, secondary, or tertiary alcohols:

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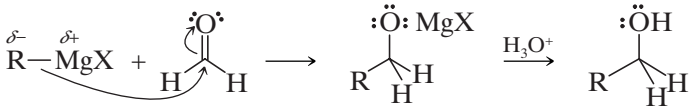
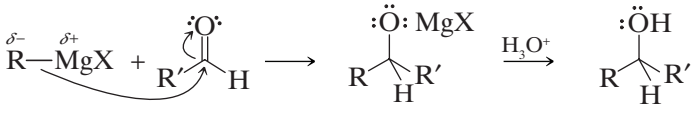
1. Grignard Reagents React with Formaldehyde to Give a Primary Alcohol



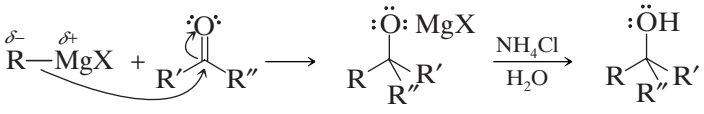
Formaldehyde **1° Alcohol**

2. Grignard Reagents React with All Other Aldehydes to Give Secondary Alcohols



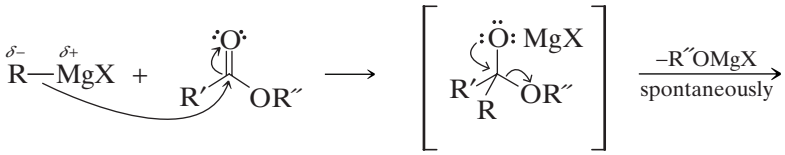
Higher aldehyde **2° Alcohol**

3. Grignard Reagents React with Ketones to Give Tertiary Alcohols

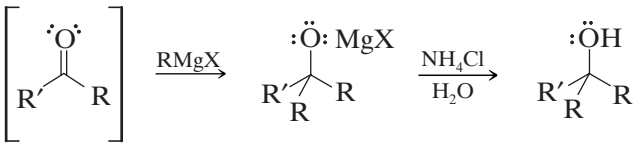


Ketone **3° Alcohol**

4. Esters React with Two Molar Equivalents of a Grignard Reagent to Form Tertiary Alcohols When a Grignard reagent adds to the carbonyl group of an ester, the initial product is unstable and loses a magnesium alkoxide to form a ketone. Ketones, however, are more reactive toward Grignard reagents than esters. Therefore, as soon as a molecule of the ketone is formed in the mixture, it reacts with a second molecule of the Grignard reagent. After hydrolysis, **the product is a tertiary alcohol with two identical alkyl groups**, groups that correspond to the alkyl portion of the Grignard reagent:

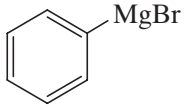
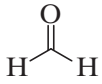
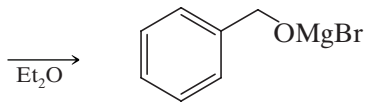
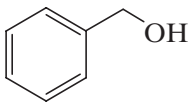
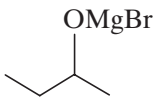
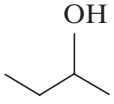


Ester **Initial product (unstable)**



Ketone **Salt of an alcohol (not isolated)** **3° Alcohol (with two or three identical R groups)**

Specific examples of these reactions are shown here.

Grignard Reagent	Carbonyl Reactant		Final Product
Reaction with Formaldehyde			
			
Phenylmagnesium bromide	**Formaldehyde**		**Benzyl alcohol (90%)**
Reaction with a Higher Aldehyde			
			
Ethylmagnesium bromide	**Acetaldehyde**		**2-Butanol (80%)**

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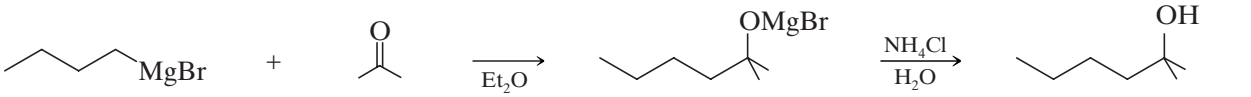
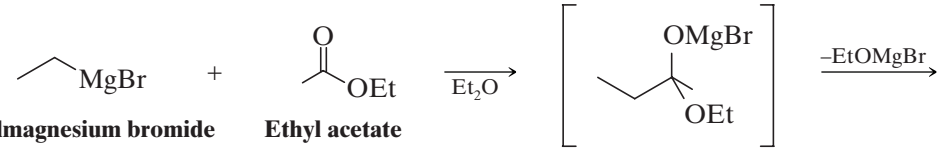
Reaction with a Ketone

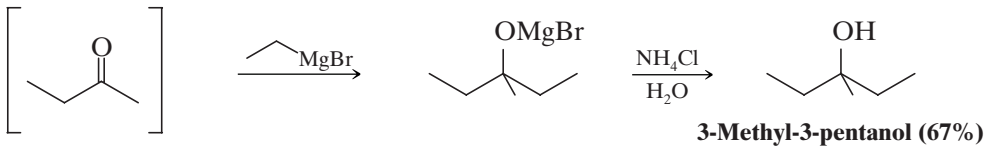


Butylmagnesium bromide **Acetone** **2-Methyl-2-hexanol (92%)**

Reaction with an Ester



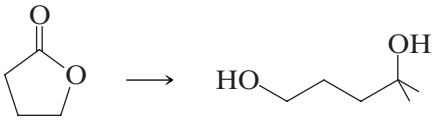
Ethylmagnesium bromide **Ethyl acetate**



3-Methyl-3-pentanol (67%)

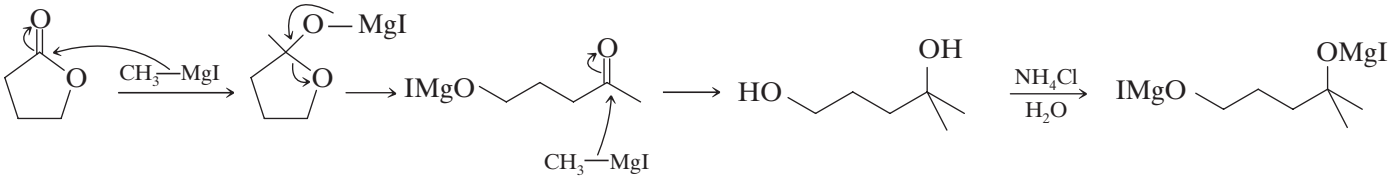
Solved Problem 11.4

How would you carry out the following synthesis?



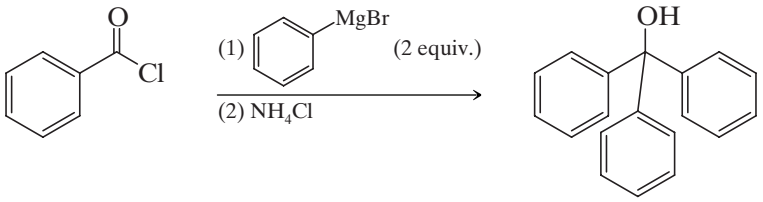
Answer

Here we are converting an ester (a cyclic ester) to **a tertiary alcohol with two identical alkyl groups** (methyl groups). So, we should use two molar equivalents of the Grignard reagent that contains the required alkyl groups, in this case, methyl magnesium iodide.



Practice Problem 11.6

Provide a mechanism for the following reaction, based on your knowledge of the reaction of esters with Grignard reagents.



11.8A HOW TO Plan a Grignard Synthesis

We can synthesize almost any alcohol we wish by skillfully using a Grignard synthesis. In planning a Grignard synthesis we must simply choose the correct Grignard reagent and the correct aldehyde, ketone, ester, or epoxide.

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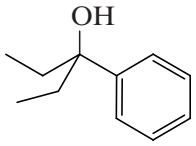
We do this by examining the alcohol we wish to prepare and by paying special attention to the groups attached to the carbon atom bearing the —OH group. Many times there may be more than one way of carrying out the synthesis. In these cases our final choice will probably be dictated by the availability of starting compounds. Let us consider an example.

Suppose we want to prepare 3-phenyl-3-pentanol. We examine its structure and we see that the groups attached to the carbon atom bearing the —OH are a *phenyl group* and *two ethyl groups*:

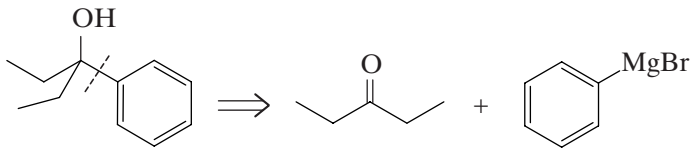


3-Phenyl-3-pentanol

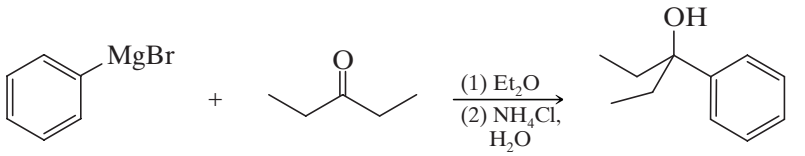
This means that we can synthesize this compound in several different ways:

1. We can use a ketone with two ethyl groups (3-pentanone) and allow it to react with phenylmagnesium bromide:

Retrosynthetic Analysis



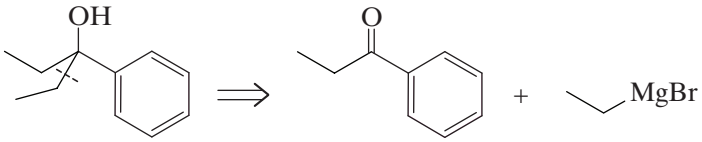
Synthesis



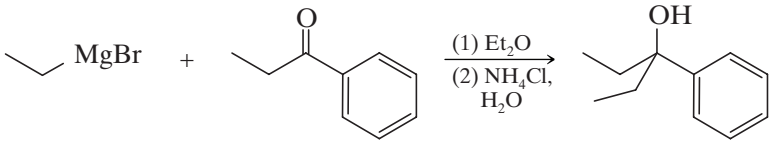
Phenylmagnesium bromide **3-Pentanone** **3-Phenyl-3-pentanol**

2. We can use a ketone containing an ethyl group and a phenyl group (ethyl phenyl ketone) and allow it to react with ethylmagnesium bromide:

Retrosynthetic Analysis



Synthesis



Ethylmagnesium bromide **Ethyl phenyl ketone** **3-Phenyl-3-pentanol**

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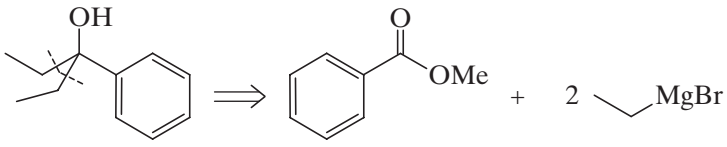
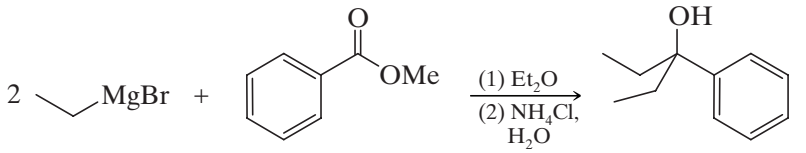
3. We can use an ester of benzoic acid and allow it to react with two molar equivalents of ethylmagnesium bromide:

Retrosynthetic Analysis



Synthesis

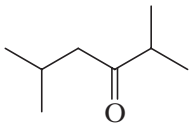


Ethylmagnesium bromide **Methyl benzoate** **3-Phenyl-3-pentanol**

All of these methods will likely give us our desired compound in high yields.

Solved Problem 11.5

Using an alcohol of no more than four carbon atoms as your only organic starting material, outline a synthesis of **A**:

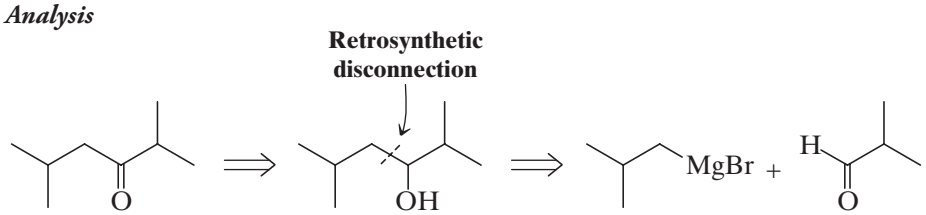


A

Answer

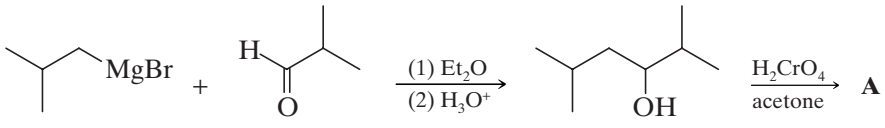
We can construct the carbon skeleton from two four-carbon compounds using a Grignard reaction. Then oxidation of the alcohol produced will yield the desired ketone.

Retrosynthetic Analysis



A **B** **C**

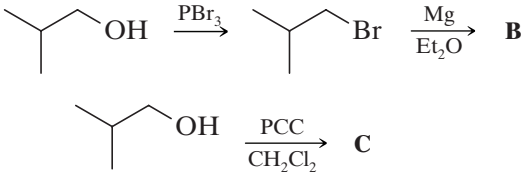
Synthesis



A

B **C**

We can synthesize the Grignard reagent (**B**) and the aldehyde (**C**) from isobutyl alcohol:



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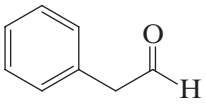
Solved Problem 11.6

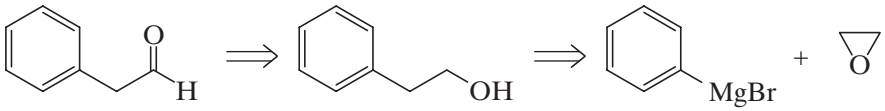
Starting with bromobenzene and any other needed reagents, outline a synthesis of the following aldehyde:



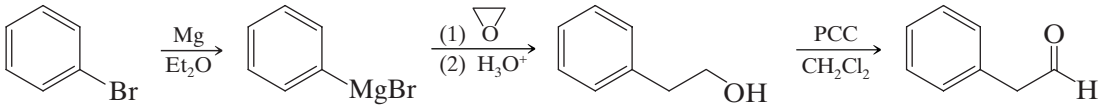
Answer

Working backward, we remember that we can synthesize the aldehyde from the corresponding alcohol by the Swern oxidation or PCC. The alcohol can be made by treating phenylmagnesium bromide with oxirane. [Adding oxirane to a Grignard reagent is a very useful method for adding a $-CH_2CH_2OH$ unit to an organic group.] Phenylmagnesium bromide can be made in the usual way, by treating bromobenzene with magnesium in an ether solvent.

Retrosynthetic Analysis

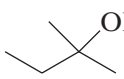


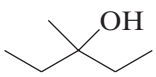
Synthesis

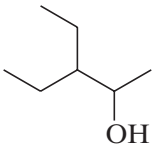


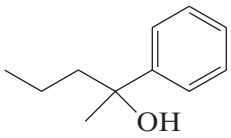
Practice Problem 11.7

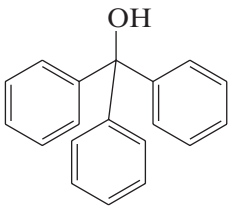
Provide retrosynthetic analyses and syntheses for each of the following alcohols, starting with appropriate alkyl or aryl halides.

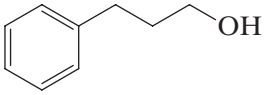
(a)  (three ways)

(b)  (three ways)

(c)  (two ways)

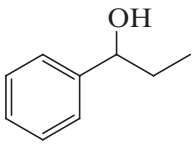
(d)  (three ways)

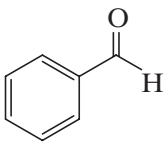
(e)  (two ways)

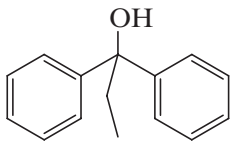
(f)  (two ways)

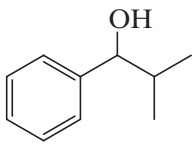
Practice Problem 11.8

Provide a retrosynthetic analysis and synthesis for each of the following compounds. Permitted starting materials are phenylmagnesium bromide, oxirane, formaldehyde, and alcohols or esters of four carbon atoms or fewer. You may use any inorganic reagents and oxidizing conditions such as Swern oxidation or pyridinium chlorochromate (PCC).

(a) 

(b) 

(c) 

(d) 

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11.8B Restrictions on the Use of Grignard Reagents

Although the Grignard synthesis is one of the most versatile of all general synthetic procedures, it is not without its limitations. Most of these limitations arise from the very feature of the Grignard reagent that makes it so useful—its *extraordinary reactivity as a nucleophile and a base*.

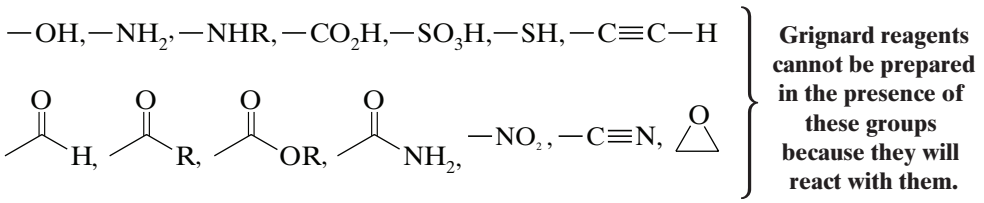
The Grignard reagent is a very powerful base; in effect it contains a carbanion.

- It is not possible to prepare a Grignard reagent from a compound that contains any hydrogen more acidic than the hydrogen atoms of an alkane or alkene.

We cannot, for example, prepare a Grignard reagent from a compound containing an —OH group, an —NH— group, an —SH group, a $-CO_2H$ group, or an $-SO_3H$ group. If we were to attempt to prepare a Grignard reagent from an organic halide containing any of these groups, the formation of the Grignard reagent would simply fail to take place. (Even if a Grignard reagent were to form, it would immediately be neutralized by the acidic group.)

- Since Grignard reagents are powerful nucleophiles, we cannot prepare a Grignard reagent from any organic halide that contains a carbonyl, epoxy, nitro, or cyano (—CN) group.

If we were to attempt to carry out this kind of reaction, any Grignard reagent that formed would only react with the unreacted starting material:



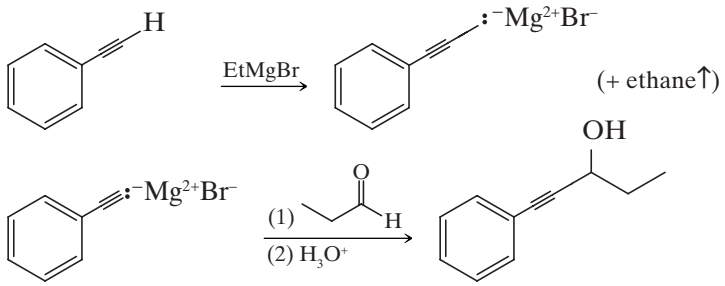
This means that when we prepare Grignard reagents, we are effectively limited to alkyl halides or to analogous organic halides containing carbon–carbon double bonds, internal triple bonds, ether linkages, and —NR_2 groups.

Grignard reactions are so sensitive to acidic compounds that when we prepare a Grignard reagent we must take special care to exclude moisture from our apparatus, and we must use an anhydrous ether as our solvent.

As we saw earlier, acetylenic hydrogens are acidic enough to react with Grignard reagents. This is a limitation that we can use, however.

- We can make acetylenic Grignard reagents by allowing terminal alkynes to react with alkyl Grignard reagents (cf. Section 10.6A).

We can then use these acetylenic Grignard reagents to carry out other syntheses. For example,



(52%)

- When we plan a Grignard synthesis, we must also take care that any aldehyde, ketone, epoxide, or ester that we use as a substrate does not also contain an acidic group (other than when we deliberately let it react with a terminal alkyne).

If we were to do this, the Grignard reagent would simply react as a base with the acidic hydrogen rather than reacting at the carbonyl or epoxide carbon as a nucleophile. If we were to treat 4-hydroxy-2-butanone with methylmagnesium bromide, for example, the reaction that would take place is

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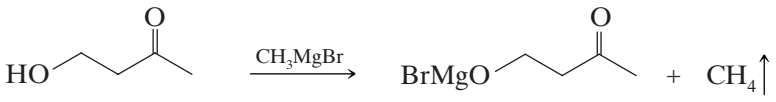
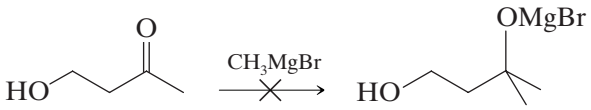
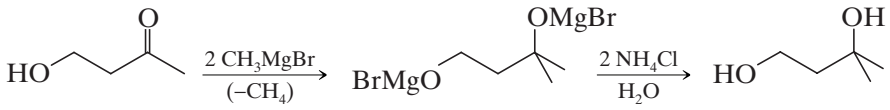


4-Hydroxy-2-butanone

rather than

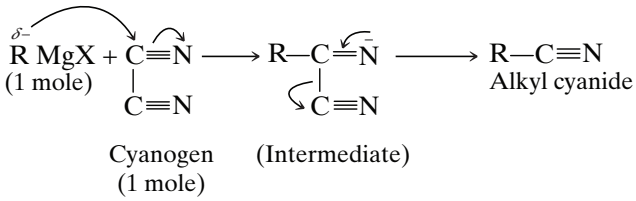


If we were prepared to waste one molar equivalent of the Grignard reagent, we can treat 4-hydroxy-2-butanone with two molar equivalents of the Grignard reagent and thereby get addition to the carbonyl group:

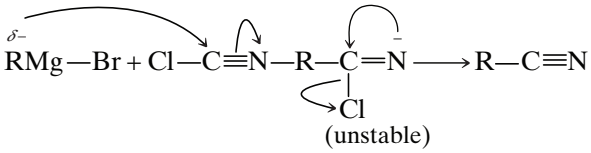


This technique is sometimes employed in small-scale reactions when the Grignard reagent is inexpensive and the other reagent is expensive.

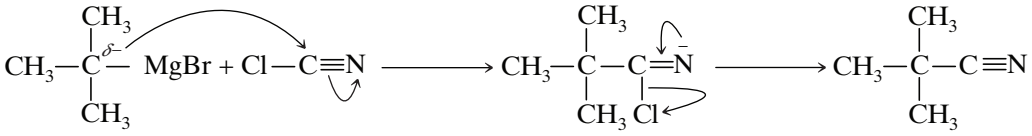
Grignard reagent can be used to prepare alkyl cyanide as follows:



One mole of Grignard reagent reacts with one mole of cyanogen to form an alkyl cyanide. When one mole of Grignard reagent is added to an ethereal solution of cyanogen chloride (one mole) alkyl cyanide is formed.



Example:



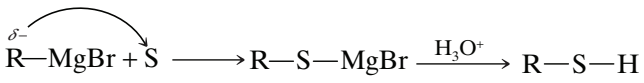
This reaction is considered as the best method for the preparation of tertiary alkyl cyanide. In the above reaction, if excess of Grignard reagent is used then the final product will give a ketone after hydrolysis.

The reactions of Grignard reagent with bromides and iodides are as follows:

$$RMgBr + Br—Br \longrightarrow R—Br$$

$$RMg + I—I \longrightarrow R—I$$

The reaction of Grignard reagent with sulphur is as follows:



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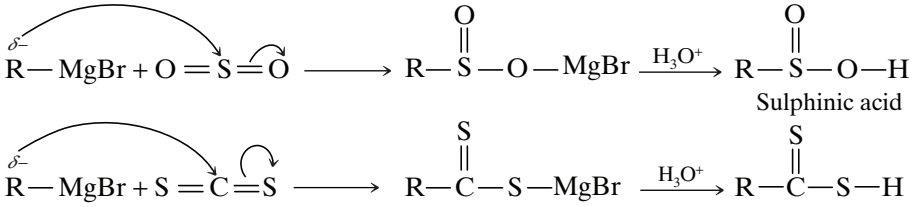
The reactions of Grignard reagent with sulphur dioxide and carbon disulphide are as follows:



The reactions of Grignard reagent with metals of groups IIB, IIIB and IVB are as follows:

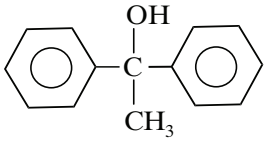
$$2RMgX + CdCl_2 \longrightarrow R_2Cd$$ (Cadmium dialkyl compounds are readily prepared by this method)

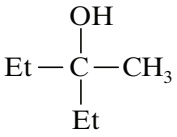
$$2RMgX + HgCl_2 \longrightarrow R_2Hg \qquad 3RMgX + BiCl_3 \longrightarrow R_3Bi$$

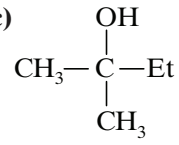
$$4RMgX + PbCl_4 \longrightarrow R_4Pb \qquad 3RMgX + SbCl_3 \longrightarrow R_3Sb$$

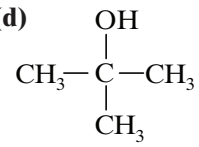
Solved Problem 11.7

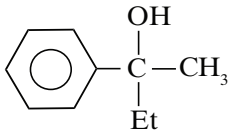
Which of following tertiary alcohols cannot be prepared by the reaction of an ester with excess of Grignard reagent?

(a) 

(b) 

(c) 

(d) 

(e) 

Answer

A tertiary alcohol is obtained from the reaction of an ester with two equivalents of a Grignard reagent; therefore, tertiary alcohol must have two identical substituents on the carbon to which alcohol (–OH) is bonded because these two substituents come from the Grignard reagent. The compound (e) cannot be prepared by this reaction because it has three different substituents attached to the carbon having the –OH group. Therefore the answer is (e).

11.8C The Use of Lithium Reagents

Organolithium reagents (RLi) react with carbonyl compounds in the same way as Grignard reagents and thus provide an alternative method for preparing alcohols.

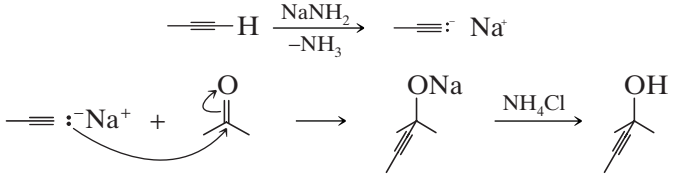


Organolithium reagent **Aldehyde or ketone** **Lithium alkoxide** **Alcohol**

Organolithium reagents have the advantage of being somewhat more reactive than Grignard reagents although they are more difficult to prepare and handle.

11.8D The Use of Sodium Alkynides

Sodium alkynides also react with aldehydes and ketones to yield alcohols. An example is the following:



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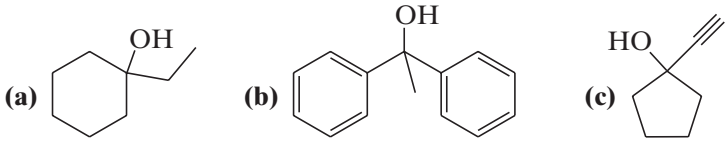
Solved Problem 11.8

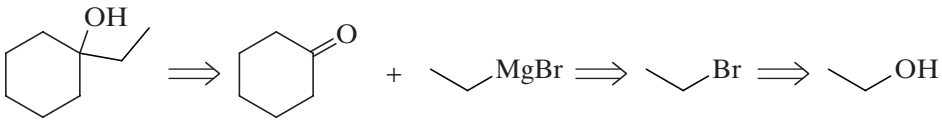
For the following compounds, write a retrosynthetic scheme and then synthetic reactions that could be used to prepare each one. Use hydrocarbons, organic halides, alcohols, aldehydes, ketones, or esters containing six carbon atoms or fewer and any other needed reagents.



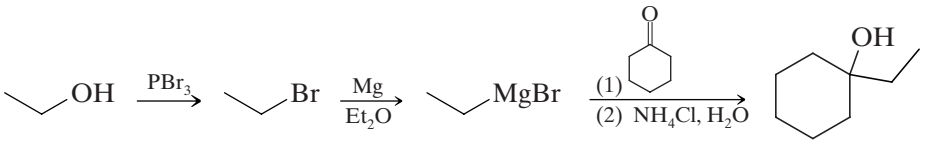
Answers

(a)

Retrosynthetic Analysis

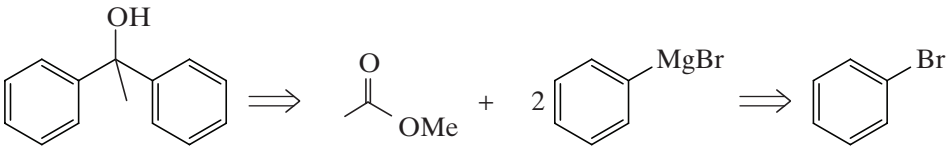


Synthesis

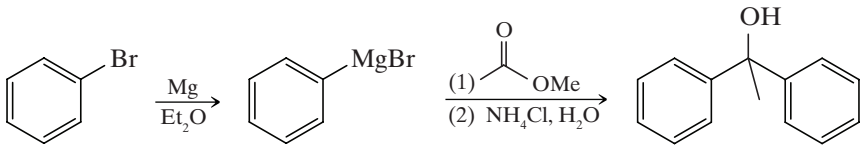


(b)

Retrosynthetic Analysis

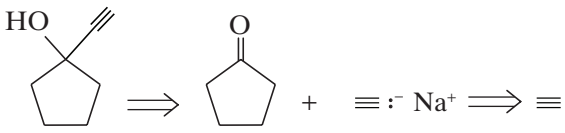


Synthesis

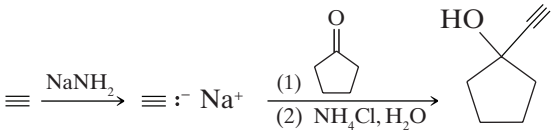


(c)

Retrosynthetic Analysis



Synthesis



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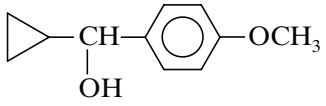
Solved Problem 11.9

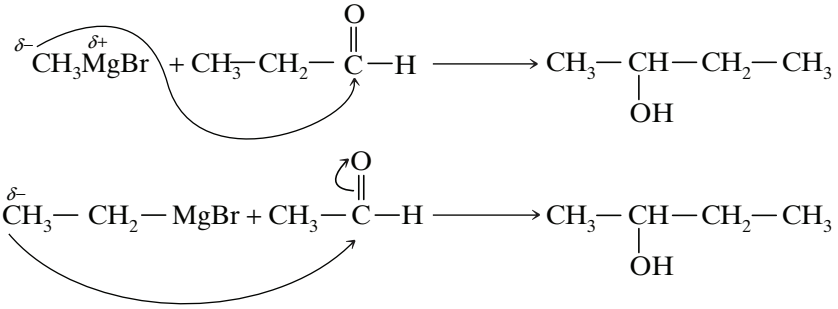
Suggest two ways for the preparation of following alcohols by using Grignard reagent.

(a) $CH_3-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_2-CH_3$ **(b)** $Ph-\overset{\displaystyle OH}{\overset{|}{\underset{\displaystyle CH_3}{\underset{|}{C}}}}-CH_3$ **(c)** 

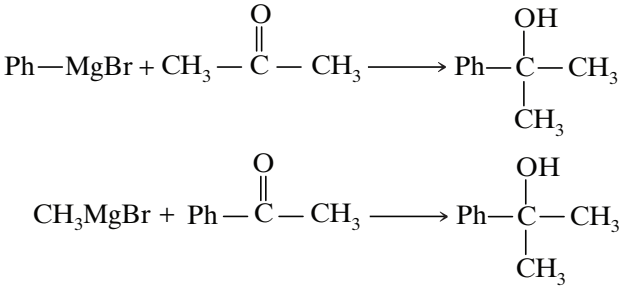
(d) $Ph-\overset{\displaystyle OH}{\overset{|}{\underset{\displaystyle Et}{\underset{|}{C}}}}-CH_3$ **(e)** CH_3-CH_2-D

Answers

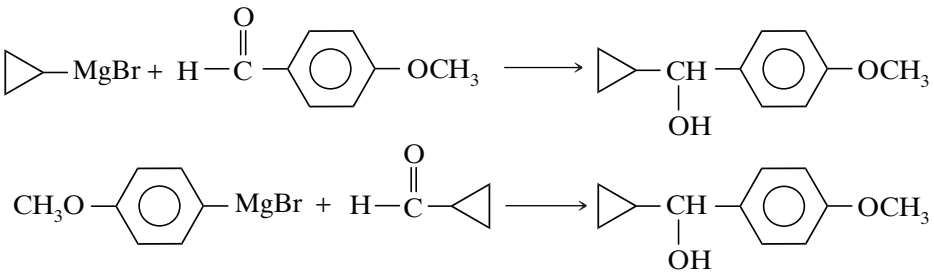
(a) 2-Butanol is a secondary alcohol. Its preparation involves the reaction of Grignard reagent with an aldehyde. Decomposition of the products takes place on treatment with H_3O^+(acidification). The following two routes can be suggested for the reaction.



(b) The preparation of tertiary alcohol, involves the reaction of a Grignard reagent with ketone and the decomposition of products with H_3O^+. The two possible routes for obtaining the given alcohol are:



(c) The two possible routes for the preparation of the given alcohol are as follows:



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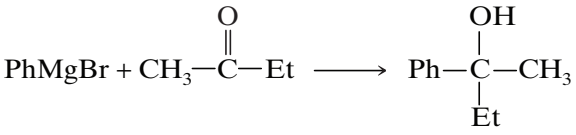
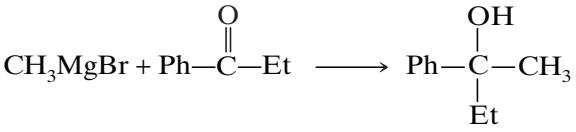
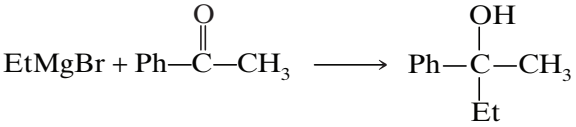
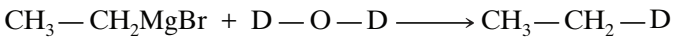
(d) The possible routes for the preparation of the alcohol are as follows:

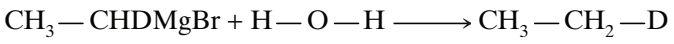






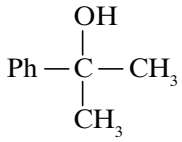
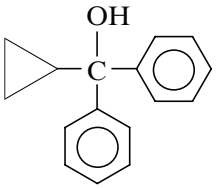
(e) The two possible routes for the preparation of the alcohol are as follows:





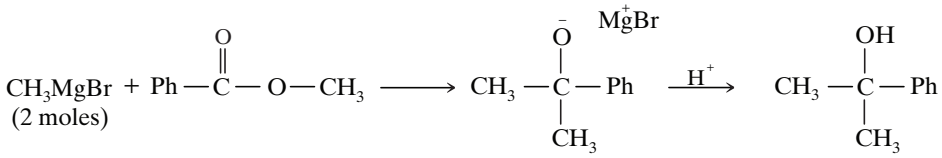
Solved Problem 11.10

What combination of an ester and a Grignard reagent could you use to prepare the following tertiary alcohols?

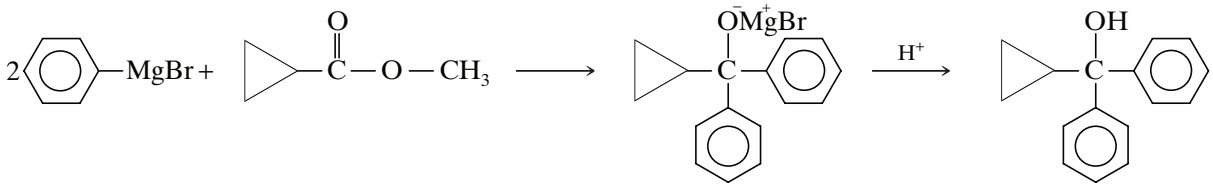
(a)  **(b)** 

Answer

(a) This alcohol can be prepared in the following way:



(b) This alcohol can be prepared in the following way:



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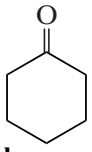
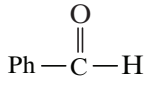
Solved Problem 11.11

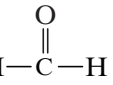
Write the structure of the product obtained from the reaction of methylmagnesium bromide with each of the following compounds. Assume that the reactions are worked up by the addition of dilute aqueous acid.

(a) 

Cyclopropanone

(b) 

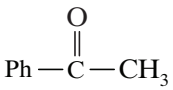
Benzaldehyde

(c) 

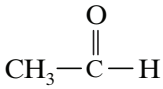
Formaldehyde

(d) 

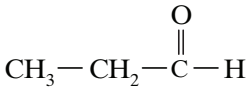
2-Butanone

(e) 

Acetophenone

(f) 

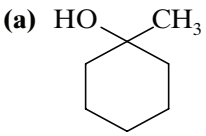
Acetaldehyde

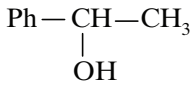
(g) 

Propanal

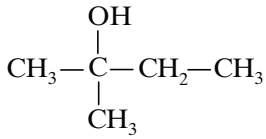
Answer

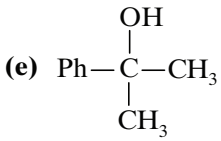
The structures of the products formed are as follows:

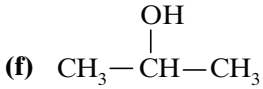
(a) 

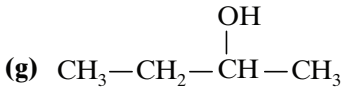
(b) 

(c) 

(d) 

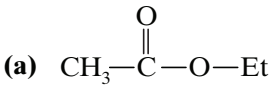
(e) 

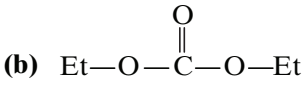
(f) 

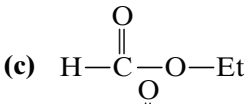
(g) 

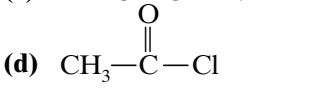
Solved Problem 11.12

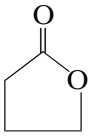
Write the structures of the products obtained from the reaction of phenylmagnesium bromide (excess) with each of the following compounds. Assume that the reactions are worked up by the addition of dilute aqueous acid.

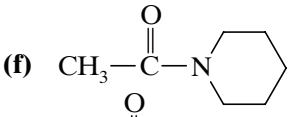
(a) 

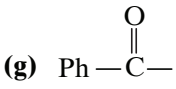
(b) 

(c) 

(d) 

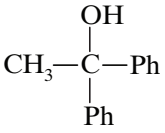
(e) 

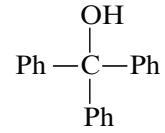
(f) 

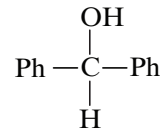
(g) 

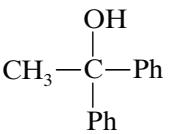
Answer

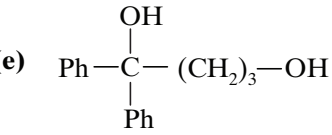
The structures of the products formed are as follows:

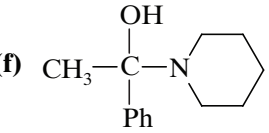
(a) 

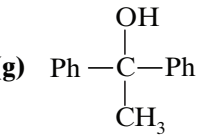
(b) 

(c) 

(d) 

(e) 

(f) 

(g) 

Solved Problem 11.13

What is the maximum number of moles of Grignard reagent consumed when it reacts in excess with each of following compounds?

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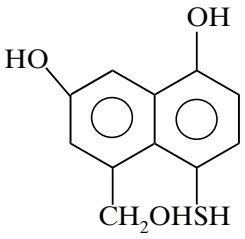
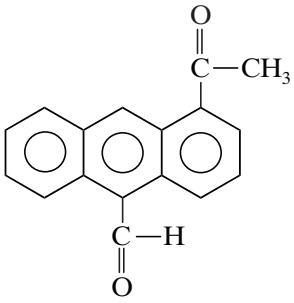
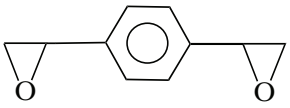
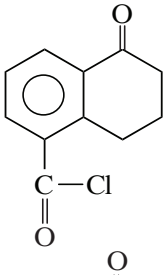
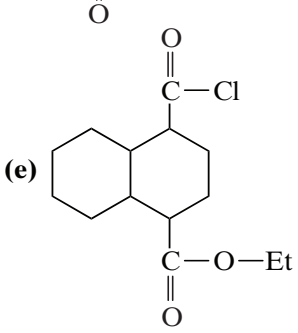
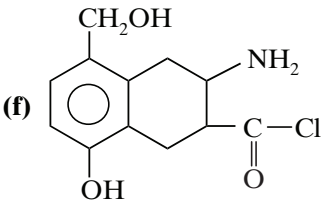
(a) 

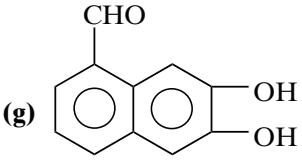
(b) 

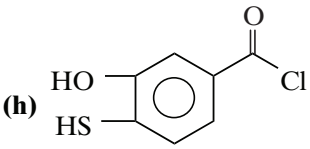
(c) 

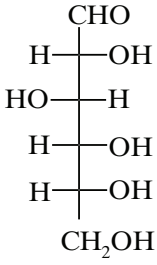
(d) 

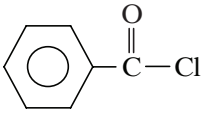
(e) 

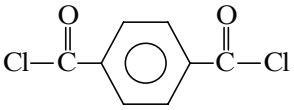
(f) 

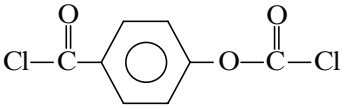
(g) 

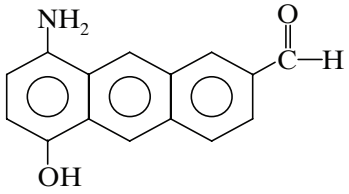
(h) 

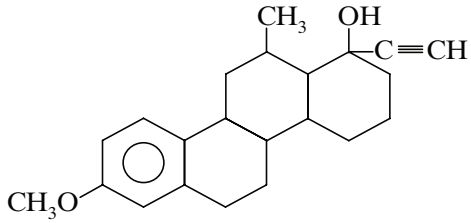
(i) 

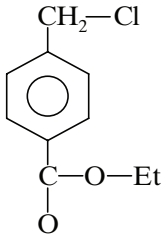
(j) 

(k) 

(l) 

(m) 

(n) 

(o) 

Answer

The number of moles of Grignard reagent consumed is as follows:
(a) 4 moles; **(b)** 2 moles; **(c)** 2 moles; **(d)** 3 moles; **(e)** 4 moles; **(f)** 5 moles; **(g)** 3 moles; **(h)** 4 moles; **(i)** 6 moles; **(j)** 2 moles; **(k)** 4 moles; **(l)** 5 moles; **(m)** 3 moles; **(n)** 2 moles; **(o)** 3 moles

11.9 | LITHIUM DIALKYLCUPRATES: THE COREY–POSNER, WHITESIDES–HOUSE SYNTHESIS

A highly versatile method for the synthesis of alkanes and other hydrocarbons from organic halides has been developed by E. J. Corey (Harvard University) and G. H. Posner (Johns Hopkins University) and by G. M. Whitesides (Harvard University) and H. O. House (Georgia Institute of Technology). Although it does not create a new functional group for use in further reactions, as does the Grignard reaction and others discussed in Section 9.7, the overall synthesis provides, for example, a way for coupling the alkyl groups of two alkyl halides to produce an alkane:

$$R{-}X + R'{-}X \xrightarrow[(-2X)]{\text{several steps}} R{-}R'$$

In order to accomplish this coupling, we must transform one alkyl halide into a lithium dialkylcuprate (R_2CuLi). This transformation requires two steps. First, the alkyl halide is treated with lithium metal in an ether solvent to convert the alkyl halide into an alkyllithium, RLi:

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$$R{-}X + 2Li \xrightarrow{\text{diethyl ether}} \underset{\textbf{Alkyllithium}}{RLi} + LiX$$

Then the alkyllithium is treated with cuprous iodide (CuI). This converts it to the lithium dialkylcuprate:

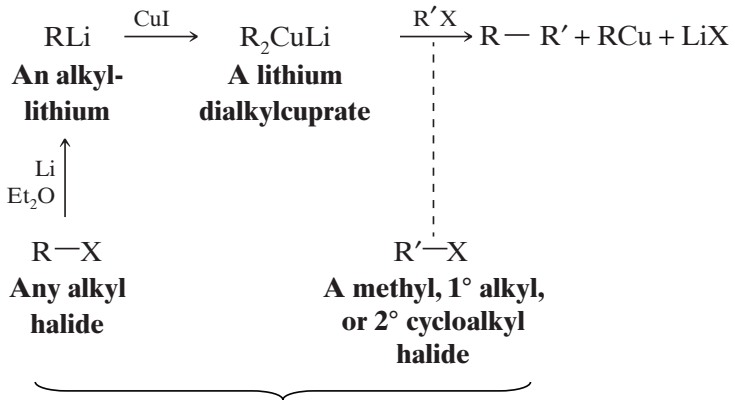
$$\underset{\textbf{Alkyllithium}}{2RLi} + CuI \longrightarrow \underset{\textbf{dialkylcuprate}}{R_2CuLi} + LiI$$

When the lithium dialkylcuprate is treated with the second alkyl halide (R′—X), coupling takes place between one alkyl group of the lithium dialkylcuprate and the alkyl group of the alkyl halide (R′—X):

$$\underset{\textbf{dialklcuprate}}{R_2CuLi} + \underset{\textbf{Alkyl halide}}{R'{-}X} \longrightarrow \underset{\textbf{Alkane}}{R{-}R'} + RCu + LiX$$

For the last step to give a good yield of the alkane, the alkyl halide R′—X must be a methyl halide, a primary alkyl halide, or a secondary cycloalkyl halide. The alkyl groups of the lithium dialkylcuprate may be methyl, 1°, 2°, or 3°. Moreover, the two alkyl groups being coupled need not be different.

The overall scheme for this alkane synthesis is shown here:



Consider as examples the synthesis of hexane from methyl iodide and pentyl iodide and the synthesis of nonane from butyl bromide and pentyl bromide:

$$CH_3I \xrightarrow[Et_2O]{Li} CH_3Li \xrightarrow{CuI} (CH_3)_2CuLi \xrightarrow{CH_3CH_2CH_2CH_2CH_2I} \underset{\textbf{Hexane (98\%)}}{CH_3{-}CH_2CH_2CH_2CH_2CH_3}$$

$$CH_3CH_2CH_2CH_2Br \xrightarrow[Et_2O]{Li} CH_3CH_2CH_2CH_2Li \xrightarrow{CuI}$$

$$(CH_3CH_2CH_2CH_2)_2CuLi \xrightarrow{CH_3CH_2CH_2CH_2CH_2Br} \underset{\textbf{Nonane (98\%)}}{CH_3CH_2CH_2CH_2{-}CH_2CH_2CH_2CH_2CH_3}$$

Lithium dialkylcuprates couple with other organic groups. Coupling reactions of lithium dimethylcuprate with two cycloalkyl halides are shown here:

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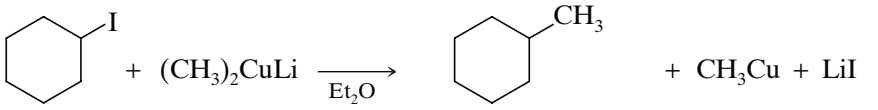
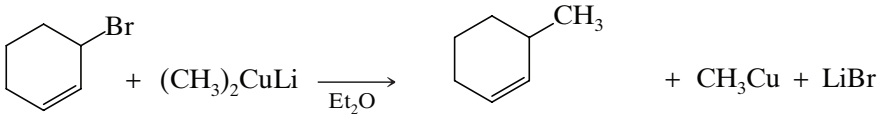
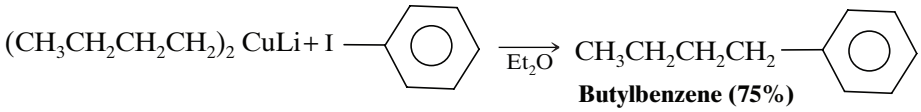


Methylcyclohexane (75%)



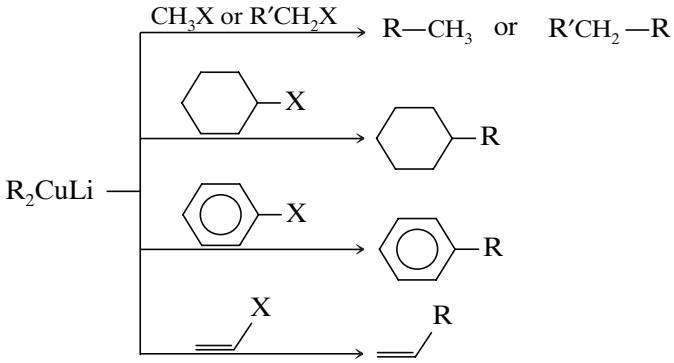
3-Methylcyclohexene (75%)

Lithium dialkylcuprates also couple with phenyl and vinyl halides. An example with a phenyl halide is the following synthesis of butylbenzene:



Butylbenzene (75%)

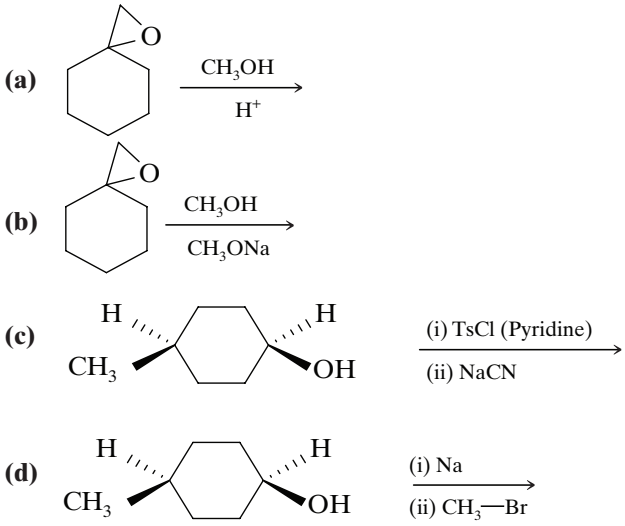
The following scheme summarizes the coupling reactions of lithium dialkylcuprates:



The mechanism of the Corey–Posner, Whitesides–House synthesis is beyond our scope.

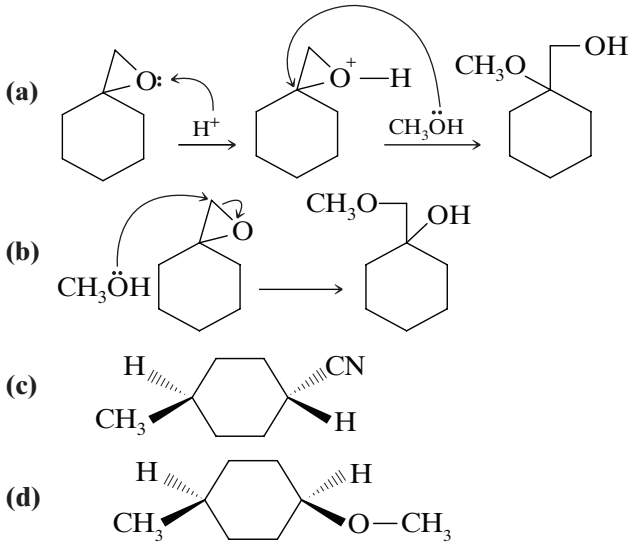
Solved Problem 11.14

Give the products of the following reactions



Answer

The products obtained from the above reactions are as follows:



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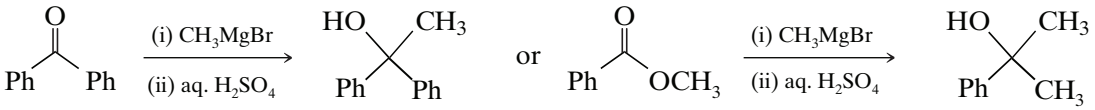
Solved Problem 11.15

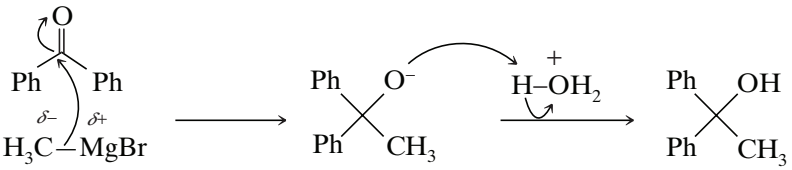
The following reactions involve the combination of a Grignard reagent of general formula RMgX with a carbonyl compound and an ester. This is to form carbon–carbon bond.



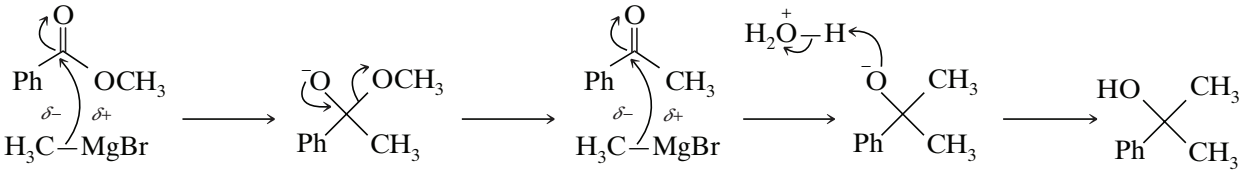
(a) Define "organometallic compound."
(b) How do organometallic reagents provide a source of nucleophilic carbon?
(c) Provide the mechanism for both the above-mentioned reactions.
(d) Although carbon and magnesium are both common elements in the human body, Grignard reactions do not occur in cells. Why is this so?

Answer

(a) An organometallic compound is a compound that has a carbon–metal bond.
(b) Carbon is more electronegative than any metal. The carbon–metal bond is therefore polar, having a $\delta-$ charge on the carbon end and a $\delta+$ charge on the metal end. This $\delta-$ charge on the carbon end represents a somewhat increased electron density, thus making the carbon end nucleophilic.
(c) Ketone addition mechanism:



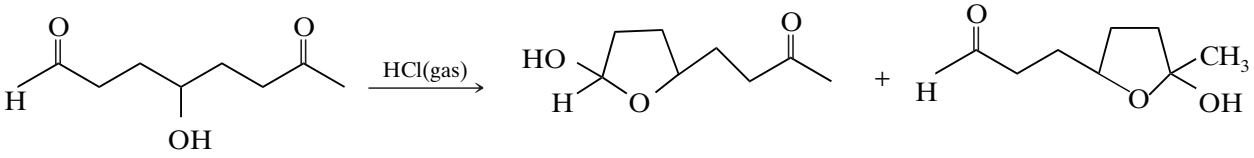
Ester substitution/addition mechanism:



Hydroxide (HO^-) and alkoxide (RO^-) ions are normally not considered to be the leaving groups. In this case, the negative charge is being transferred from the oxygen atom of the tetrahedral intermediate to the oxygen atom of the leaving group. These negative charges being of equal stability, the change does not require much energy. Thus, hydroxide and alkoxide can leave when expelled by the fragmentation of a negatively charged tetrahedral intermediate. An alternate explanation is that the negative charge is shared by two oxygen atoms in the transition state. This charge delocalization provides sufficient stabilization to lower the free energy of activation by a large amount so that this step can proceed at a reasonable rate. (d) Grignard reagents are strong bases, and hence would be rapidly protonated by the water present in the living cells. The formation of a Grignard reagent usually requires Mg metal, which is not found in living cells.

Solved Problem 11.16

Consider the following reaction



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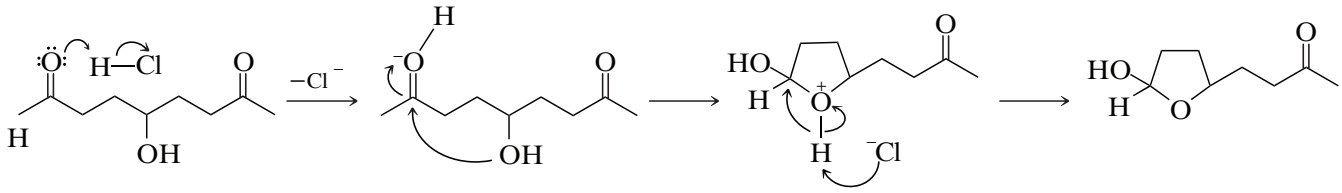
Write a complete and detailed curved arrow mechanism for the formation of the major product. Briefly explain the choice of the major product.

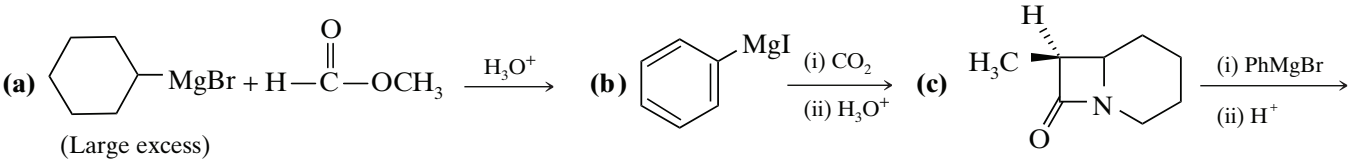
Answer



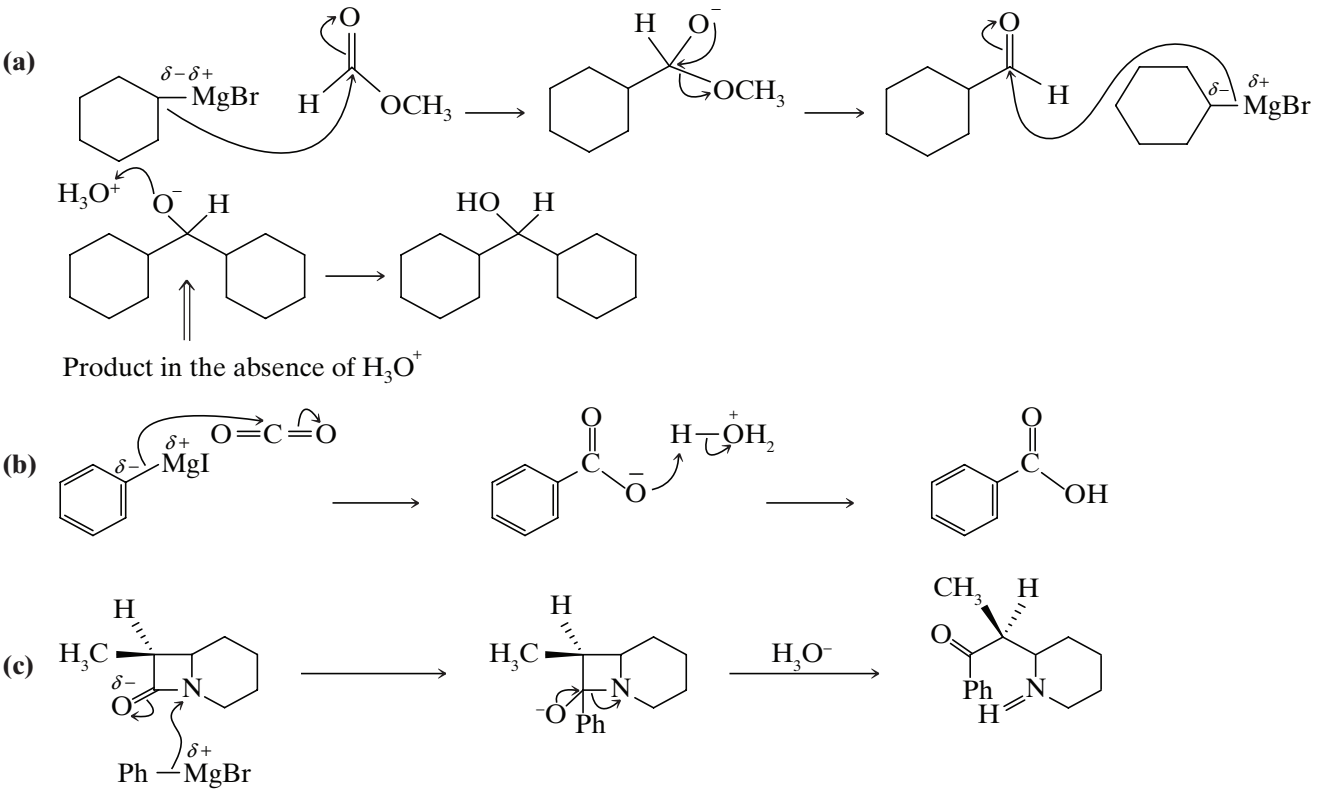
The aldehyde carbonyl is attacked preferrably for the following two reasons:
(a) An aldehyde carbonyl group has less steric hindrance to nucleophilic attack than the ketone carbonyl group.
(b) An aldehyde has a greater $\delta+$ charge on carbon of carbonyl than that of a ketone carbonyl carbon due to the electron donating effect of the ketone methyl group. The same reasoning applies to a protonated aldehyde carbonyl versus a protonated ketone carbonyl.

Solved Problem 11.17

Complete the following reactions providing mechanism of the formation of product.



Answer



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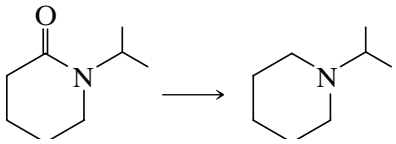
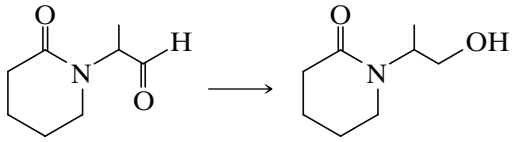
Solved Problem 11.18

Suggest the appropriate reagent(s) to carry out the following reactions.

(a)



(b)

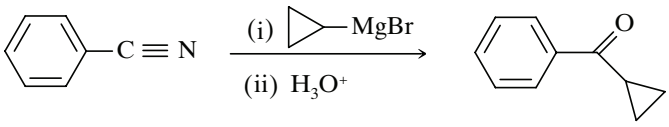


Answer

(a) $LiAlH_4$; **(b)** $NaBH_4$, CH_3OH. Note that $NaBH_4$ reduces ketones and aldehydes but not esters, amides or carboxylic acids.

Solved Problem 11.19

Nitriles undergo nucleophilic attack by Grignard reagents to afford ketones after a hydrolysis step with aqueous acid.

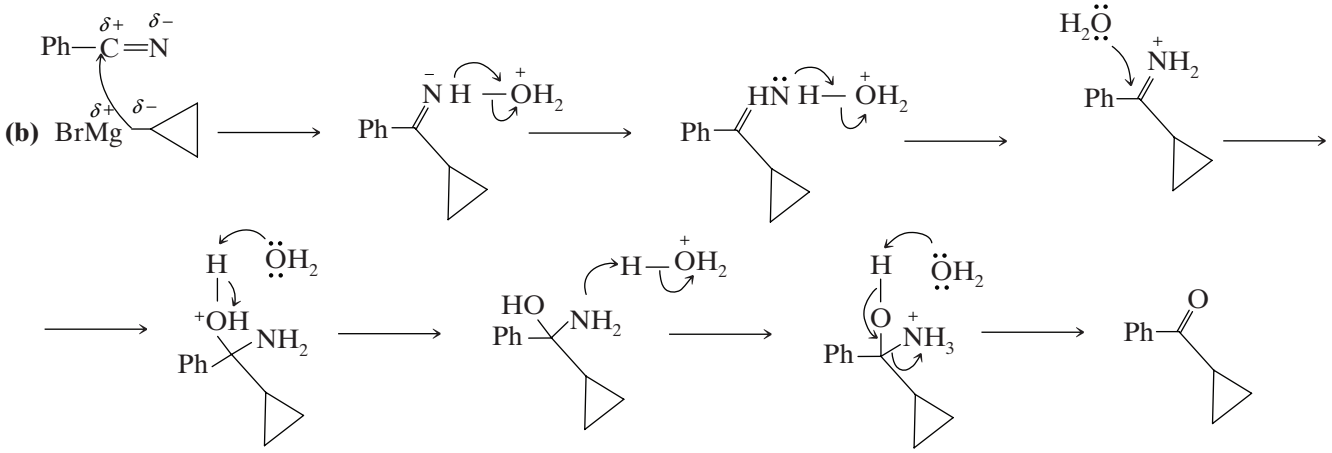


(a) Why is the nitrile group subject to nucleophilic attack?
(b) Draw a detailed curved arrow mechanism for this reaction.
(c) Nucleophilic addition of a Grignard reagent to the carbonyl group results in replacement of the C–O π bond by a C—C σ bond. A nitrile group has two C—N π bonds, yet there is replacement of only one π bond, not of two, even in the presence of a large excess of the Grignard reagent. Explain.

Answer

(a) The nitrile group is subject to nucleophilic attack because it has a polarized π bond. Nitrogen is more electronegative than carbon, so the carbon bears a $\delta+$ charge, much in the same way as in a carbonyl or imine group. A combination of this $\delta+$ charge and the nitrogen atom's ability to accept the π bond electrons allow the nitrile group to invite a nucleophile attack.

(b)



(c) Addition of the first molecule of cyclopropyl magnesium bromide to the nitrile, replacing the C–N π bond with a new C–C σ bond, affords a negatively charged nitrogen atom. Addition of the second molecule of Grignard reagent to replace the second C–N π bond would result in a nitrogen atom with a +2 charge. This is thermodynamically very expensive, so the second addition cannot occur. Addition of acid rapidly protonates any Grignard reagent present, so addition to the C=NH bond, formed during the hydrolysis step, also cannot occur.

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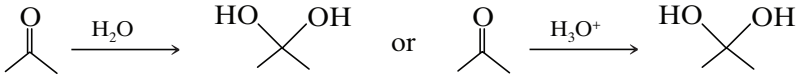
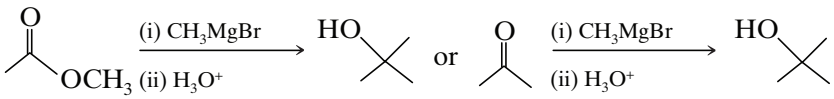
Solved Problem 11.20

Select the faster reaction of each of the following pairs, and briefly explain to support your choice.

(a) 

(b) 

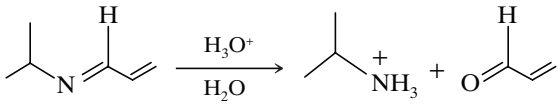
Answer

(a) The H_3O^+ reaction is faster. Protonation of the carbonyl oxygen makes this oxygen atom even more electron deficient. This results in a greater carbonyl carbon $\delta+$ for the protonated carbonyl than for a carbonyl that is not protonated. Greater $\delta+$ allows more rapid attack by a nucleophile (water).

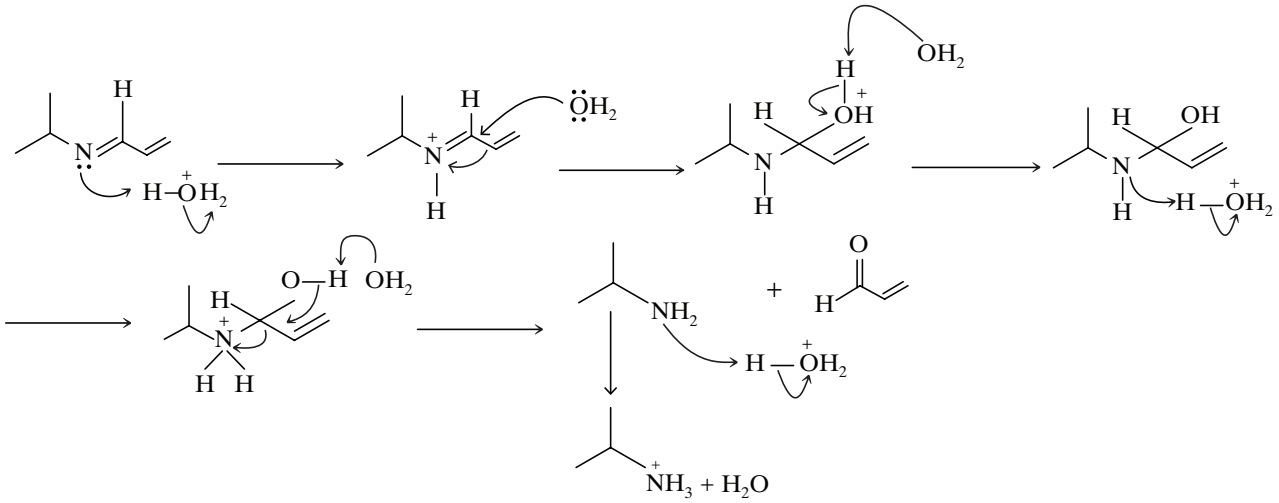
(b) Nucleophilic addition to an ester is slower than addition to a ketone because the carbonyl carbon of the ester is less electrophilic. The ester carbonyl is less electrophilic because it has a smaller $\delta+$, due to resonance with the lone pairs of the OCH_3 oxygen atom. In addition, the ester loses resonance when attacked, but the ketone does not. Thus, nucleophilic attack on the ester is further inhibited.

Solved Problem 11.21

Write a mechanism for the hydrolysis of the model imine shown below.



Answer



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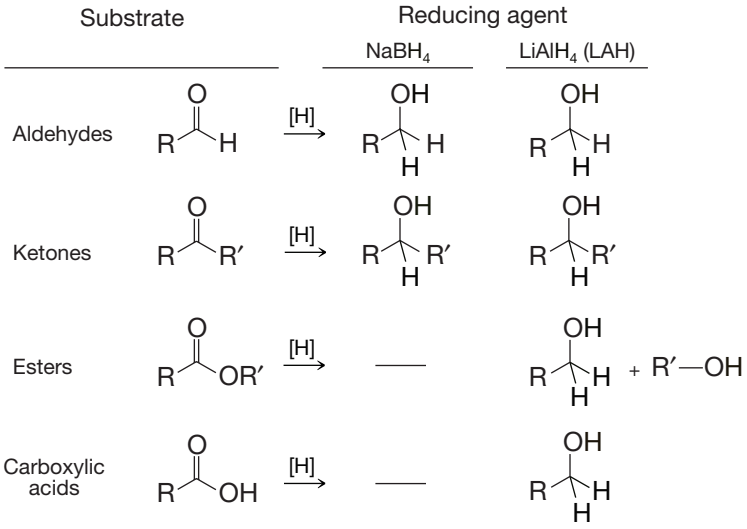
SUMMARY AND REVIEW TOOLS

Synthetic Connections of Alcohols and Carbonyl Compounds

1. Carbonyl Reduction Reactions

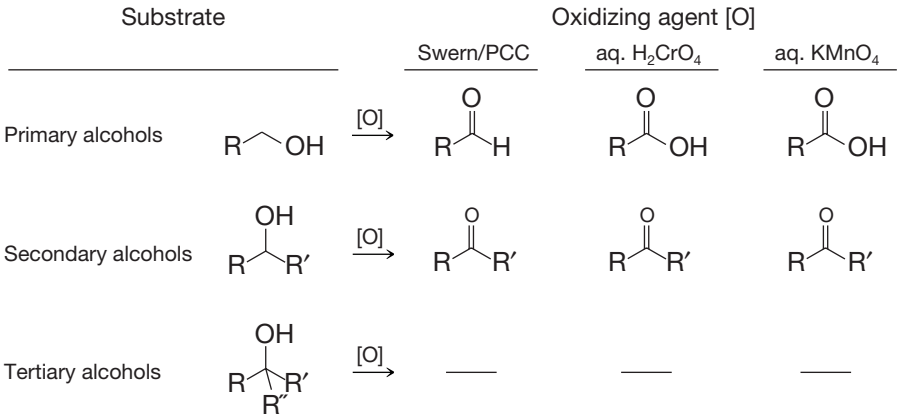
- Aldehydes to primary alcohols
- Ketones to secondary alcohols
- Esters to alcohols
- Carboxylic acids to primary alcohols



(Hydrogen atoms in blue are added during the reaction workup by water or aqueous acid.)

2. Alcohol Oxidation Reactions

- Primary alcohols to aldehydes
- Primary alcohols to carboxylic acids
- Secondary alcohols to ketones



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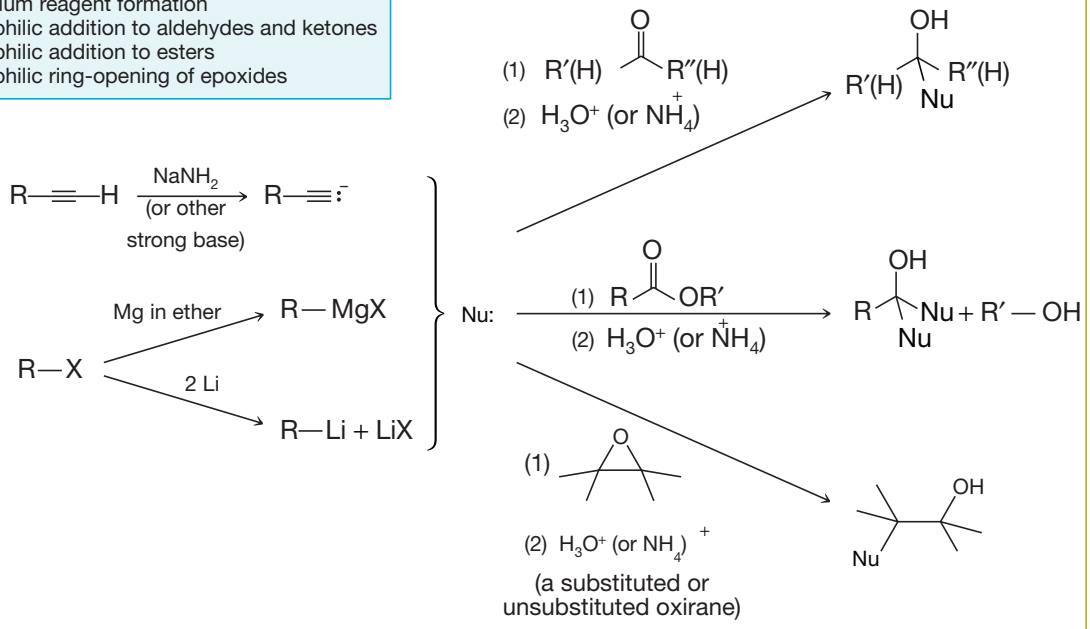
[SUMMARY AND REVIEW TOOLS]

Synthetic Connections of Alcohols and Carbonyl Compounds

3. Carbon-Carbon Bond Forming Reactions

- Alkynide anion formation
- Grignard reagent formation
- Alkyllithium reagent formation
- Nucleophilic addition to aldehydes and ketones
- Nucleophilic addition to esters
- Nucleophilic ring-opening of epoxides



Nu = alkynyl group, or alkyl group from Grignard or alkyllithium reagent

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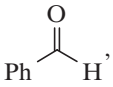
REVIEW PROBLEMS

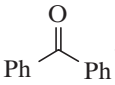
Reagents and Reactions

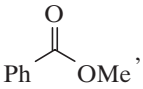
11.9 What products would you expect from the reaction of ethylmagnesium bromide (CH_3CH_2MgBr) with each of the following reagents?

(a) H_2O

(b) D_2O

(c) , then H_3O^+

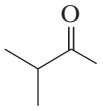
(d) , then NH_4Cl, H_2O

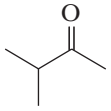
(e) , then NH_4Cl, H_2O

(f) , then NH_4Cl, H_2O

(g) H, then , then H_3O^+

11.10 What products would you expect from the reaction of propyllithium ($CH_3CH_2CH_2Li$) with each of the following reagents?

(a) H, then H_3O^+

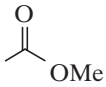
(b) , then NH_4Cl, H_2O

(c) 1-Pentyne, then , then NH_4Cl, H_2O

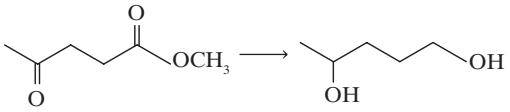
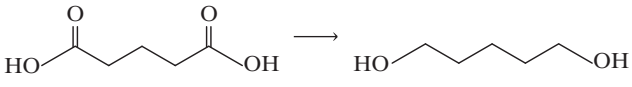
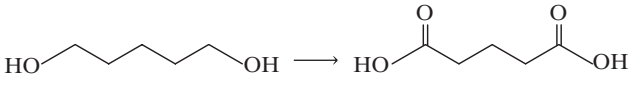
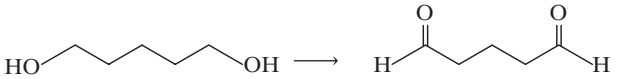
(d) Ethanol

(e) 

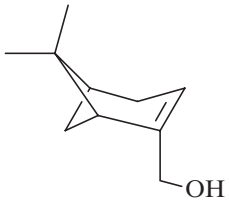
11.11 What product (or products) would be formed from the reaction of 1-bromo-2-methylpropane (isobutyl bromide) under each of the following conditions?

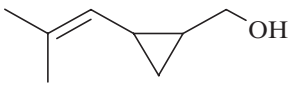
(a) HO^-, H_2O
(b) NC^-, ethanol
(c) *t*-BuOK, *t*-BuOH
(d) MeONa, MeOH
(e) (1) Li, Et_2O; (2) ; (3) NH_4Cl, H_2O
(f) Mg, Et_2O, then , then H_3O^+
(g) (1) Mg, Et_2O; (2) ; (3) NH_4Cl, H_2O
(h) (1) Mg, Et_2O; (2) ; (3) H_3O^+
(i) (1) Mg, Et_2O; (2) ; (3) NH_4Cl, H_2O
(j) Li, Et_2O; (2) MeOH
(k) Li, Et_2O; (2) H—≡—H

11.12 Which oxidizing or reducing agent would you use to carry out the following transformations?

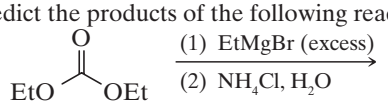
(a) 
(b) 
(c) 
(d) 
(e) 

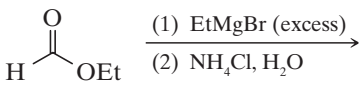
11.13 Write reaction conditions and the product from Swern oxidation of the following compounds.

(a) 
Myrtenol

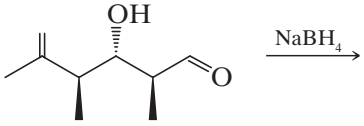
(b) 
Chrysanthemyl alcohol

11.14 Predict the products of the following reactions.

(a) 

(b) 

11.15 Predict the organic product from each of the following reduction reactions.

(a) 

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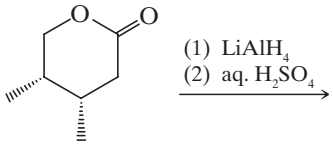
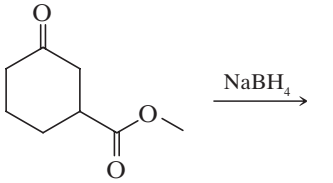
(b)

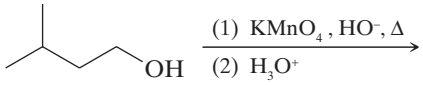


(c)

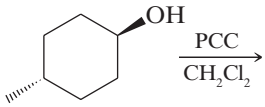


11.16 Predict the organic product from each of the following oxidation reactions.

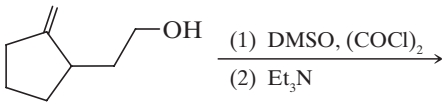
(a)



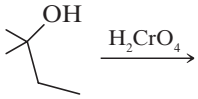
(b)



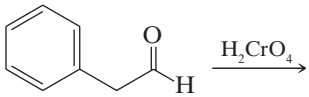
(c)



(d)

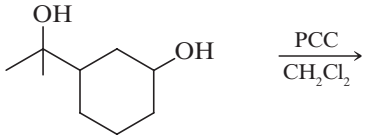


(e)

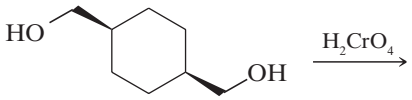


11.17 Predict the organic product from each of the following oxidation and reduction reactions.

(a)



(b)



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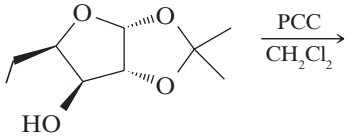

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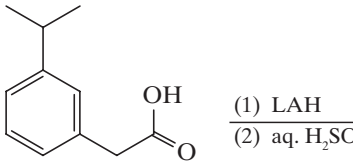

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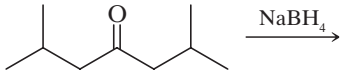
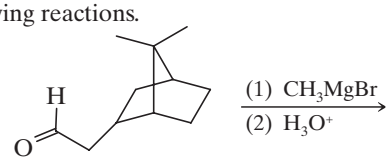


11.18 Predict the major organic product from each of the following reactions.

(a)



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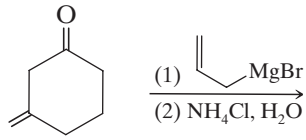

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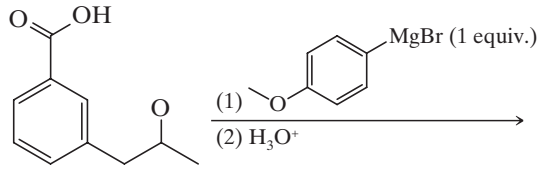
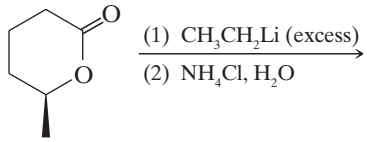
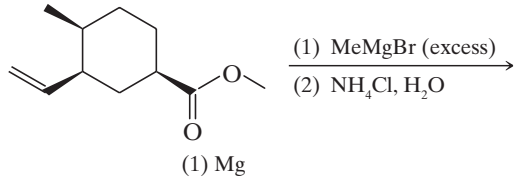


(d)



11.19 Predict the major organic product from each of the following reaction sequences.

(a)



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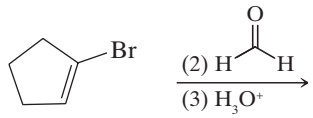

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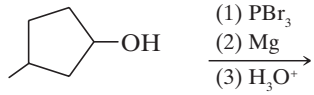

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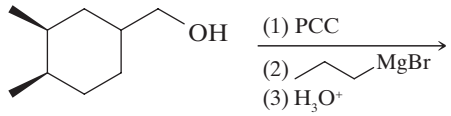

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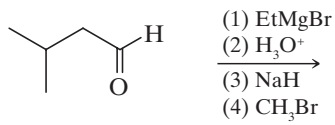
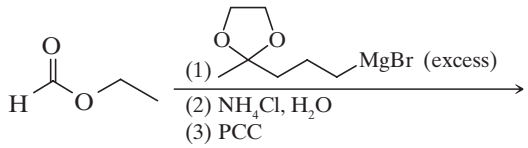
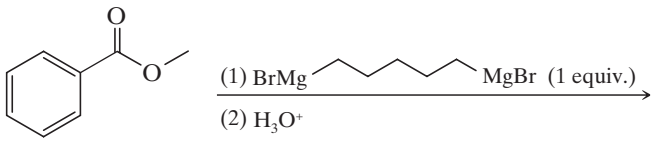


(f)



11.20 Predict the product of the following reaction.



Mechanisms

11.21 Synthesize each of the following compounds from cyclohexanone. Use D to specify deuterium in any appropriate reagent or solvent where it would take the place of hydrogen.

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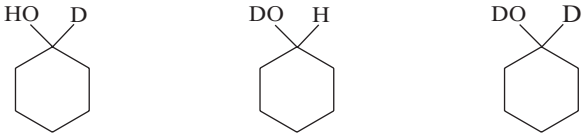
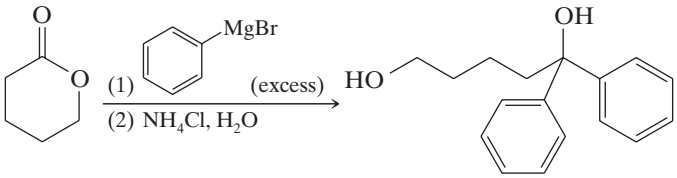
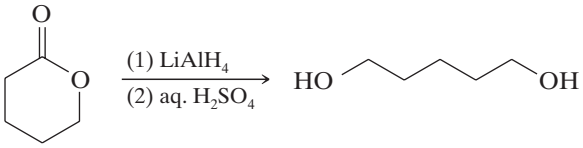


11.22 Write a mechanism for the following reaction. Include formal charges and curved arrows to show the movement of electrons in all steps.



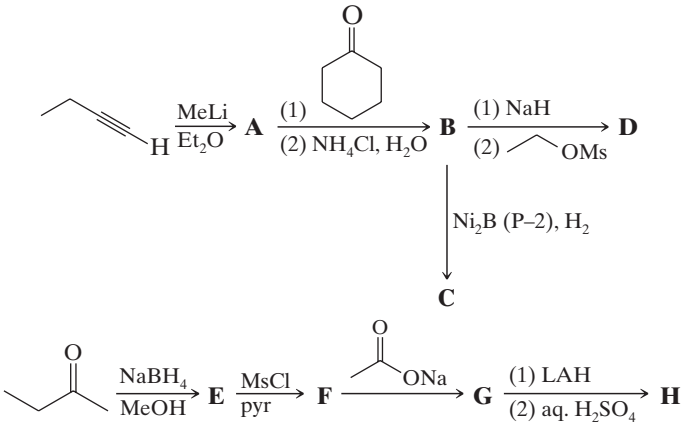
11.23 Write a mechanism for the following reaction. You may use H^- to represent hydride ions from $LiAlH_4$ in your mechanism. Include formal charges and curved arrows to show the movement of electrons in all steps.



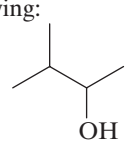
11.24 Although oxirane (oxacyclopropane) and oxetane (oxacyclobutane) react with Grignard and organolithium reagents to form alcohols, tetrahydrofuran (oxacyclopentane) is so unreactive that it can be used as the solvent in which these organometallic compounds are prepared. Explain the difference in reactivity of these oxygen heterocycles.

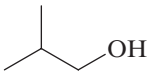
Synthesis

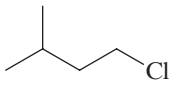
11.25 What organic products **A–H** would you expect from each of the following reactions?

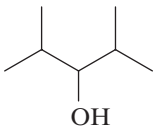


11.26 Outline all steps in a synthesis that would transform 2-propanol (isopropyl alcohol) into each of the following:

(a) 

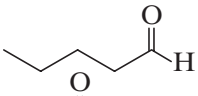
(b) 

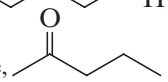
(c) 

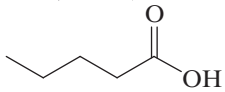
(d) 

(e) 

11.27 Show how 1-pentanol could be transformed into each of the following compounds. (You may use any needed inorganic reagents and you need not show the synthesis of a particular compound more than once.)

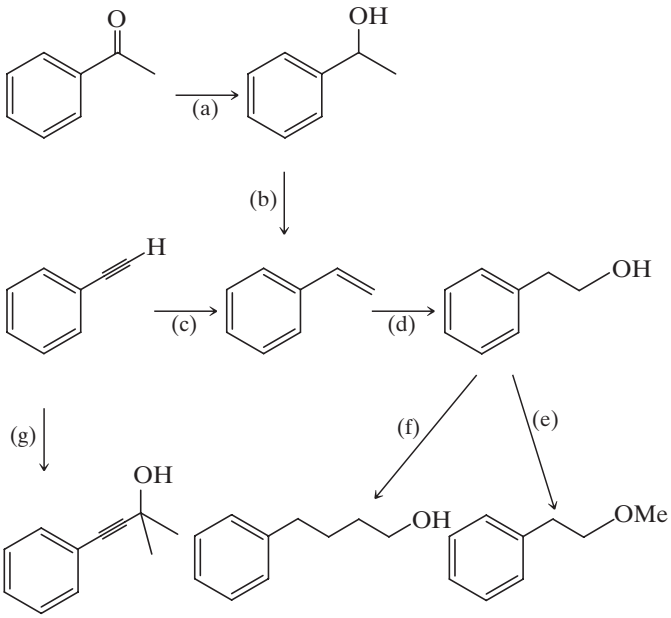
(a) 1-Bromopentane
(b) 1-Pentene
(c) 2-Pentanol
(d) Pentane
(e) 2-Bromopentane
(f) 1-Hexanol
(g) 1-Heptanol
(h) Pentanal, 

(i) 2-Pentanone, 

(j) Pentanoic acid, 

(k) Dipentyl ether (two ways)
(l) 1-Pentyne
(m) 2-Bromo-1-pentene
(n) Pentyllithium
(o) 4-Methyl-4-nonanol

11.28 Provide the reagents needed to accomplish transformations **(a)–(g)**. More than one step may be necessary.



11.29 Assuming that you have available only alcohols or esters containing no more than four carbon atoms, show how you might synthesize each of the following compounds.

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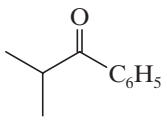
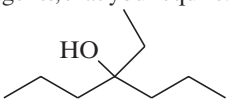
Begin by writing a retrosynthetic analysis for each. You must use a Grignard reagent at one step in the synthesis. If needed, you may use oxirane and you may use bromobenzene, but you must show the synthesis of any other required organic compounds. Assume you have available any solvents and any inorganic compounds, including oxidizing and reducing agents, that you require.

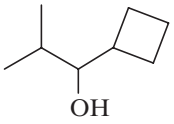
(a)



(b)



(c)



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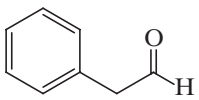

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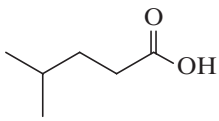

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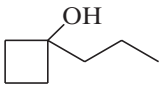

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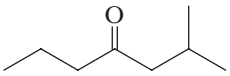

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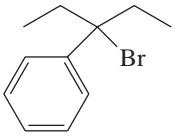
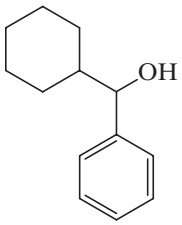
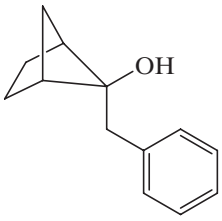


11.30 For each of the following alcohols, write a retrosynthetic analysis and synthesis that involves an appropriate organometallic reagent (either a Grignard or alkyllithium reagent).

(a)



(b)



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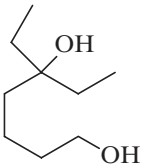
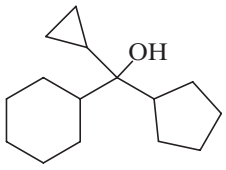
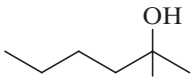


11.31 Synthesize each of the following compounds starting from primary or secondary alcohols containing seven carbons or less and, if appropriate, bromobenzene.

(a)



(b)



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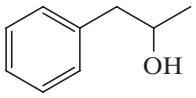
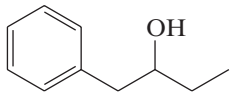
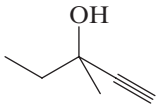


11.32 The alcohol shown here is used in making perfumes. Write a retrosynthetic analysis and then synthetic reactions that could be used to prepare this alcohol from bromobenzene and 1-butene.

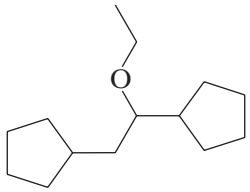


11.33 Write a retrosynthetic analysis and then synthetic reactions that could be used to prepare racemic Meparfynol, a mild hypnotic (sleep-inducing compound), starting with compounds of four carbon atoms or fewer.



Meparfynol

11.34 Synthesize the following compound using cyclopentane and ethyne (acetylene) as the sole source of carbon atoms.



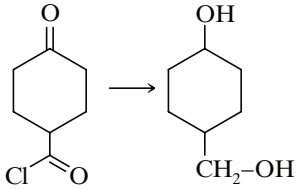
ADDITIONAL OBJECTIVE QUESTIONS

Single Correct Choice Type

1. Which of the following alcohols forms a ketone when oxidized?

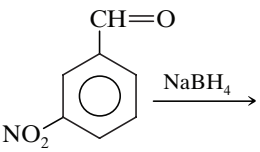
(a) 1-propanol **(b)** Methanol
(c) 2-methyl-2-propanol **(d)** 2-propanol

2. Reagent used for the following conversion is

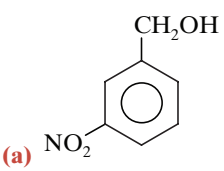


(a) $LiAlH_4$ **(b)** $NaBH_4$
(c) DIBAL – H **(d)** Both (a) and (b)

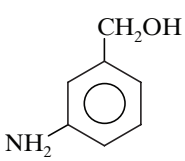
3. What will be the final product?



(a)



(b)



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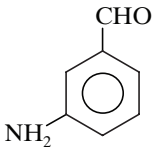
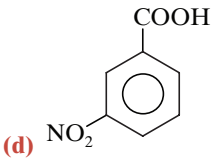
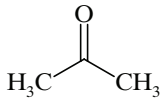
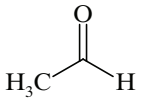
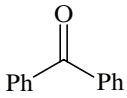
(c) 

(d) 

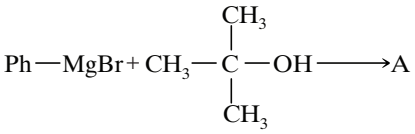
4. The order of reactivity of phenyl magnesium bromide with the following compounds is

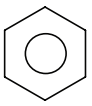
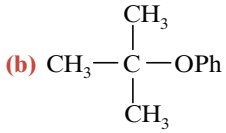
(I)  (II)  (III) 

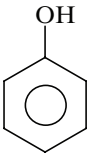
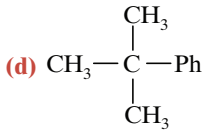
(a) II > III > I (b) I > III > II
(c) II > I > III (d) All react with the same rate

5. When $CH_2{=}CH{-}COOH$ is reduced with $LiAlH_4$, the compound obtained will be
(a) $CH_3{-}CH_2{-}COOH$ (b) $CH_2{=}CH{-}CH_2OH$
(c) $CH_3{-}CH_2{-}CH_2OH$ (d) $CH_3{-}CH_2{-}CHO$

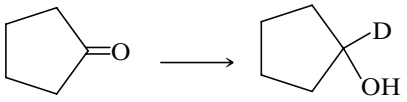
6. For the following reaction, A is



(a)  (b) 

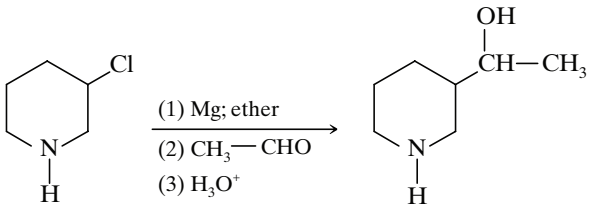
(c)  (d) 

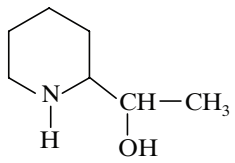
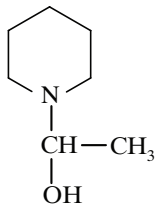
7. What reagents would be required to perform the following reaction?

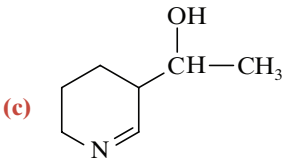
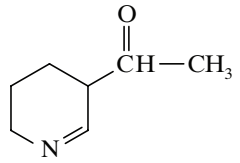


(a) $NaBH_4, CH_3OD$ (b) $NaBH_4, CH_3OH$
(c) $NaBD_4, CH_3OD$ (d) $NaBD_4, CH_3OH$

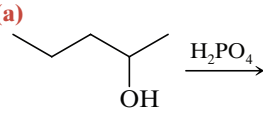
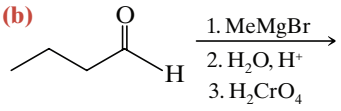
8. The given product cannot be obtained in the following reaction. Identify the correct product obtained.

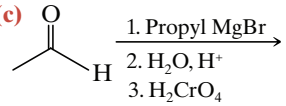


(a)  (b) 

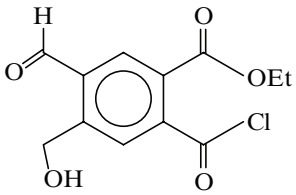
(c)  (d) 

9. Which method would produce 2-pentanone as the major product?

(a)  (b) 

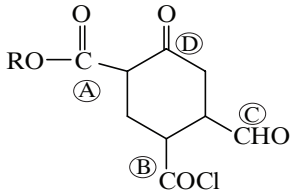
(c)  (d) All

10. How many moles of RMgX will get consumed in the given compound?



(a) 6 (b) 5
(c) 4 (d) 7

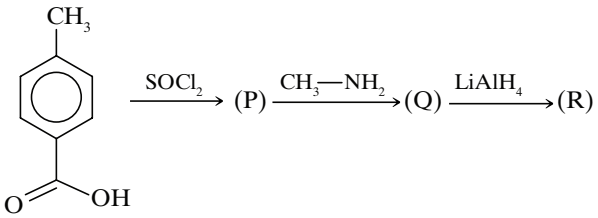
11. Find out the reactivity order of the carbonyl groups with $LiAlH_4$

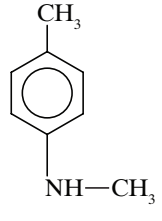
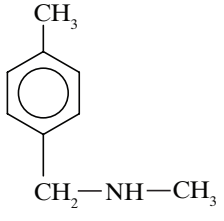


(a) A > B > C > D (b) B > C > D > A
(c) D > C > B > A (d) B > D > C > A

12. How many isomers (excluding stereoisomer) of $C_4H_{10}O$ react with CH_3MgBr to evolve CH_4 gas?
(a) 2 (b) 4 (c) 6 (d) 8

13. Final product, (R) of the following reaction sequence:



(a)  (b) 

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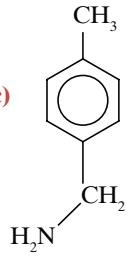
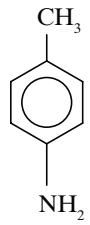
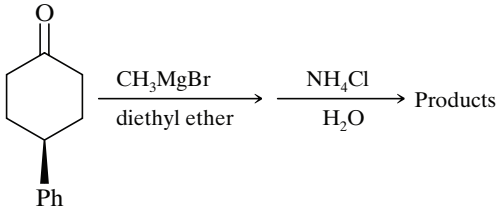
(c) 

(d) 

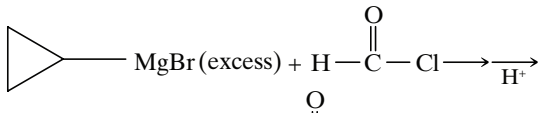
Multiple Correct Choice Type

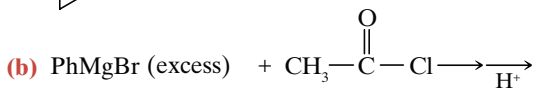
1. Comment on optical activity of the products of the following reaction:

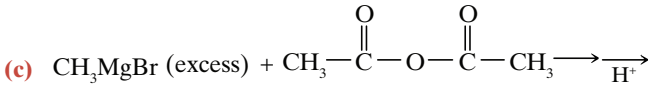


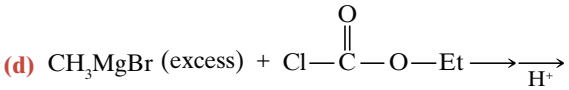
(a) They form a racemic mixture.
(b) They are diastereomers.
(c) They are meso forms.
(d) They are optically inactive due to absence of chiral center.

2. In which of the following reactions, tertiary alcohol will be obtained as a product?

(a) 

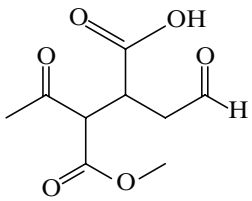
(b) 

(c) 

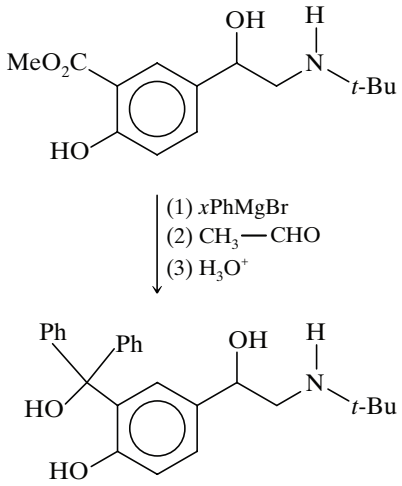
(d) 

Integer Type

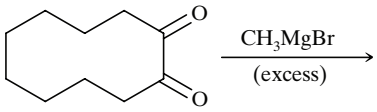
1. In the following compound how many functional groups are reduced by LAH (Lithium alluminium hydride) and SBH (sodium borohydride) respectively.



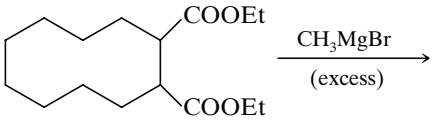
2. The number of equivalents of Grignard reagent (x) used in following reaction is _____.



3. The number of stereoisomers of the product possible in the following reaction is _____.

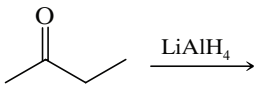
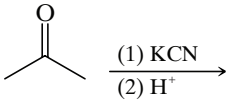
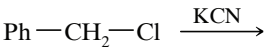
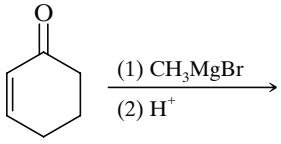


4. The number of stereoisomers of the product possible in the following reaction is _____.



Matrix Match Type

1.

Column I	Column II
(a) 	**(p)** Racemic mixture
(b) 	**(q)** Diastereomers
(c) 	**(r)** Nucleophilic addition reaction
(d) 	**(s)** Nucleophilic substitutions reaction

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ANSWER KEY

Single Correct Choice Type

1. (d) **2.** (d) **3.** (a) **4.** (c)
5. (b) **6.** (a) **7.** (d) **8.** (b)
9. (d) **10.** (a) **11.** (b) **12.** (b)
13. (b)

Multiple Correct Choice Type

1. (b), (d) **2.** (b), (c), (d)

Integer Type

1. (4), (2) **2.** (2) **3.** (3) **4.** (3)

Matrix Match Type

1. a→(p, r); b→(r); c→(s); d→(p, r)

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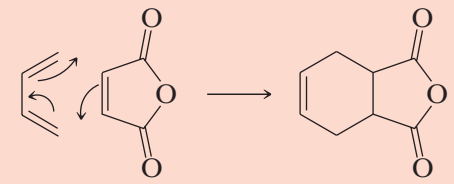
12

Conjugated Unsaturated Systems



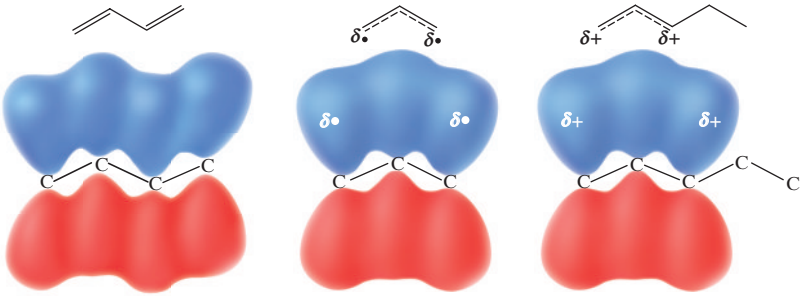
Diene **Dienophile** **Adduct**

Contents

12.1 | Introduction
12.2 | Alkadienes and Polyunsaturated Hydrocarbons
12.3 | 1,3-Butadiene: Electron Delocalization
12.4 | Electrophilic Attack on Conjugated Dienes: 1,4-Addition
12.5 | The Diels–Alder Reaction: A 1,4-Cycloaddition Reaction of Dienes

12.1 | INTRODUCTION

At its essence, a **conjugated system** involves at least one atom with a *p* orbital adjacent to at least one π bond. The adjacent atom with the *p* orbital can be part of another π bond, as in 1,3-butadiene, or a radical, cationic, or anionic reaction intermediate. If an example derives specifically from a propenyl group, the common name for this group is **allyl**. In general when we are considering a radical, cation, or anion that is adjacent to one or more π bonds in a molecule other than propene, the adjacent position is called **allylic**. Below we show the formula for butadiene, resonance hybrids for the allyl radical and an **allylic carbocation**, and molecular orbital representations for each one.



1,3-butadiene (a conjugated diene) **The allyl radical** **An allylic carbocation**

Radical substitution at an allylic position, as we saw in Chapter 9, is especially favorable pre*cis*ely because the intermediate radical is part of a conjugated system.

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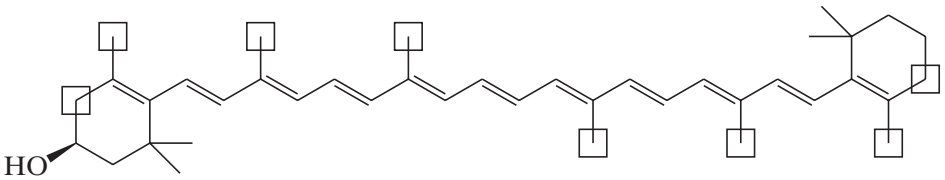
Solved Problem 12.1

Identify all of the positions bearing allylic hydrogen atoms in cryptoxanthin (a natural pigment).

Answer

Allylic hydrogen atoms in cryptoxanthin are found on the sp^3-hybridized carbons adjacent to π bonds. These positions are labeled by boxes in the formula below.

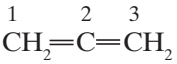


Cryptoxanthin (with positions bearing allylic hydrogen atoms shown in boxes)

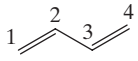
12.2 | ALKADIENES AND POLYUNSATURATED HYDROCARBONS

Many hydrocarbons are known that contain more than one double or triple bond. A hydrocarbon that contains two double bonds is called an **alkadiene**; one that contains three double bonds is called an **alkatriene**, and so on. Colloquially, these compounds are often referred to simply as dienes or trienes. A hydrocarbon with two triple bonds is called an **alkadiyne**, and a hydrocarbon with a double and triple bond is called an **alkenyne**.

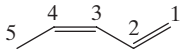
The following examples of polyunsaturated hydrocarbons illustrate how specific compounds are named. Recall from IUPAC rules (Sections 5.5 and 5.6) that the numerical locants for double and triple bonds can be placed at the beginning of the name or immediately preceding the respective suffix. We provide examples of both styles.



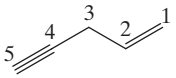
1,2-Propadiene
(allene, or propa-1,2-diene)



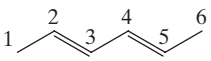
1,3-Butadiene
(buta-1,3-diene)



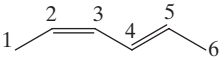
(3*Z*)-Penta-1,3-diene
(*cis*-penta-1,3-diene)



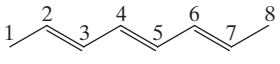
Pent-1-en-4-yne



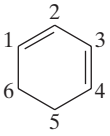
(2*E*,4*E*)-2,4-Hexadiene
(*trans,trans*-2,4-hexadiene)



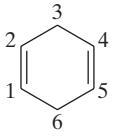
(2*Z*,4*E*)-Hexa-2,4-diene
(*cis,trans*-hexa-2,4-diene)



(2*E*,4*E*,6*E*)-Octa-2,4,6-triene
(*trans,trans,trans*-octa-2,4,6-triene)



1,3-Cyclohexadiene



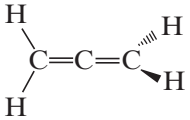
1,4-Cyclohexadiene

The multiple bonds of polyunsaturated compounds are classified as being **cumulated, conjugated**, or **isolated**.

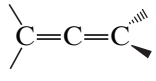
- The double bonds of a 1,2-diene (such as 1,2-propadiene, also called allene) are said to be **cumulated** because one carbon (the central carbon) participates in two double bonds.

Hydrocarbons whose molecules have cumulated double bonds are called **cumulenes**. The name **allene** (Section 4.18) is also used as a class name for molecules with two cumulated double bonds:

Cumulated double bonds



Allene



A cumulated diene

An example of a conjugated diene is 1,3-butadiene.

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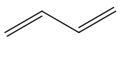
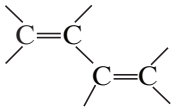
- In **conjugated** polyenes the double and single bonds *alternate* along the chain:

Conjugated double bonds



1,3-Butadiene



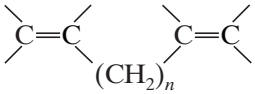
A conjugated diene

(2*E*,4*E*,6*E*)-Octa-2,4,6-triene is an example of a conjugated alkatriene.

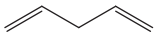
- If one or more saturated carbon atoms intervene between the double bonds of an alkadiene, the double bonds are said to be **isolated**.

An example of an isolated diene is 1,4-pentadiene:

Isolated double bonds



An isolated diene ($n \neq 0$)



1,4-Pentadiene

Practice Problem 12.1

(a) Which other compounds in Section 12.2 are conjugated dienes?
(b) Which other compounds are isolated dienes?
(c) Which compound is an isolated enyne?

In Chapter 4 we saw that appropriately substituted cumulated dienes (allenes) give rise to chiral molecules. Cumulated dienes have had some commercial importance, and cumulated double bonds are occasionally found in naturally occurring molecules. In general, cumulated dienes are less stable than isolated dienes.

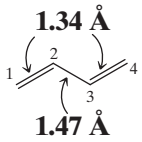
The double bonds of isolated dienes behave just as their name suggests—as isolated "enes." They undergo all of the reactions of alkenes, and, except for the fact that they are capable of reacting twice, their behavior is not unusual. Conjugated dienes are far more interesting because we find that their double bonds interact with each other. This interaction leads to unexpected properties and reactions. We shall therefore consider the chemistry of conjugated dienes in detail.

12.3 | 1,3-BUTADIENE: ELECTRON DELOCALIZATION

12.3A Bond Lengths of 1,3-Butadiene

The carbon–carbon bond lengths of 1,3-butadiene have been determined and are shown here:

Double bonds are shorter than single bonds.



The C1—C2 bond and the C3—C4 bond are (within experimental error) the same length as the carbon–carbon double bond of ethene. The central bond of 1,3-butadiene (1.47 Å), however, is considerably shorter than the single bond of ethane (1.54 Å).

This should not be surprising. All of the carbon atoms of 1,3-butadiene are sp^2 hybridized and, as a result, the central bond of butadiene results from overlapping sp^2 orbitals. And, as we know, a sigma bond that is sp^3–sp^3 is *longer*. There is, in fact, a steady decrease in bond length of carbon–carbon single bonds as the hybridization state of the bonded atoms changes from sp^3 to sp (Table 12.1).

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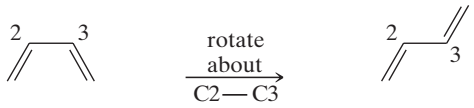
Table 12.1 Carbon–Carbon Single-Bond Lengths and Hybridization State

Compound	Hybridization State	Bond Length (Å)
$H_3C—CH_3$	sp^3–sp^3	1.54
$CH_2{=}CH—CH_3$	sp^2–sp^3	1.50
$CH_2{=}CH—CH{=}CH_2$	sp^2–sp^2	1.47
$HC{\equiv}C—CH_3$	sp–sp^3	1.46
$HC{\equiv}C—CH{=}CH_2$	sp–sp^2	1.43
$HC{\equiv}C—C{\equiv}CH$	sp–sp	1.37

12.3B Conformations of 1,3-Butadiene

There are two possible planar conformations of 1,3-butadiene: the s-*cis* and the s-*trans* conformations.



s-*cis* Conformation of 1,3-butadiene — **s-*trans* Conformation of 1,3-butadiene**

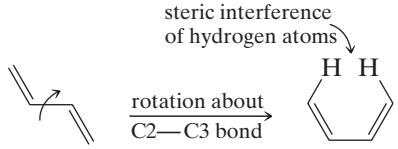
These are not true *cis* and *trans* forms since the s-*cis* and s-*trans* conformations of 1,3-butadiene can be interconverted through rotation about the single bond (hence the prefix s). The s-*trans* conformation is the predominant one at room temperature. We shall see that the s-*cis* conformation of 1,3-butadiene and other 1,3-conjugated alkenes is necessary for the Diels–Alder reaction (Section 12.5).

Solved Problem 12.2

Provide an explanation for the fact that many more molecules are in the s-*trans* conformation of 1,3-butadiene at equilibrium.

Answer

The s-*cis* conformation of 1,3-butadiene is less stable, and therefore less populated, than the s-*trans* conformer because it has steric interference between the hydrogen atoms at carbons 1 and 4. Interference of this kind does not exist in the s-*trans* conformation, and therefore, the s-*trans* conformation is more stable and more populated at equilibrium.



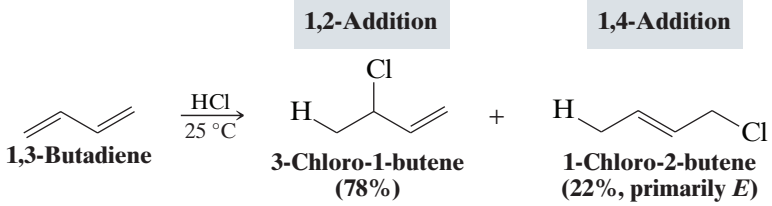
s-*trans* Conformation is more stable — **s-*cis* Conformation is less stable**

12.4 | ELECTROPHILIC ATTACK ON CONJUGATED DIENES: 1,4-ADDITION

Not only are conjugated dienes somewhat more stable than nonconjugated dienes, they also display special behavior when they react with electrophilic reagents.

- Conjugated dienes undergo both 1,2- and 1,4-addition through an allylic intermediate that is common to both.

For example, 1,3-butadiene reacts with one molar equivalent of hydrogen chloride to produce two products, 3-chloro-1-butene and 1-chloro-2-butene:



1,3-Butadiene — **3-Chloro-1-butene (78%)** + **1-Chloro-2-butene (22%, primarily *E*)**

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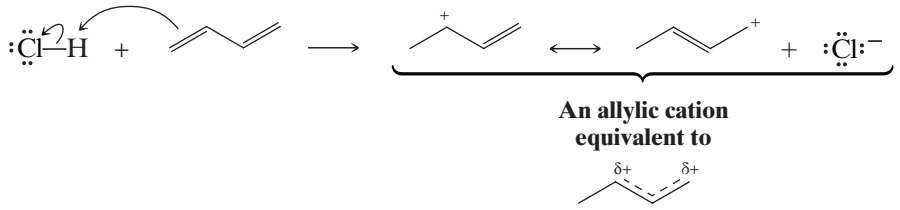
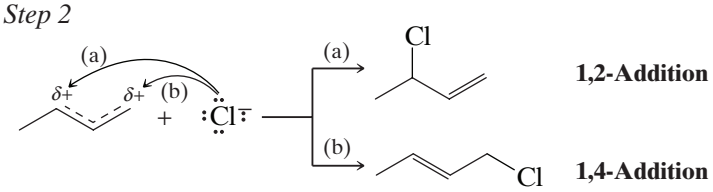
If only the first product (3-chloro-1-butene) were formed, we would not be particularly surprised. We would conclude that hydrogen chloride had added to one double bond of 1,3-butadiene in the usual way. It is the second product, 1-chloro-2-butene, that is initially surprising. Its double bond is between the central atoms, and the elements of hydrogen chloride have added to the C1 and C4 atoms.

To understand how both 1,2- and 1,4-addition products result from reaction of 1,3-butadiene with HCl, consider the following mechanism.

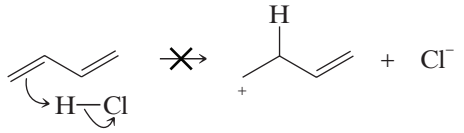
Step 1



Step 2



In step 1 a proton adds to one of the terminal carbon atoms of 1,3-butadiene to form, as usual, the more stable carbocation, in this case a resonance-stabilized allylic cation. Addition to one of the inner carbon atoms would have produced a much less stable primary cation, one that could not be stabilized by resonance:



Addition of the electrophile in this fashion does not lead to an allylic (resonance-stabilized) carbocation.

In step 2 a chloride ion forms a bond to one of the carbon atoms of the allylic cation that bears a partial positive charge. Reaction at one carbon atom results in the 1,2-addition product; reaction at the other gives the 1,4-addition product.

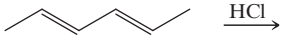
Note that the designations 1,2 and 1,4 only coincidentally relate to the IUPAC numbering of carbon atoms in this example.

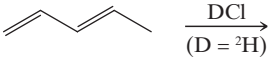
- Chemists typically use 1,2 and 1,4 to refer to modes of addition to any conjugated diene system, regardless of where the conjugated double bonds are in the overall molecule.

Thus, addition reactions of 2,4-hexadiene would still involve references to 1,2 and 1,4 modes of addition.

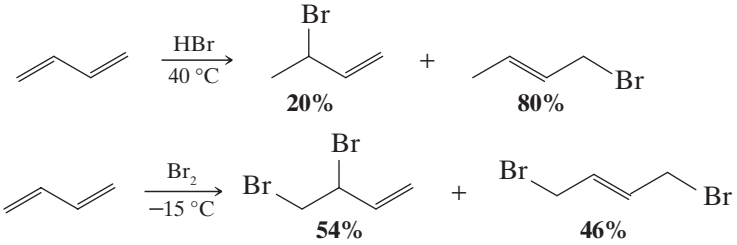
Practice Problem 12.2

Predict the products of the following reactions.

(a) 

(b) 

1,3-Butadiene shows 1,4-addition reactions with electrophilic reagents other than hydrogen chloride. Two examples are shown here, the addition of hydrogen bromide (in the absence of peroxides) and the addition of bromine:



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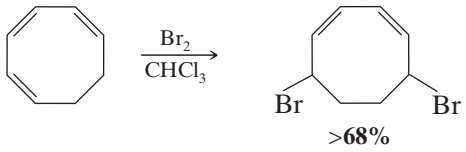
Reactions of this type are quite general with other conjugated dienes. Conjugated trienes often show 1,6-addition. An example is the 1,6-addition of bromine to 1,3,5-cyclooctatriene:



12.4A Kinetic Control versus Thermodynamic Control of a Chemical Reaction

The addition of hydrogen bromide to 1,3-butadiene allows the illustration of another important aspect of reactivity—the way temperature affects product distribution in a reaction that can take multiple paths. In general:

- The favored products in a reaction at *lower temperature* are those formed by the pathway having the smallest energy of activation barrier. In this case the reaction is said to be under **kinetic (or rate) control**, and the predominant products are called the **kinetic products**.
- The favored products at *higher temperature* in a *reversible* reaction are those that are most stable. In this case the reaction is said to be under **thermodynamic (or equilibrium) control**, and the predominant products are called the **thermodynamic (or equilibrium) products**.

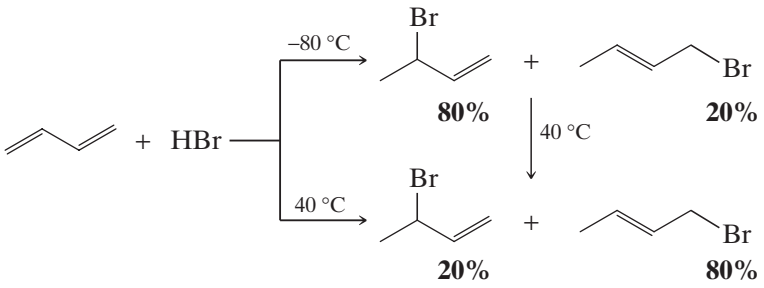
Let's consider specific reaction conditions for the ionic addition of hydrogen bromide to 1,3-butadiene.

Case 1. When 1,3-butadiene and hydrogen bromide react at low temperature (–80 °C), the major product is formed by 1,2-addition. We obtain 80% of the 1,2-product and 20% of the 1,4-product.

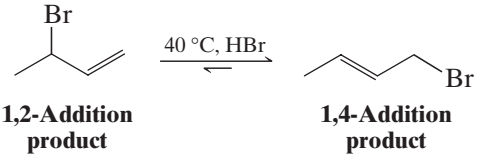
Case 2. When 1,3-butadiene and hydrogen bromide react at high temperature (40 °C), the major product is formed by 1,4-addition. We obtain about 20% of the 1,2-product and about 80% of the 1,4-product.

Case 3. When the product mixture from the low temperature reaction is warmed to the higher temperature, the product distribution becomes the same as when the reaction was carried out at high temperature—that is, the 1,4-product predominates.

We summarize these scenarios here:



Furthermore, when a pure sample of 3-bromo-1-butene (the predominant product at low temperature) is subjected to the high temperature reaction conditions, an equilibrium mixture results in which the 1,4-addition product predominates.



Because this equilibrium favors the 1,4-addition product, *that product must be more stable*.

The reactions of hydrogen bromide with 1,3-butadiene serve as a striking illustration of the way that the outcome of a chemical reaction can be determined, in one instance, by relative rates of competing reactions and, in another, by the relative stabilities of the final products. At the lower temperature, the relative amounts of the products of the addition are determined by the relative rates at which the two additions occur; 1,2-addition occurs faster so the 1,2-addition product is the major product. At the higher temperature, the relative amounts of the products are determined by the position of an equilibrium. The 1,4-addition product is the more stable, so it is the major product.

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This behavior of 1,3-butadiene and hydrogen bromide can be more fully understood if we examine the diagram shown in Fig. 12.1.

- The step that determines the overall outcome of this reaction is the step in which the hybrid allylic cation combines with a bromide ion.

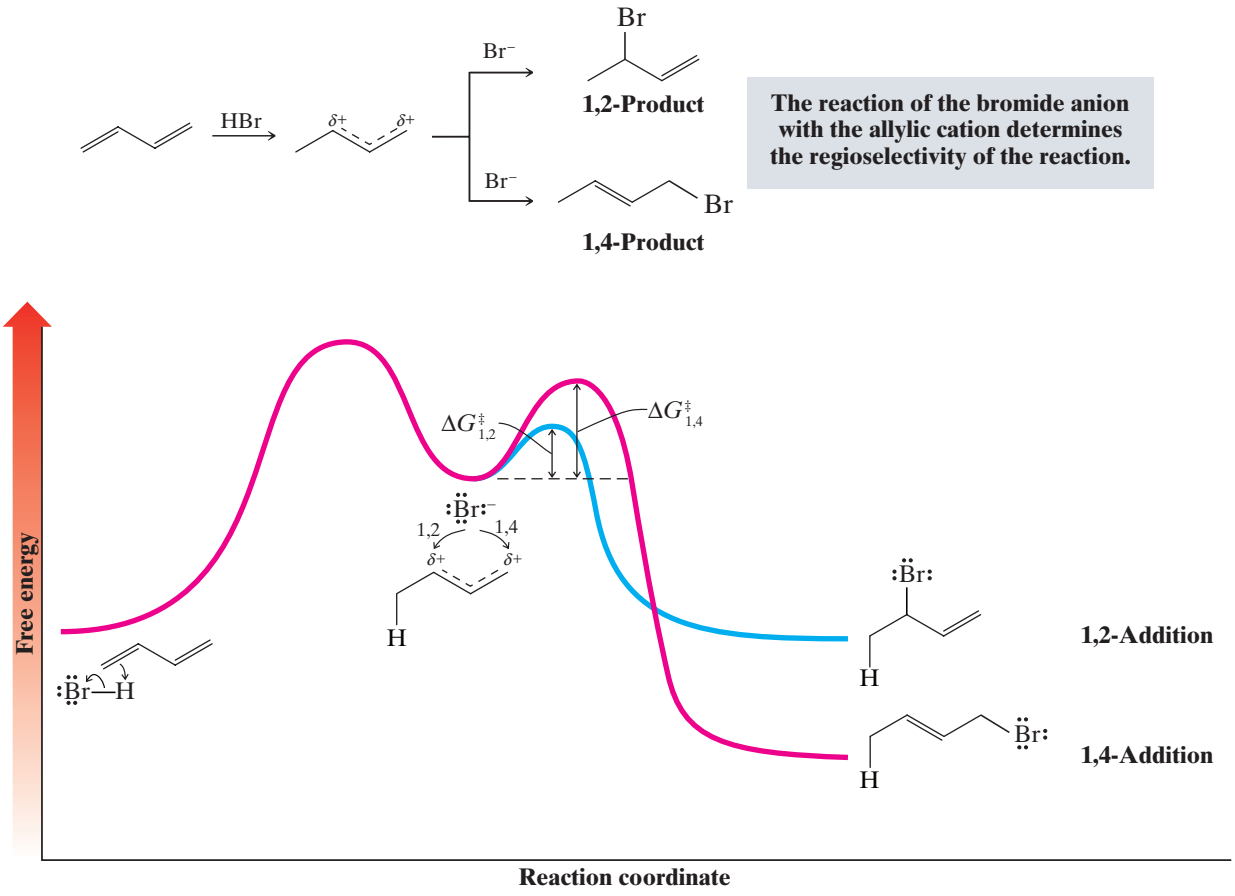

Figure 12.1 A schematic free-energy versus reaction coordinate diagram for the 1,2- and 1,4-addition of HBr to 1,3-butadiene. An allylic carbocation is common to both pathways. The energy barrier for attack of bromide ion on the allylic cation to form the 1,2-addition product is less than that to form the 1,4-addition product. The 1,2-addition product is kinetically favored. The 1,4-addition product is more stable, and so it is the thermodynamically favored product.

We see in Fig. 12.1 that the free energy of activation leading to the 1,2-addition product is less than the free energy of activation leading to the 1,4-addition product, even though the 1,4-product is more stable.

- At **low temperature**, the fraction of collisions capable of surmounting the higher energy barrier leading to formation of the 1,4-product is smaller than the fraction that can cross the barrier leading to the 1,2-product.
- At low temperature, formation of the 1,2- and 1,4-products is essentially *irreversible* because there is not enough energy for either product to cross back over the barrier to reform the allylic cation. Thus, the 1,2-product predominates at lower temperature because it is formed faster and it is not formed reversibly. It is the **kinetic product** of this reaction.
- At **higher temperature**, collisions between the intermediate ions are sufficiently energetic to allow rapid formation of *both* the 1,2- and 1,4-products. *But*, there is also sufficient energy for both products to revert to the **allylic carbocation**.
- Because the 1,2-product has a smaller energy barrier for conversion back to the allylic cation than does the 1,4-product, more of the 1,2-product reverts to the allylic cation than does the 1,4-product. But since both the 1,4- and the 1,2-products readily form from the allylic cation at high temperature, eventually this equilibrium leads to a preponderance of the 1,4-product because it is more stable. The 1,4-product is the **thermodynamic** or **equilibrium product** of this reaction.

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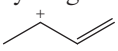
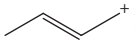
Before we leave this subject, one final point should be made. This example clearly demonstrates that predictions of relative reaction rates made on the basis of product stabilities alone can be wrong. This is not always the case, however. For many reactions in which a common intermediate leads to two or more products, the most stable product is formed fastest.

Practice Problem 12.3

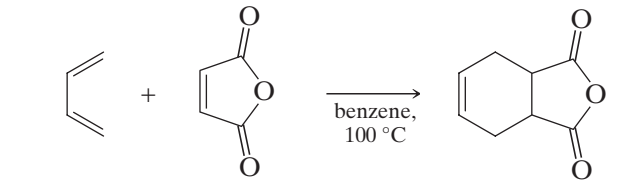
(a) Suggest a structural explanation for the fact that the 1,2-addition reaction of 1,3-butadiene and hydrogen bromide occurs faster than 1,4-addition. (*Hint*: Consider the relative contributions that the two forms  and  make to the resonance hybrid of the allylic cation.)

(b) How can you account for the fact that the 1,4-addition product is more stable?

12.5 | THE DIELS–ALDER REACTION: A 1,4-CYCLOADDITION REACTION OF DIENES

In 1928 two German chemists, Otto Diels and Kurt Alder, developed a **1,4-cycloaddition** reaction of dienes that has since come to bear their names. The reaction proved to be one of such great versatility and synthetic utility that Diels and Alder were awarded the Nobel Prize in Chemistry in 1950.

An example of the Diels–Alder reaction is the reaction that takes place when 1,3-butadiene and maleic anhydride are heated together at 100 °C. The product is obtained in quantitative yield:

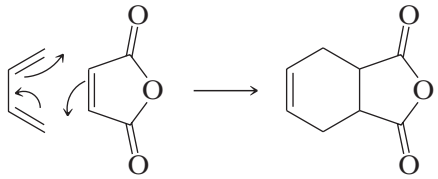


1,3-Butadiene (diene) + **Maleic anhydride (dienophile)** → **Adduct (100%)**

- In general terms, the **Diels–Alder reaction** is one between a conjugated **diene** (a 4π-electron system) and a compound containing a double bond (a 2π-electron system) called a **dienophile** (diene + *philia*, Greek: to love). The product of a Diels–Alder reaction is often called an **adduct**.

In the Diels–Alder reaction, two new σ bonds are formed at the expense of two π bonds of the diene and dienophile. The adduct contains a new six-membered ring with a double bond. Since σ bonds are usually stronger than π bonds, formation of the adduct is usually favored energetically, *but most Diels–Alder reactions are reversible*.

We can account for all of the bond changes in a Diels–Alder reaction like that above by using curved arrows in the following way:



Diene **Dienophile** **Adduct**

The Diels–Alder reaction is an example of a **pericyclic reaction**. **Pericyclic reactions are concerted reactions that take place in one step through a cyclic transition state in which symmetry characteristics of molecular orbitals control the course of the reaction.**

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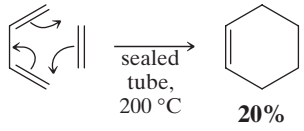
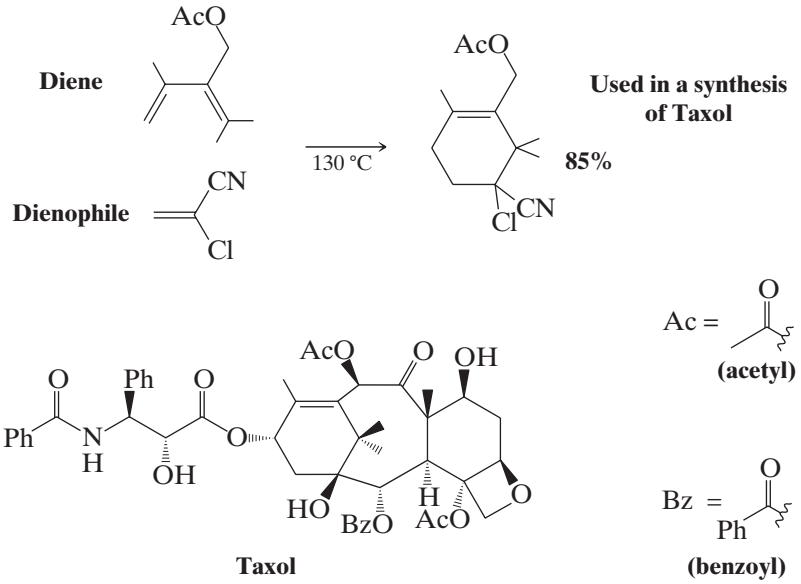
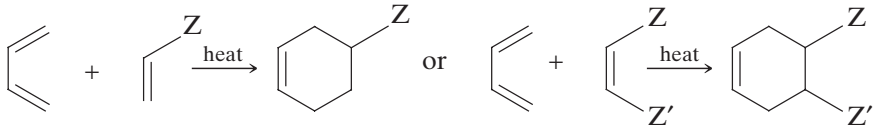
The simplest example of a Diels–Alder reaction is the one that takes place between 1,3-butadiene and ethene. This reaction, however, takes place much more slowly than the reaction of butadiene with maleic anhydride and also must be carried out under pressure:



Another example is the preparation of an intermediate in the synthesis of the anticancer drug Taxol (paclitaxel) by K. C. Nicolaou (The Scripps Research Institute and the University of California, San Diego):

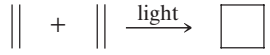


In general, the dienophile reacts with a conjugated diene by 1,4-addition to form a six-membered ring. The process is called a [4+2] **cycloaddition**, named according to the number of atoms from each reactant that join to form the ring, and it is brought about by heat (a thermal reaction). Any position on either side of the diene or dienophile can be substituted. Some representative electron-withdrawing groups that can be part of the dienophile are shown below as Z and Z′.



Where Z and Z′ can be CHO, COR, CO_2H, CO_2R, CN, Ar, CO-O-CO, or halogen, as well as others.

Pericyclic reactions in which two alkenes combine in the following way are also known.



These are called [2 + 2] cycloadditions and require light energy (they are photochemical reactions).

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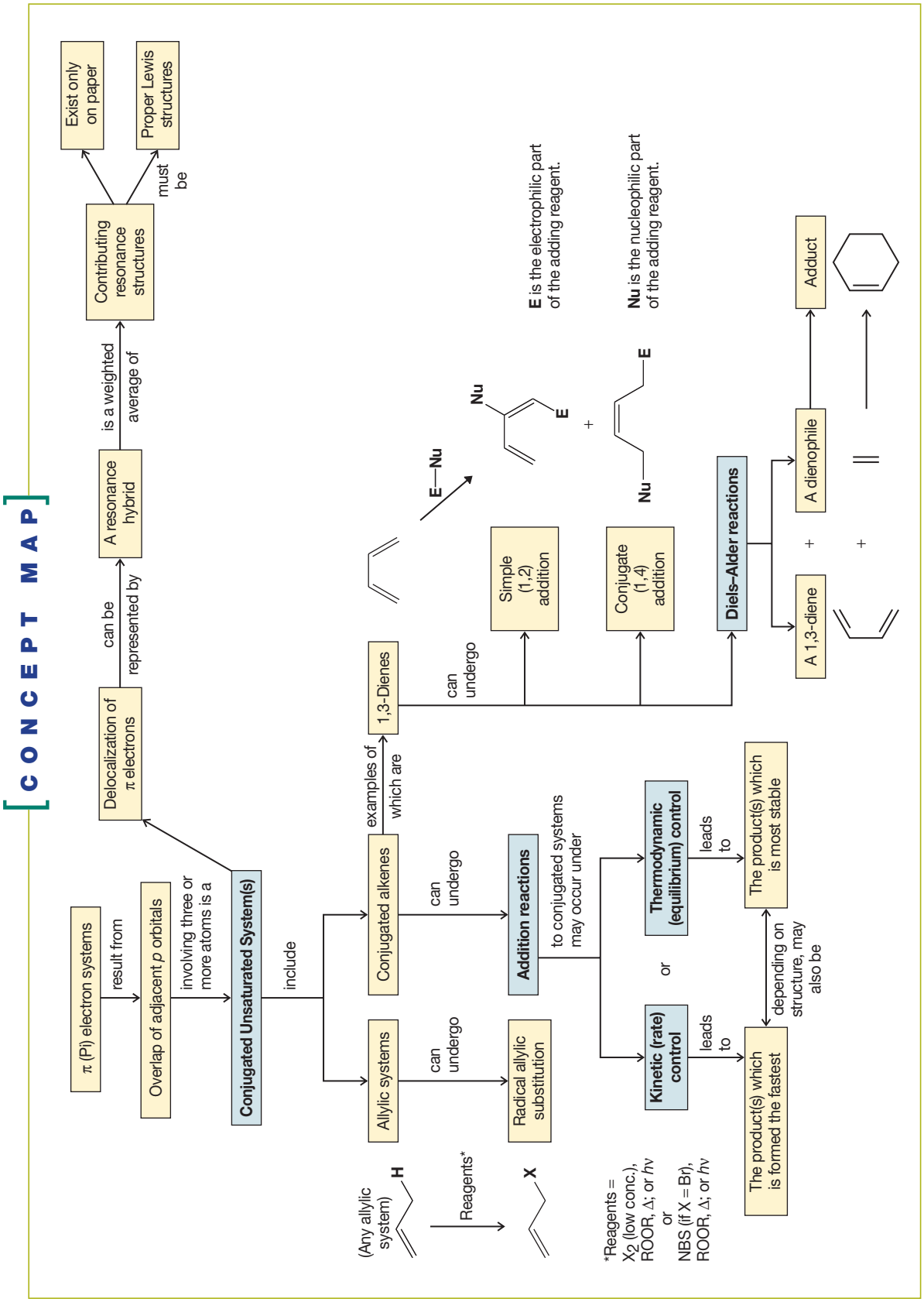
[CONCEPT MAP]



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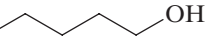
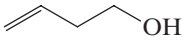
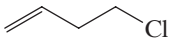
REVIEW PROBLEMS

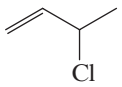
Conjugated Systems

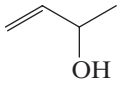
12.4 Provide the reagents needed to synthesize 1,3-butadiene starting from

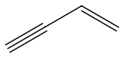
(a) 1,4-Dibromobutane **(b)** 

(c) 

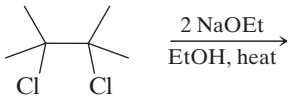
(d) 

(e) 

(f) 

(g) 

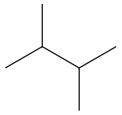
12.5 What product would you expect from the following reaction?

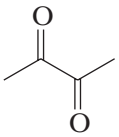


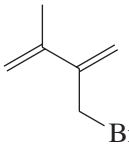
12.6 What products would you expect from the reaction of 1 mol of 1,3-butadiene and each of the following reagents? (If no reaction would occur, you should indicate that as well.)

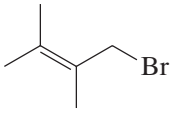
(a) 1 mol of Cl_2
(b) 2 mol of Cl_2
(c) 2 mol of Br_2
(d) 2 mol of H_2, Ni
(e) 1 mol of Cl_2 in H_2O
(f) Hot $KMnO_4$ (excess)
(g) H_2O, cat. H_2SO_4

12.7 Provide the reagents necessary to *trans*form 2,3-dimethyl-1,3-butadiene into each of the following compounds.

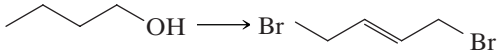
(a) 

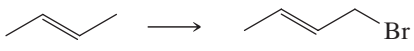
(b) 

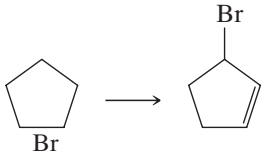
(c) 

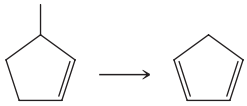
(d) 

12.8 Provide the reagents necessary for each of the following *trans*formations. In some cases several steps may be necessary.

(a) 1-Butene ⟶ 1,3-butadiene
(b) 1-Pentene ⟶ 1,3-pentadiene
(c) 

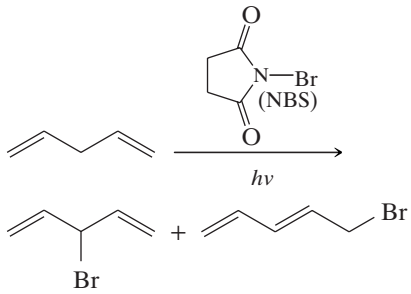
(d) 

(e) 

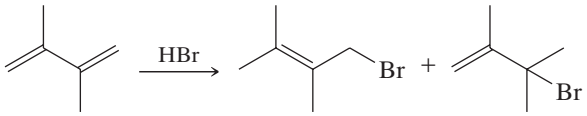
(f) 

12.9 When 1-pentene reacts with *N*-bromosuccinimide (NBS), two products with the formula C_5H_9Br are obtained. What are these products and how are they formed?

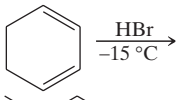
12.10 Provide a mechanism that explains formation of the following products. Include all intermediates, formal charges, and arrows showing electron flow.

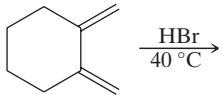


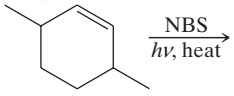
12.11 Provide a mechanism for the following reaction. Draw a reaction energy coordinate diagram that illustrates the kinetic and thermodynamic pathways for this reaction.



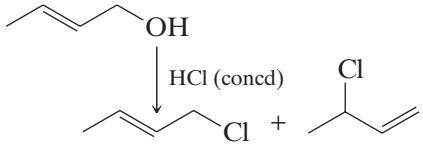
12.12 Predict the products of the following reactions.

(a) 

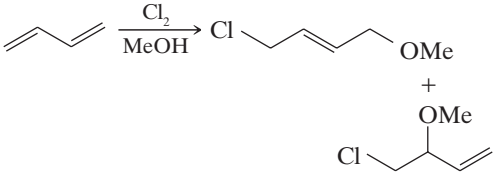
(b) 

(c) 

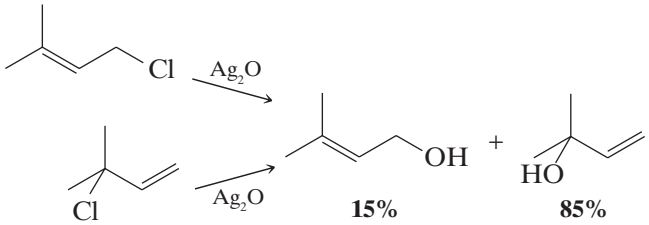
12.13 Provide a mechanism that explains formation of the following products.



12.14 Provide a mechanism that explains formation of the following products.



12.15 Treating either 1-chloro-3-methyl-2-butene or 3-chloro-3-methyl-1-butene with Ag_2O in water gives (in addition to AgCl) the following mixture of alcohol products.



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(a) Write a mechanism that accounts for the formation of these products.

(b) What might explain the relative proportions of the two alkenes that are formed?

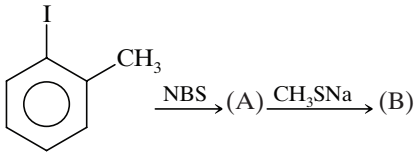
12.16 The heat of hydrogenation of allene is 298 kJ mol^{-1}, whereas that of propyne is 290 kJ mol^{-1}. **(a)** Which compound is more stable? **(b)** Treating allene with a strong base causes it to isomerize to propyne. Explain.

12.17 Although both 1-bromobutane and 4-bromo-1-butene are primary halides, the latter undergoes elimination more rapidly. How can this behavior be explained?

ADDITIONAL OBJECTIVE QUESTIONS

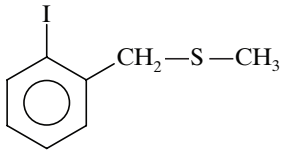
Single Correct Choice Type

1.

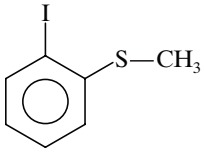


Product (B) is

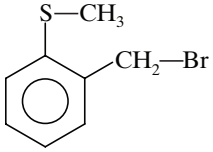
(a)



(b)

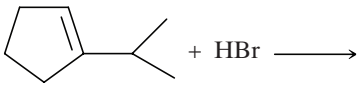


(c)

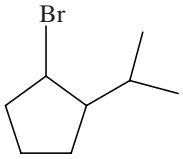


(d) None of these

2. Which of the following products is not formed in the following reaction?



(a)



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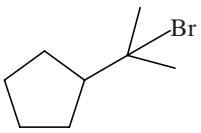

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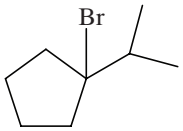

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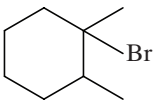
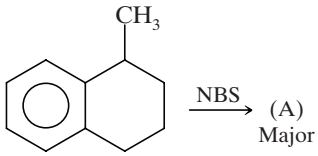
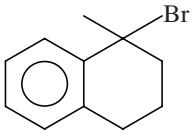


3.

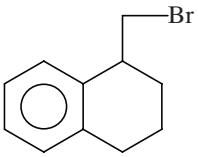


Major product (A) is

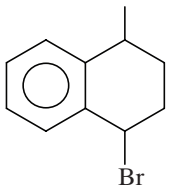
(a)



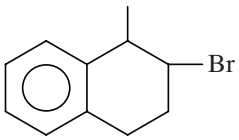
(b)



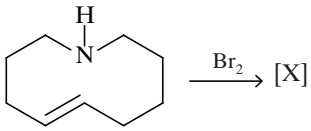
(c)



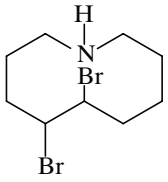
(d)



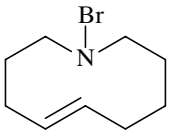
4. In the given reaction, X is



(a)



(b)



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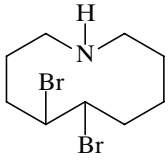
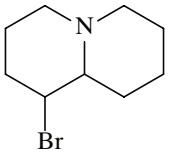
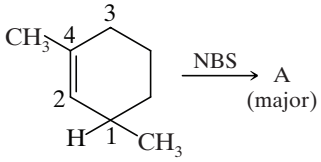


(d)



5. Bromination takes place at which carbon

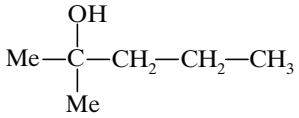


(a) C1 **(b)** C2 **(c)** C3 **(d)** C4

6. $Me_2C=CH-CH_2-CH_2-Cl \xrightarrow[CaCO_3]{H_2O} (X)$

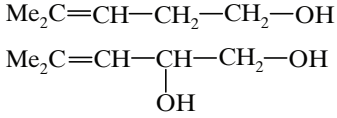
The major product of the above the reaction is

(a)

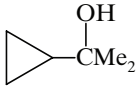


(b) $Me_2C=CH-CH_2-CH_2-OH$

(c)



(d)



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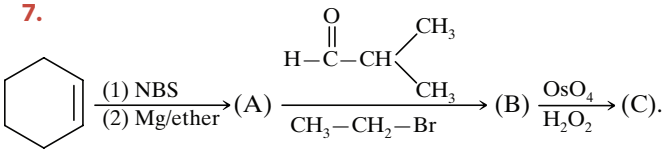
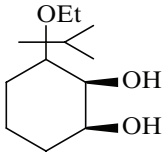
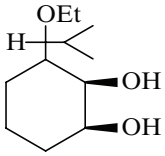
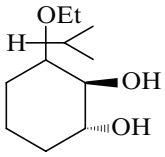
7.



Product (C) is

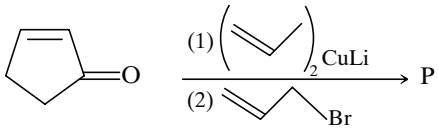
(a) 

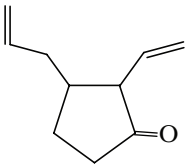
(b) 

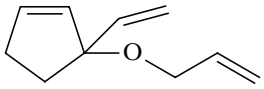
(c) 

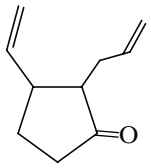
(d) Both (a) and (b)

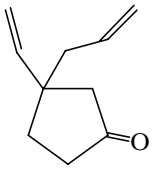
8. In the following reaction, P is



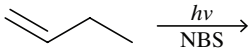
(a) 

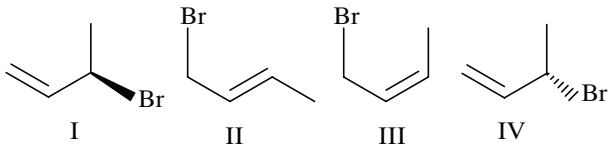
(b) 

(c) 

(d) 

9. Which of the following are products of the reaction shown below?

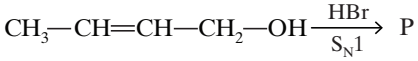




(a) I, II
(b) II, III
(c) I, III
(d) I, II, III, IV

Multiple Correct Choice Type

1. Consider the given reaction and identify the product P



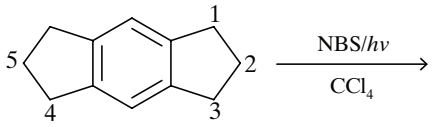
(a) $CH_3—CH=CH—CH_2—Br$

(b) $CH_3—\underset{\displaystyle Br}{\underset{|}{CH}}—CH=CH_2$

(c) $CH_2=CH—CH=CH_2$

(d) $CH_3—\underset{\displaystyle Br}{\underset{|}{CH}}—CH_2—CH_2—OH$

2. Bromination can take place at which carbon

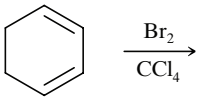


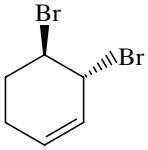
(a) C1
(b) C2
(c) C3
(d) C4

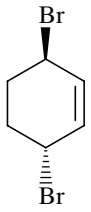
3. Products formed when HCl adds to 2,4-hexadiene are

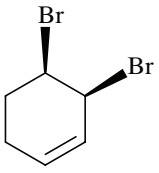
(a) 4-chloro-2-hexene.
(b) 2-chloro-3-hexene.
(c) 2-chloro-4-hexene.
(d) 1-chloro-2-hexene.

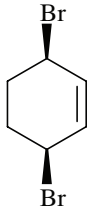
4. The products in the following reaction are



(a) 

(b) 

(c) 

(d) 

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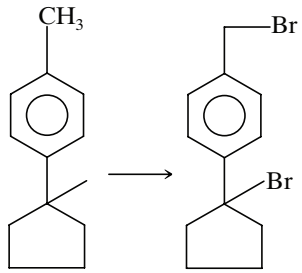
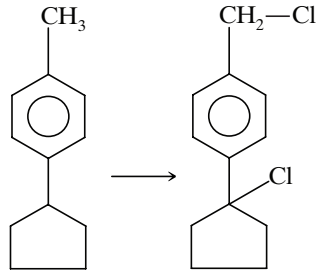
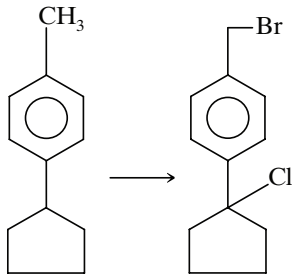
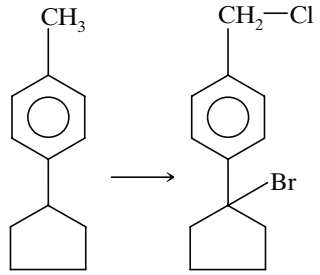
Matrix Match Type

1.

Column I (Conversion)	Column II (Reagent)
(a) 	**(p)** $SO_2Cl_2/h\nu$ (2 equivalent)
(b) 	**(q)** NBS (2 equivalent)
(c) 	**(r)** NBS then $SO_2Cl_2/h\nu$
(d) 	**(s)** $SO_2Cl_2/h\nu$ then NBS

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ANSWER KEY

Single Correct Choice Type

1. (d)
2. (a)
3. (a)
4. (d)
5. (a)
6. (d)
7. (b)
8. (c)
9. (d)

Multiple Correct Choice Type

1. (a), (b)
2. (a), (c), (d)
3. (a), (b)
4. (a), (b), (d)

Matrix Match Type

1. a $\rightarrow$ (q); b $\rightarrow$ (p); c $\rightarrow$ (s); d $\rightarrow$ (r)

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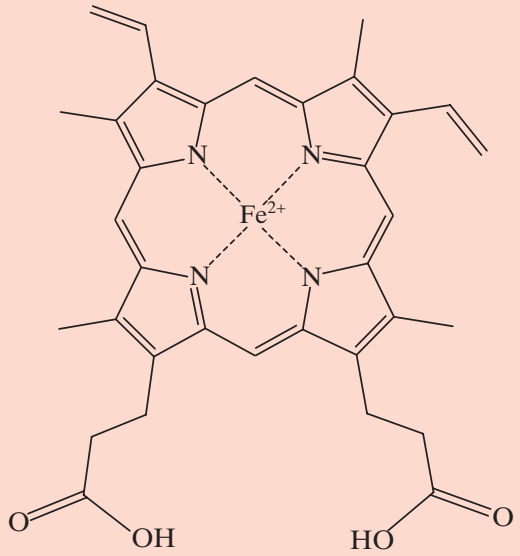
13

Aromatic Compounds



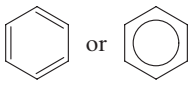
Heme
[18 electron system; $n = 4$]

Contents

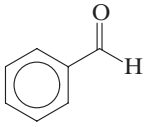
13.1 | The Discovery of Benzene
13.2 | Nomenclature of Benzene Derivatives
13.3 | Reactions of Benzene
13.4 | The Kekulé Structure for Benzene
13.5 | The Thermodynamic Stability of Benzene
13.6 | Modern Theories of the Structure of Benzene
13.7 | Hückel's Rule: The $4n + 2$ π Electron Rule
13.8 | Other Aromatic Compounds
13.9 | Heterocyclic Aromatic Compounds

13.1 | THE DISCOVERY OF BENZENE

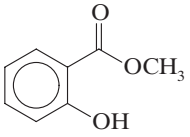
The following are a few examples of aromatic compounds, including benzene itself. In these formulas we foreshadow our discussion of the special properties of the benzene ring by using a circle in a hexagon to depict the six π electrons and six-membered ring of these compounds, whereas up to now we have shown benzene rings only as indicated in the left-hand formula for benzene below.



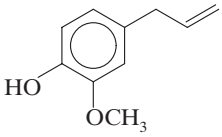
Benzene



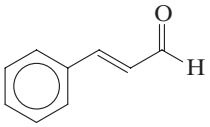
Benzaldehyde
(in oil of almonds)



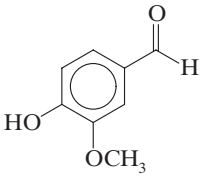
Methyl salicylate
(in oil of wintergreen)



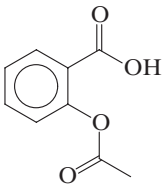
Eugenol
(in oil of cloves)



Cinnamaldehyde
(in oil of cinnamon)



Vanillin
(in oil of vanilla)



Acetylsalicylic acid
(aspirin)

The study of the class of compounds that organic chemists call aromatic compounds (Section 2.1D) began with the discovery in 1825 of a new hydrocarbon by the English chemist Michael Faraday (Royal Institution). Faraday called this new hydrocarbon "bicarburet of hydrogen"; we now call it benzene. Faraday isolated benzene from a compressed illuminating gas that had been made by pyrolyzing whale oil.

In 1834 the German chemist Eilhardt Mitscherlich (University of Berlin) synthesized benzene by heating benzoic acid with calcium oxide. Using vapor density measurements, Mitscherlich further showed that benzene has the molecular formula C_6H_6:

$$\underset{\text{Benzoic acid}}{C_6H_5CO_2H} + CaO \xrightarrow{\text{heat}} \underset{\text{Benzene}}{C_6H_6} + CaCO_3$$

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The molecular formula itself was surprising. Benzene has *only as many hydrogen atoms as it has carbon atoms*. Most compounds that were known then had a far greater proportion of hydrogen atoms, usually twice as many. Benzene, having the formula of C_6H_6, should be a highly unsaturated compound because it has an index of hydrogen deficiency equal to 4. Eventually, chemists began to recognize that benzene was a member of a new class of organic compounds with unusual and interesting properties. **As we shall see in Section 13.3, benzene does not show the behavior expected of a highly unsaturated compound**.

During the latter part of the nineteenth century the Kekulé–Couper–Butlerov theory of valence was systematically applied to all known organic compounds. One result of this effort was the placing of organic compounds in either of two broad categories; compounds were classified as being either **aliphatic** or **aromatic**. To be classified as aliphatic meant then that the chemical behavior of a compound was "fatlike." (Now it means that the compound reacts like an alkane, an alkene, an alkyne, or one of their derivatives.) To be classified as aromatic meant then that the compound had a low hydrogen-to-carbon ratio and that it was "fragrant." Most of the early aromatic compounds were obtained from balsams, resins, or essential oils.

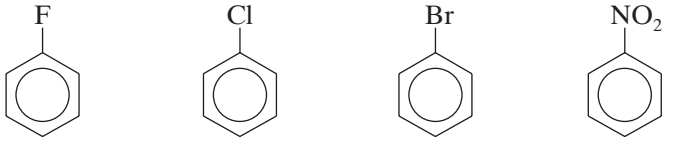
Kekulé was the first to recognize that these early aromatic compounds all contain a six-carbon unit and that they retain this six-carbon unit through most chemical transformations and degradations. Benzene was eventually recognized as being the parent compound of this new series. It was not until the development of quantum mechanics in the 1920s, however, that a reasonably clear understanding of its structure emerged.

13.2 | NOMENCLATURE OF BENZENE DERIVATIVES

Two systems are used in naming monosubstituted benzenes.

- In many simple compounds, *benzene* is the parent name and the substituent is simply indicated by a prefix.

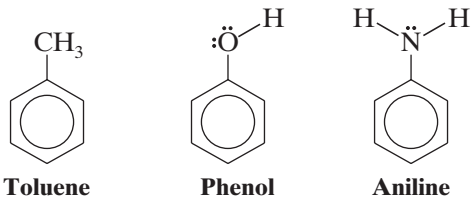
  We have, for example,



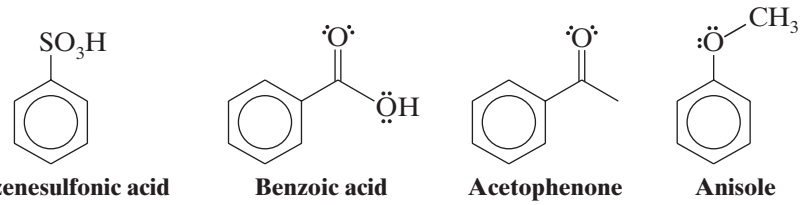
Fluorobenzene **Chlorobenzene** **Bromobenzene** **Nitrobenzene**

- For other simple and common compounds, the substituent and the benzene ring taken together may form a commonly accepted parent name.

Methylbenzene is usually called *toluene*, hydroxybenzene is almost always called *phenol*, and aminobenzene is almost always called *aniline*. These and other examples are indicated here:



Toluene **Phenol** **Aniline**



Benzenesulfonic acid **Benzoic acid** **Acetophenone** **Anisole**

- When two substituents are present, their relative positions are indicated by the prefixes ***ortho-***, ***meta-***, and ***para-*** (abbreviated ***o-***, ***m-***, and ***p-***) or by the use of numbers.

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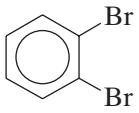
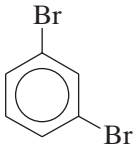
For the dibromobenzenes we have



1,2-Dibromobenzene (*o*-dibromobenzene) ortho

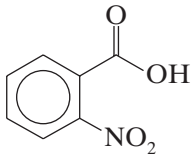


1,3-Dibromobenzene (*m*-dibromobenzene) meta

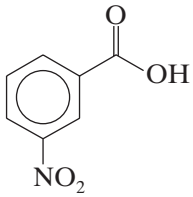


1,4-Dibromobenzene (*p*-dibromobenzene) para

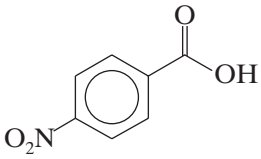
and for the nitrobenzoic acids



2-Nitrobenzoic acid (*o*-nitrobenzoic acid)

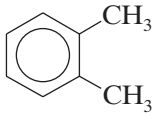


3-Nitrobenzoic acid (*m*-nitrobenzoic acid)

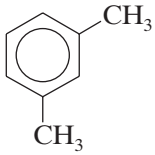


4-Nitrobenzoic acid (*p*-nitrobenzoic acid)

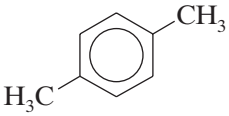
The dimethylbenzenes are often called *xylenes*:



1,2-Dimethylbenzene (*o*-xylene)



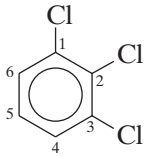
1,3-Dimethylbenzene (*m*-xylene)



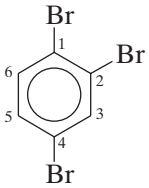
1,4-Dimethylbenzene (*p*-xylene)

- If more than two groups are present on the benzene ring, their positions must be indicated by the use of *numbers*.

As examples, consider the following two compounds:

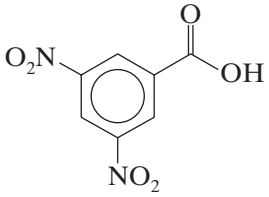


1,2,3-Trichlorobenzene

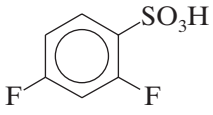


1,2,4-Tribromobenzene (*not* 1,3,4-tribromobenzene)

- The benzene ring is numbered so as to give ***the lowest possible numbers to the substituents***.
- When more than two substituents are present and the substituents are different, they are listed in alphabetical order.
- When a substituent is one that together with the benzene ring gives a new base name, that substituent is assumed to be in position 1 and the new parent name is used.



3,5-Dinitrobenzoic acid



2,4-Difluorobenzenesulfonic acid

- When the C_6H_5— group is named as a substituent, it is called a **phenyl** group. The phenyl group is often abbreviated as C_6H_5—, Ph—, or φ—.

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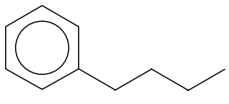
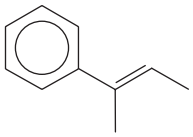
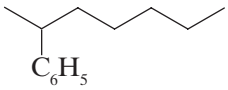
A hydrocarbon composed of one saturated chain and one benzene ring is usually named as a derivative of the larger structural unit. However, if the chain is unsaturated, the compound may be named as a derivative of that chain, regardless of ring size. The following are examples:



Butylbenzene

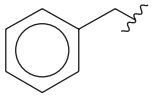


(*E*)-2-Phenyl-2-butene

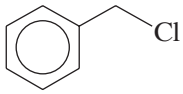


2-Phenylheptane

- **Benzyl** is an alternative name for the phenylmethyl group. It is sometimes abbreviated Bn.



The benzyl group (the phenylmethyl group)

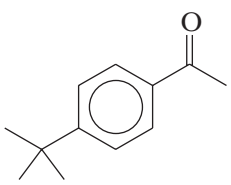


Benzyl chloride (phenylmethyl chloride or BnCl)

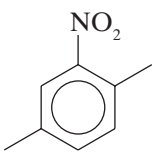
Solved Problem 13.1

Provide a name for each of the following compounds.

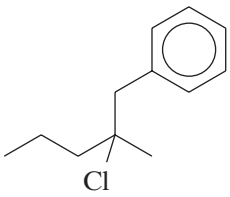
(a)



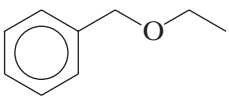
(b)



(c)



(d)



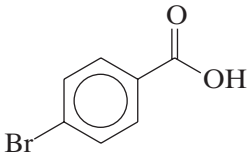
Answer

In each compound we look first to see if a commonly named unit containing a benzene ring is present. If not, we consider whether the compound can be named as a simple derivative of benzene, or if the compound incorporates the benzene ring as a phenyl or benzyl group. In **(a)** we recognize the common structural unit of acetophenone, and find a *tert*-butyl group in the para position. The name is thus *p*-*tert*-butylacetophenone or 4-*tert*-butylacetophenone. Compound **(b)**, having three substituents on the ring, must have its substituents named in alphabetical order and their positions numbered. The name is 1,4-dimethyl-2-nitrobenzene. In **(c)** there would appear to be a benzyl group, but the benzene ring can be considered a substituent on the alkyl chain, so it is called phenyl in this case. The name is 2-chloro-2-methyl-1-phenylpentane. Because **(d)** contains an ether functional group, we name it according to the groups bonded to the ether oxygen. The name is benzyl ethyl ether, or ethyl phenylmethyl ether.

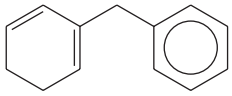
Practice Problem 13.1

Provide a name for each of the following compounds.

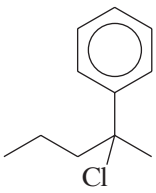
(a)



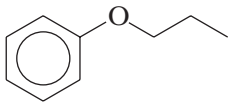
(b)



(c)



(d)



13.3 | REACTIONS OF BENZENE

In the mid-nineteenth century, benzene presented chemists with a real puzzle. They knew from its formula (Section 13.1) that benzene was highly unsaturated, and they expected it to react accordingly. They expected it to react like an alkene by decolorizing bromine through *addition*. They expected that it would change the color of aqueous potassium permanganate by being *oxidized*, that it would *add hydrogen* rapidly in the presence of a metal catalyst, and that it would *add water* in the presence of strong acids.

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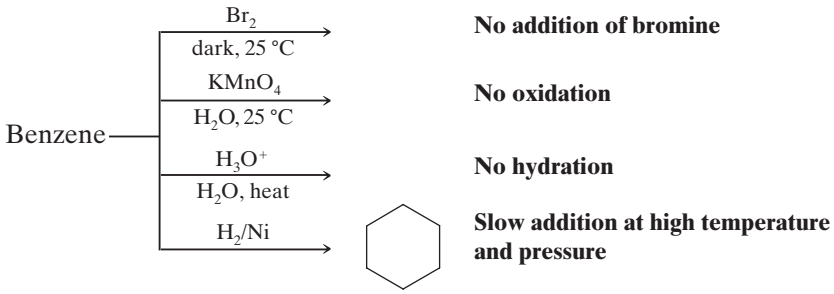
Benzene does none of these. When benzene is treated with bromine in the dark or with aqueous potassium permanganate or with dilute acids, none of the expected reactions occurs. Benzene does add hydrogen in the presence of finely divided nickel, but only at high temperatures and under high pressures:



Benzene *does* react with bromine but only in the presence of a Lewis acid catalyst such as ferric bromide. Most surprisingly, however, it reacts not by addition but by *substitution*—**benzene substitution**.

Substitution

$$C_6H_6 + Br_2 \xrightarrow{FeBr_3} C_6H_5Br + HBr$$

Substitution is observed.

Addition

$$C_6H_6 + Br_2 \not\longrightarrow C_6H_6Br_2 + C_6H_6Br_4 + C_6H_6Br_6$$

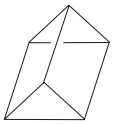
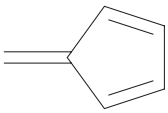
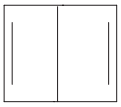
Addition is not observed.

When benzene reacts with bromine, *only one monobromobenzene* is formed. That is, only one compound with the formula C_6H_5Br is found among the products. Similarly, when benzene is chlorinated, *only one monochlorobenzene* results.

Two possible explanations can be given for these observations. The first is that only one of the six hydrogen atoms in benzene is reactive toward these reagents. The second is that all six hydrogen atoms in benzene are equivalent, and replacing any one of them with a substituent results in the same product. As we shall see, the second explanation is correct.

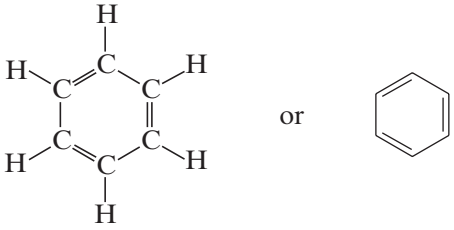
Practice Problem 13.2

Listed below are four compounds that have the molecular formula C_6H_6. Which of these compounds would yield only one monosubstitution product, if, for example, one hydrogen were replaced by bromine?

(a)  **(b)**  **(c)**  **(d)** 

13.4 | THE KEKULÉ STRUCTURE FOR BENZENE

In 1865, August Kekulé, the originator of the structural theory (Section 1.4), proposed the first definite structure for benzene, a structure that is still used today (although as we shall soon see, we give it a meaning different from the meaning Kekulé gave it). Kekulé suggested that the carbon atoms of benzene are in a ring, that they are bonded to each other by alternating single and double bonds, and that one hydrogen atom is attached to each carbon atom. This structure satisfied the requirements of the structural theory that carbon atoms form four bonds and that all the hydrogen atoms of benzene are equivalent:



The Kekulé formula for benzene

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A problem soon arose with the **Kekulé structure**, however. The Kekulé structure predicts that there should be two different 1,2-dibromobenzenes, but there are not. In one of these hypothetical compounds (below), the carbon atoms that bear the bromines would be separated by a single bond, and in the other they would be separated by a double bond.



These 1,2-dibromobenzenes do not exist as isomers.

- *Only one 1,2-dibromobenzene has ever been found, however.*

To accommodate this objection, Kekulé proposed that the two forms of benzene (and of benzene derivatives) are in a state of equilibrium and that this equilibrium is so rapidly established that it prevents isolation of the separate compounds. Thus, the two 1,2-dibromobenzenes would also be rapidly equilibrated, and this would explain why chemists had not been able to isolate the two forms:



There is no such equilibrium between benzene ring bond isomers.

- We now know that this proposal was also incorrect and that *no such equilibrium exists*.

Nonetheless, the Kekulé formulation of benzene's structure was an important step forward and, for very practical reasons, it is still used today. Now we understand its meaning differently, however.

The tendency of benzene to react by substitution rather than addition gave rise to another concept of **aromaticity**. For a compound to be called aromatic meant, experimentally, that it gave substitution reactions rather than addition reactions even though it was highly unsaturated.

Before 1900, chemists assumed that the ring of alternating single and double bonds was the structural feature that gave rise to the aromatic properties. Since benzene and benzene derivatives (i.e., compounds with six-membered rings) were the only aromatic compounds known, chemists naturally sought other examples. The compound cyclooctatetraene seemed to be a likely candidate:



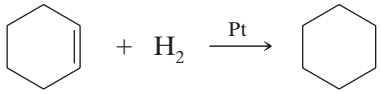
Cyclooctatetraene

In 1911, Richard Willstätter succeeded in synthesizing cyclooctatetraene. Willstätter found, however, that it is not at all like benzene. Cyclooctatetraene reacts with bromine by addition, it adds hydrogen readily, it is oxidized by solutions of potassium permanganate, and thus it is clearly *not aromatic*. While these findings must have been a keen disappointment to Willstätter, they were very significant for what they did not prove. Chemists, as a result, had to look deeper to discover the origin of benzene's aromaticity.

13.5 | THE THERMODYNAMIC STABILITY OF BENZENE

We have seen that benzene shows unusual behavior by undergoing substitution reactions when, on the basis of its Kekulé structure, we should expect it to undergo addition. Benzene is unusual in another sense: it is *more stable thermodynamically* than the Kekulé structure suggests. To see how, consider the following thermochemical results.

Cyclohexene, a six-membered ring containing one double bond, can be hydrogenated easily to cyclohexane. When the $\Delta H°$ for this reaction is measured, it is found to be –120 kJ mol^{-1}, very much like that of any similarly substituted alkene:



$\Delta H° = -120$ kJ mol^{-1}

Cyclohexene **Cyclohexane**

We would expect that hydrogenation of 1,3-cyclohexadiene would liberate roughly twice as much heat and thus have a $\Delta H°$ equal to about –240 kJ mol^{-1}. When this experiment is done, the result is $\Delta H° = -232$ kJ mol^{-1}. This result is quite

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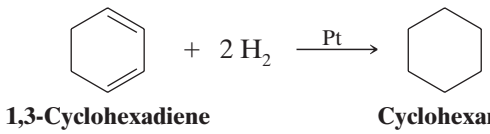
close to what we calculated, and the difference can be explained by taking into account the fact that compounds containing conjugated double bonds are usually somewhat more stable than those that contain isolated double bonds (Section 13.8):

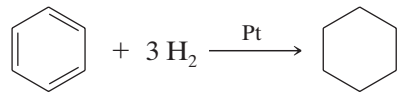


1,3-Cyclohexadiene **Cyclohexane**

Calculated
$\Delta H° = 2 \times (-120) = -240$ kJ mol^{-1}

Observed
$\Delta H° = -232$ kJ mol^{-1}

If we extend this kind of thinking, and if benzene is simply 1,3,5-cyclohexatriene, we would predict benzene to liberate approximately 360 kJ mol^{-1} [3 × (−120)] when it is hydrogenated. When the experiment is actually done, the result is surprisingly different. The reaction is exothermic, but only by 208 kJ mol^{-1}:



Benzene **Cyclohexane**

Calculated		
$\Delta H° = 3 \times (-120)$	=	−360 kJ mol^{-1}
Observed	$\Delta H°$ =	−208 kJ mol^{-1}
Difference	=	152 kJ mol^{-1}

When these results are represented as in Fig. 13.1, it becomes clear that benzene is much more stable than we calculated it to be. Indeed, it is more stable than the hypothetical 1,3,5-cyclohexatriene by 152 kJ mol^{-1}. This difference between the amount of heat actually released and that calculated on the basis of the Kekulé structure is now called the **resonance energy** of the compound.

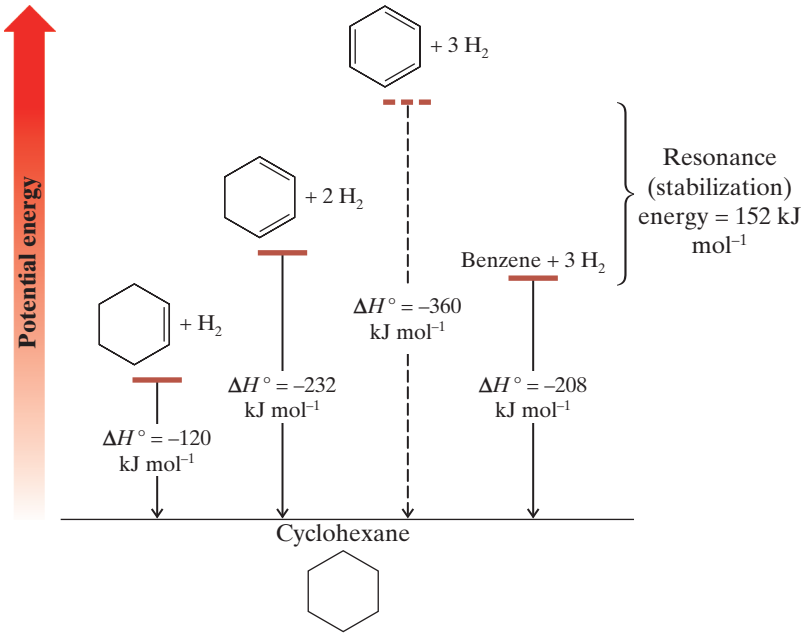


Figure 13.1 Relative stabilities of cyclohexene, 1,3-cyclohexadiene, 1,3,5-cyclohexatriene (hypothetical), and benzene.

13.6 | MODERN THEORIES OF THE STRUCTURE OF BENZENE

It was not until the development of quantum mechanics in the 1920s that the unusual behavior and stability of benzene began to be understood. Quantum mechanics, as we have seen, produced two ways of viewing bonds in molecules: resonance theory and molecular orbital theory. We now look at both of these as they apply to benzene.

13.6A The Resonance Explanation of the Structure of Benzene

A basic postulate of resonance theory (Section 1.5) is that whenever two or more Lewis structures can be written for a molecule that *differ only in the positions of their electrons*, none of the structures will be in complete accord with the

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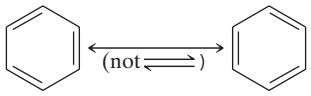
compound's chemical and physical properties. If we recognize this, we can now understand the true nature of the two Kekulé structures (**I** and **II**) for benzene.

- Kekulé structures **I** and **II** below differ only in the positions of their electrons; they do not represent two separate molecules in equilibrium as Kekulé had proposed.

Instead, structures **I** and **II** are the closest we can get to a structure for benzene within the limitations of its molecular formula, the classic rules of valence, and the fact that the six hydrogen atoms are chemically equivalent. The problem with the Kekulé structures is that they are Lewis structures, and Lewis structures portray electrons in localized distributions. (With benzene, as we shall see, the electrons are delocalized.) Resonance theory, fortunately, does not stop with telling us when to expect this kind of trouble; it also gives us a way out.

- According to resonance theory, we consider Kekulé structures **I** and **II** below as *resonance contributors* to the real structure of benzene, and we relate them to each other with one double-headed, double-barbed arrow (not two separate arrows, which we reserve for equilibria).

Resonance contributors, we emphasize again, are not in equilibrium. They are not structures of real molecules. They are the closest we can get if we are bound by simple rules of valence, but they are very useful in helping us visualize the actual molecule as a hybrid:



I **II**

Look at the structures carefully. All of the single bonds in structure **I** are double bonds in structure **II**.

- A hybrid (average) of Kekulé structures **I** and **II** would have neither pure single bonds nor pure double bonds between the carbons. The bond order would be between that of a single and a double bond.

Experimental evidence bears this out. Spectroscopic measurements show that the molecule of benzene is planar and that all of its carbon–carbon bonds are of equal length. Moreover, the carbon–carbon bond lengths in benzene (Fig. 13.2) are 1.39 Å, a value in between that for a carbon–carbon single bond between sp^2-hybridized atoms (1.47 Å) (see Table 12.1) and that for a carbon–carbon double bond (1.34 Å).

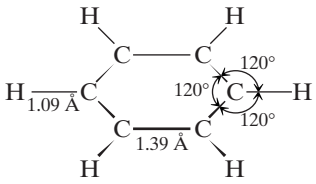


Figure 13.2 Bond lengths and angles in benzene. (Only the σ bonds are shown.)

- The hybrid structure of benzene is represented by inscribing a circle inside the hexagon as shown in formula **III** below.



III

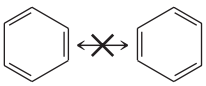
There are times when an accounting of the π electron pairs must be made, however, and for these purposes we use either Kekulé structure **I** or **II**. We do this simply because the electron pairs and total π electron count is obvious in a Kekulé structure, whereas the number of π electron pairs represented by a circle can be ambiguous. As we shall see later in this chapter, there are systems having different ring sizes and different numbers of delocalized π electrons that can also be represented by a circle. In benzene, however, the circle is understood to represent six π electrons that are delocalized around the six carbons of the ring.

- An actual molecule of benzene (depicted by the resonance hybrid **III**) is more stable than either contributing resonance structure because more than one equivalent resonance structure can be drawn for benzene (**I** and **II** above).

The difference in energy between hypothetical 1,3,5-cyclohexatriene (which if it existed would have higher energy) and benzene is called *resonance energy*, and it is an indication of the extra stability of benzene due to electron delocalization.

Practice Problem 13.3

If benzene were 1,3,5-cyclohexatriene, the carbon–carbon bonds would be alternately long and short as indicated in the following structures. However, to consider the structures here as resonance contributors (or to connect them by a double-headed arrow) violates a basic principle of resonance theory. Explain.



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13.6B The Molecular Orbital Explanation of the Structure of Benzene

The fact that the bond angles of the carbon atoms in the benzene ring are all 120° strongly suggests that the carbon atoms are sp^2 hybridized. If we accept this suggestion and construct a planar six-membered ring from sp^2 carbon atoms, representations like those shown in Figs. 13.3*a* and *b* emerge. In these models, each carbon is sp^2 hybridized and has a *p* orbital available for overlap with *p* orbitals of its neighboring carbons. If we consider favorable overlap of these *p* orbitals all around the ring, the result is the model shown in Fig. 13.3*c*.

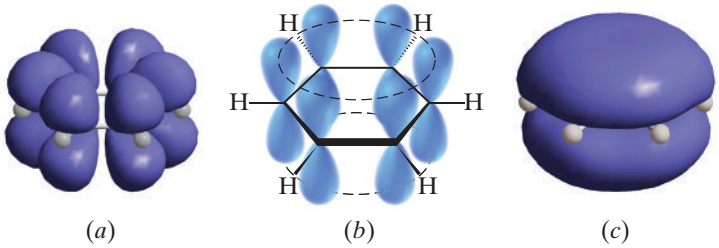

Figure 13.3 (*a*) Six sp^2-hybridized carbon atoms joined in a ring (each carbon also bears a hydrogen atom). Each carbon has a *p* orbital with lobes above and below the plane of the ring. (*b*) A stylized depiction of the *p* orbitals in (*a*). (*c*) Overlap of the *p* orbitals around the ring results in a molecular orbital encompassing the top and bottom faces of the ring. (Differences in the mathematical phase of the orbital lobes are not shown in these representations.)

- The number of molecular orbitals in a molecule is the same as the number of atomic orbitals from which they are derived, and each orbital can accommodate a maximum of two electrons if their spins are opposed.

If we consider only the *p* atomic orbitals contributed by the carbon atoms of benzene, there should be six π molecular orbitals. These orbitals are shown in Fig. 13.4.

The electronic configuration of the ground state of benzene is obtained by adding the six π electrons to the π molecular orbitals shown in Fig. 13.4, starting with the orbitals of lowest energy. The lowest energy π molecular

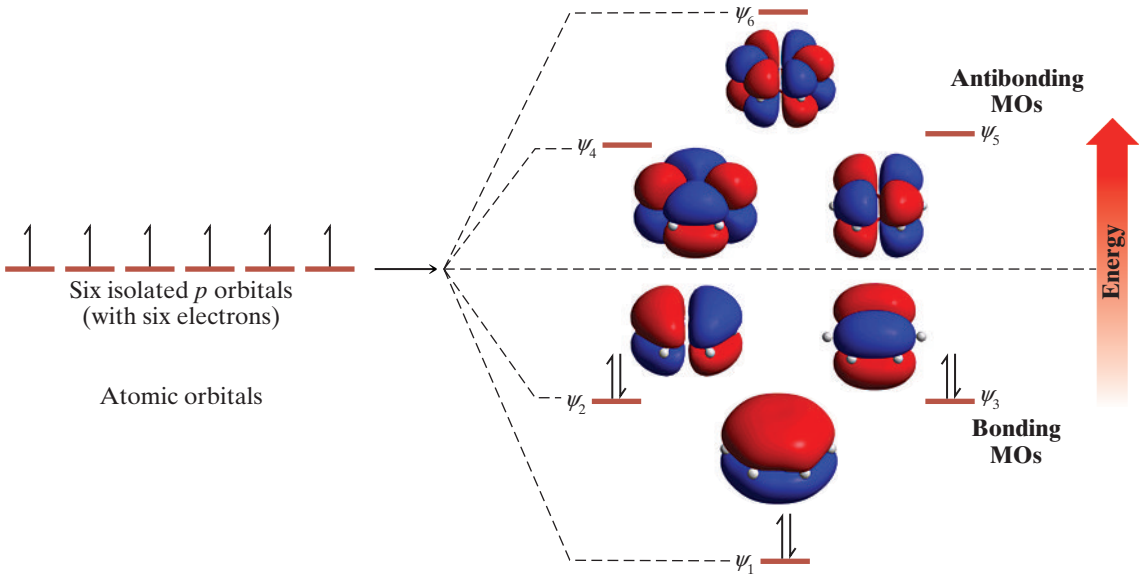

Figure 13.4 How six *p* atomic orbitals (one from each carbon of the benzene ring) combine to form six π molecular orbitals. Three of the molecular orbitals have energies lower than that of an isolated *p* orbital; these are the bonding molecular orbitals. Three of the molecular orbitals have energies higher than that of an isolated *p* orbital; these are the antibonding molecular orbitals. Orbitals ψ_2 and ψ_3 have the same energy and are said to be degenerate; the same is true of orbitals ψ_4 and ψ_5.

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orbital in benzene has overlap of *p* orbitals with the same mathematical phase sign all around the top and bottom faces of the ring. In this orbital there are no nodal planes (changes in orbital phase sign) perpendicular to the atoms of the ring. The orbitals of next higher energy each have one nodal plane. (In general, each set of higher energy π molecular orbitals has an additional nodal plane.) Each of these orbitals is filled with a pair of electrons, as well. These orbitals are of equal energy (degenerate) because they both have one nodal plane. Together, these three orbitals comprise the bonding π molecular orbitals of benzene. The next higher energy set of π molecular orbitals each has two nodal planes, and the highest energy π molecular orbital of benzene has three nodal planes. These three orbitals are the antibonding π molecular orbitals of benzene, and they are unoccupied in the ground state. Benzene is said to have a closed bonding shell of delocalized π electrons because all of its bonding orbitals are filled with electrons that have their spins paired, and no electrons are found in antibonding orbitals. This closed bonding shell accounts, in part, for the stability of benzene.

It is interesting to note the recent discovery that crystalline benzene involves perpendicular interactions between benzene rings, so that the relatively positive periphery of one molecule associates with the relatively negative faces of the benzene molecules aligned above and below it.

13.7 | HÜCKEL'S RULE: THE $4n + 2$ π ELECTRON RULE

In 1931 the German physicist Erich Hückel carried out a series of mathematical calculations based on the kind of theory that we have just described. **Hückel's rule** is concerned with compounds containing **one planar ring in which each atom has a *p* orbital** as in benzene. His calculations showed that planar monocyclic rings containing $4n + 2$ π electrons, where $n = 0, 1, 2, 3$, and so on (i.e., rings containing 2, 6, 10, 14,…, etc., π electrons), have closed shells of delocalized electrons like benzene and should have substantial resonance energies.

- In other words, Hückel's rule states that **planar monocyclic rings with 2, 6, 10, 14,…, delocalized electrons should be aromatic**.

13.7A How to Diagram the Relative Energies of π Molecular Orbitals in Monocyclic Systems Based on Hückel's Rule

There is a simple way to make a diagram of the relative energies of orbitals in monocyclic conjugated systems based on Hückel's calculations. To do so, we use the following procedure.

1. We start by drawing a polygon corresponding to the number of carbons in the ring, *placing a corner of the polygon at the bottom*.
2. Next we surround the polygon with a circle that touches each corner of the polygon.
3. At the points where the polygon touches the circle, we draw short horizontal lines outside the circle. The height of each line represents the relative energy of each π molecular orbital.
4. Next we draw a dashed horizontal line across and halfway up the circle. The energies of bonding π molecular orbitals are below this line. The energies of antibonding π molecular orbitals are above, and those for nonbonding orbitals are at the level of the dashed line.
5. Based on the number of π electrons in the ring, we then place electron arrows on the lines corresponding to the respective orbitals, beginning at the lowest energy level and working upward. In doing so, we fill degenerate orbitals each with one electron first, then add to each unpaired electron another with opposite spin if it is available.

Applying this method to benzene, for example (Fig. 13.5), furnishes the same energy levels that we saw earlier in Fig. 13.4, energy levels that were based on quantum mechanical calculations.

We can now understand why cyclooctatetraene is not aromatic. Cyclooctatetraene has a total of eight π electrons. Eight is not a Hückel number; it is a *4n number*, not a *4n + 2 number*. Using the polygon-and-circle method (Fig. 13.6), we find that cyclooctatetraene, if it were planar, *would not* have a closed shell of π electrons like benzene; it would have an unpaired electron in each of two nonbonding orbitals. Molecules with unpaired electrons (radicals) are *not* unusually stable; they are typically highly reactive and unstable. A planar form of cyclooctatetraene, therefore, should not be at all like benzene and should not be aromatic.

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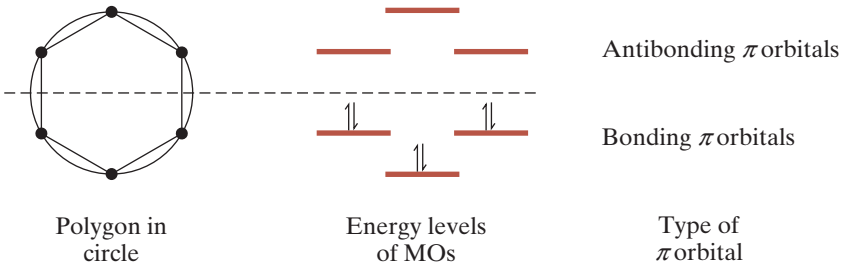


Figure 13.5 The polygon-and-circle method for deriving the relative energies of the π molecular orbitals of benzene. A horizontal line halfway up the circle divides the bonding orbitals from the antibonding orbitals. If an orbital falls on this line, it is a nonbonding orbital. This method was developed by C. A. Coulson (of Oxford University).

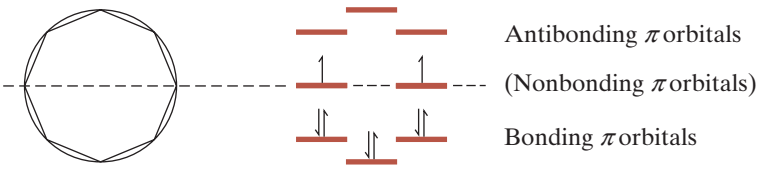
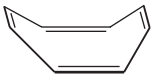


Figure 13.6 The π molecular orbitals that cyclooctatetraene would have if it were planar. Notice that, unlike benzene, this molecule is predicted to have two nonbonding orbitals, and because it has eight π electrons, it would have an unpaired electron in each of the two nonbonding orbitals. Such a system would not be expected to be aromatic.

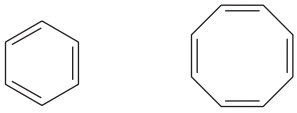
Because cyclooctatetraene does not gain stability by becoming planar, it assumes the tub shape shown below. The bonds of cyclooctatetraene are known to be alternately long and short; X-ray studies indicate that they are 1.48 and 1.34 Å, respectively.



13.7B The Annulenes

The word **annulene** is incorporated into the class name for monocyclic compounds that can be represented by structures having alternating single and double bonds. The ring size of an annulene is indicated by a number in brackets. Thus, benzene is [6]annulene and cyclooctatetraene is [8]annulene.

- Hückel's rule predicts that annulenes will be aromatic if their molecules have $4n + 2$ π electrons and have a planar carbon skeleton:



Benzene ([6]annulene) **Cyclooctatetraene ([8]annulene)**

Before 1960 the only annulenes that were available to test Hückel's predictions were benzene and cyclooctatetraene. During the 1960s, and largely as a result of research by F. Sondheimer, a number of large-ring annulenes were synthesized, and the predictions of Hückel's rule were verified.

Consider the [14], [16], [18], [20], [22], and [24]annulenes as examples. Of these, *as Hückel's rule predicts*, the [14], [18], and [22]annulenes ($4n + 2$ when $n = 3, 4, 5$, respectively) have been found to be aromatic. The [16]annulene and the [24]annulene are not aromatic; they are *antiaromatic* (see Section 13.7E). They are $4n$ compounds, not $4n + 2$ compounds:

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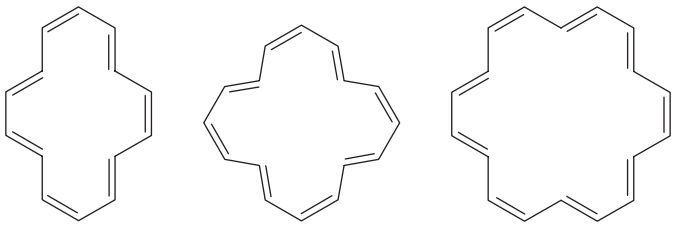
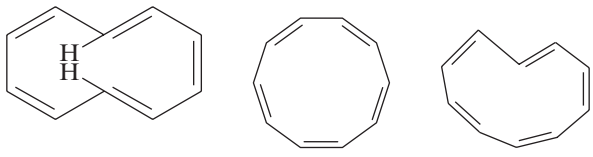


[14]Annulene (aromatic) **[16]Annulene (antiaromatic)** **[18]Annulene (aromatic)**

Examples of [10] and [12]annulenes have also been synthesized and none is aromatic. We would not expect [12]annulenes to be aromatic since they have 12 π electrons and do not obey Hückel's rule. The following [10]annulenes would be expected to be aromatic on the basis of electron count, but their rings are not planar.



I **II** **III**

[10]Annulenes
None is aromatic because none is planar.

The [10]annulene **I** has two trans double bonds. Its bond angles are approximately 120°; therefore, it has no appreciable angle strain. The carbon atoms of its ring, however, are prevented from becoming coplanar because the two hydrogen atoms in the center of the ring interfere with each other. Because the ring is not planar, the *p* orbitals of the carbon atoms are not parallel and, therefore, cannot overlap effectively around the ring to form the π molecular orbitals of an aromatic system.

The [10]annulene with all cis double bonds (**II**) would, if it was planar, have considerable angle strain because the internal bond angles would be 144°. Consequently, any stability this isomer gained by becoming planar in order to become aromatic would be more than offset by the destabilizing effect of the increased angle strain. A similar problem of a large angle strain associated with a planar form prevents molecules of the [10]annulene isomer with one trans double bond (**III**) from being aromatic.

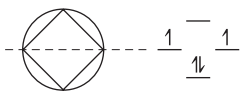
After many unsuccessful attempts over many years, in 1965 [4]annulene (or cyclobutadiene) was synthesized by R. Pettit and co-workers at the University of Texas, Austin. Cyclobutadiene is a $4n$ molecule, not a $4n + 2$ molecule, and, as we would expect, it is a highly unstable compound and *it is antiaromatic* (see Section 13.7D):



Cyclobutadiene or [4]annulene (antiaromatic)

Solved Problem 13.2

Using the polygon-and-circle method to outline the molecular orbitals of cyclobutadiene, explain why cyclobutadiene is not aromatic.



Antibonding MO
Nonbonding MOs
Bonding MO

Answer

We inscribe a square inside a circle with one corner at the bottom.

We see that cyclobutadiene, according to this model, would have an unpaired electron in each of its two nonbonding molecular orbitals. We would, therefore, not expect cyclobutadiene to be aromatic.

13.7C Aromatic Ions

In addition to the neutral molecules that we have discussed so far, there are a number of monocyclic species that bear either a positive or a negative charge. Some of these ions show unexpected stabilities that suggest that they are

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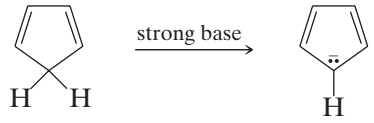
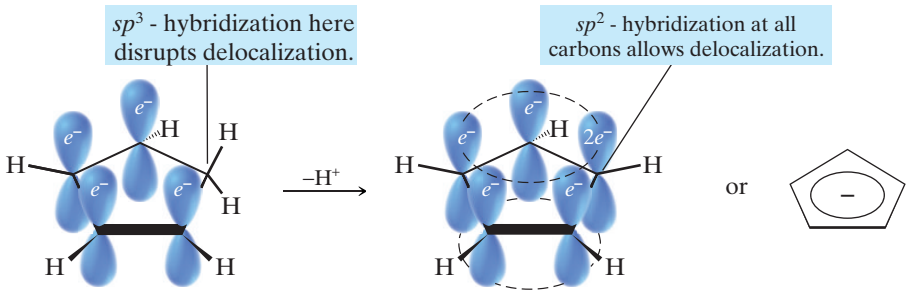
aromatic ions. Hückel's rule is helpful in accounting for the properties of these ions as well. We shall consider two examples: the cyclopentadienyl anion and the cycloheptatrienyl cation.

Cyclopentadiene is not aromatic; however, it is unusually acidic for a hydrocarbon. (The pK_a for cyclopentadiene is 16 and, by contrast, the pK_a for cycloheptatriene is 36.) Because of its acidity, cyclopentadiene can be converted to its anion by treatment with moderately strong bases. The cyclopentadienyl anion, moreover, is unusually stable, and NMR spectroscopy shows that all five hydrogen atoms in the cyclopentadienyl anion are equivalent and absorb downfield.



Cyclopentadiene **Cyclopentadienyl anion**

The orbital structure of cyclopentadiene (Fig. 13.7) shows why cyclopentadiene, itself, is not aromatic. Not only does it not have the proper number of π electrons, but the π electrons cannot be delocalized about the entire ring because of the intervening sp^3-hybridized —CH_2— group with no available *p* orbital.



Cyclopentadiene **Cyclopentadienyl anion**

Figure 13.7 Cyclopentadiene is not aromatic because it has only four π electrons and the sp^3-hybridized carbon prevents complete delocalization around the ring. Removal of a proton produces the cyclopentadienyl anion, which is aromatic because it has 6 π electrons and all of its carbon atoms have a *p* orbital.

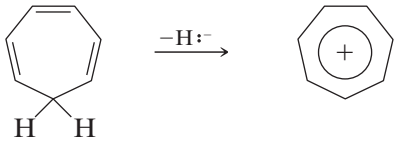
On the other hand, if the —CH_2— carbon atom becomes sp^2 hybridized after it loses a proton (Fig. 13.7), the two electrons left behind can occupy the new *p* orbital that is produced. Moreover, this new *p* orbital can overlap with the *p* orbitals on either side of it and give rise to a ring with *six* delocalized π electrons. Because the electrons are delocalized, all of the hydrogen atoms are equivalent, and this agrees with what NMR spectroscopy tells us.

Six, the number of π electrons in the cyclopentadienyl anion is, of course, a Hückel number ($4n + 2$, where $n = 1$).

- The cyclopentadienyl anion is, therefore, an **aromatic anion**, and the unusual acidity of cyclopentadiene is a result of the unusual stability of its anion.

Cycloheptatriene (Fig. 13.8) (a compound with the common name tropylidene) has six π electrons. However, the six π electrons of cycloheptatriene cannot be fully delocalized because of the presence of the —CH_2— group, a group that does not have an available *p* orbital (Fig. 13.8).

When cycloheptatriene is treated with a reagent that can abstract a hydride ion, it is converted to the cycloheptatrienyl (or tropylium) cation. The loss of a hydride ion from cycloheptatriene occurs with unexpected ease, and the cycloheptatrienyl cation is found to be unusually stable. The NMR spectrum of the cycloheptatrienyl cation indicates that all seven hydrogen atoms are equivalent. If we look closely at Fig. 13.8, we see how we can account for these observations.



Cycloheptatriene **Cycloheptatrienyl cation (tropylium cation)**

As a hydride ion is removed from the —CH_2— group of cycloheptatriene, a vacant *p* orbital is created, and the carbon atom becomes sp^2 hybridized. The cation that results has seven overlapping *p* orbitals containing *six* delocalized

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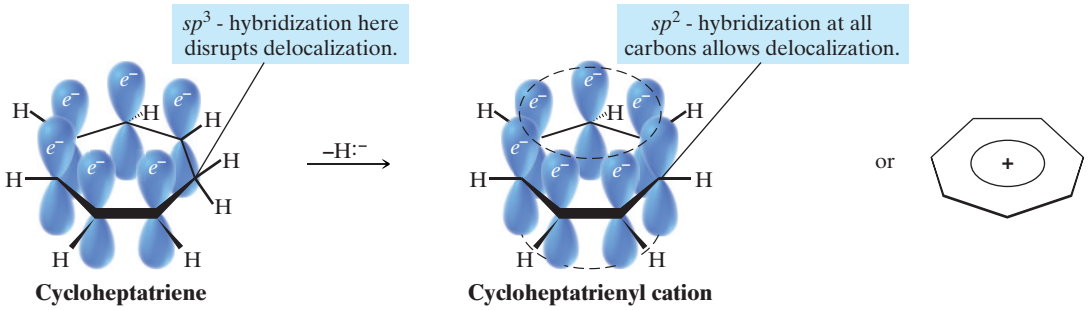


Figure 13.8 Cycloheptatriene is not aromatic, even though it has six π electrons, because it has an sp^3-hybridized carbon that prevents delocalization around the ring. Removal of a hydride ($H:^-$) produces the cycloheptatrienyl cation, which is aromatic because all of its carbon atoms now have a *p* orbital, and it still has 6 π electrons.

π electrons. The cycloheptatrienyl cation is, therefore, an aromatic cation, and all of its hydrogen atoms should be equivalent; again, this is exactly what we find experimentally.

13.7D Aromatic, Antiaromatic, and Nonaromatic Compounds

- An aromatic compound has its π electrons *delocalized* over the entire ring and it is *stabilized* by the π-electron delocalization.

As we have seen, a good way to determine whether the π electrons of a cyclic system are delocalized is through the use of NMR spectroscopy. It provides direct physical evidence of whether or not the π electrons are delocalized.

But what do we mean by saying that a compound is stabilized by π-electron delocalization? We have an idea of what this means from our comparison of the heat of hydrogenation of benzene and that calculated for the hypothetical 1,3,5-cyclohexatriene. We saw that benzene—in which the π electrons are delocalized—is much more stable than 1,3,5-cyclohexatriene (a model in which the π electrons are not delocalized). We call the energy difference between them the resonance energy (delocalization energy) or stabilization energy.

In order to make similar comparisons for other aromatic compounds, we need to choose proper models. But what should these models be?

One way to evaluate whether a cyclic compound is stabilized by delocalization of π electrons through its ring is to compare it with an open-chain compound having the same number of π electrons. This approach is particularly useful because it furnishes us with models not only for annulenes but for aromatic cations and anions, as well. (Corrections need to be made, of course, when the cyclic system is strained.)

To use this approach we do the following:

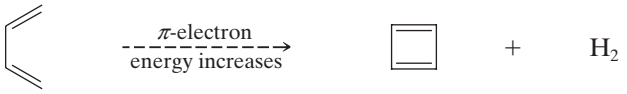
1. We take as our model a linear chain of sp^2-hybridized atoms having the same number of π electrons as our cyclic compound.
2. Then we imagine removing a hydrogen atom from each end of the chain and joining the ends to form a ring.

- If, based on sound calculations or experiments, the ring has *lower* π-electron energy, then the ring is aromatic.
- If the ring and the chain have the *same* π-electron energy, then the ring is nonaromatic.
- If the ring has *greater* π-electron energy than the open chain, then the ring is **antiaromatic**.

The actual calculations and experiments used in determining π-electron energies are beyond our scope, but we can study four examples that illustrate how this approach has been used.

Cyclobutadiene

For cyclobutadiene we consider the change in π-electron energy for the following *hypothetical* transformation:



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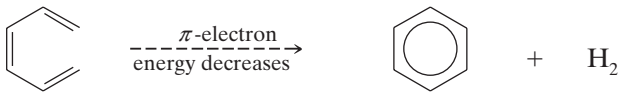
Calculations indicate and experiments appear to confirm that the π-electron energy of cyclobutadiene is higher than that of its open-chain counterpart. Thus cyclobutadiene is classified as antiaromatic.

Benzene

Here our comparison is based on the following hypothetical transformation:



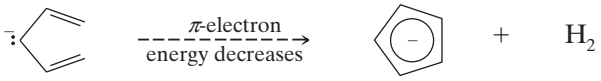
1,3,5-Hexatriene
6 π electrons

Benzene
6 π electrons (aromatic)

Calculations indicate and experiments confirm that benzene has a much lower π-electron energy than 1,3,5-hexatriene. Benzene is classified as being aromatic on the basis of this comparison as well.

Cyclopentadienyl Anion

Here we use a linear anion for our hypothetical transformation:



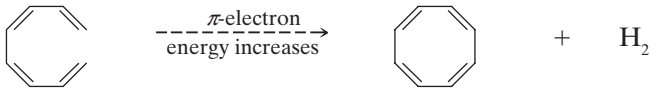
6 π electrons

Cyclopentadienyl anion
6 π electrons (aromatic)

Both calculations and experiments confirm that the cyclic anion has a lower π-electron energy than its open-chain counterpart. Therefore the cyclopentadienyl anion is classified as aromatic.

Cyclooctatetraene

For cyclooctatetraene we consider the following hypothetical transformation:



8 π electrons

Hypothetical planar cyclooctatetraene
8 π electrons (antiaromatic)

Here calculations and experiments indicate that a planar cyclooctatetraene would have higher π-electron energy than the open-chain octatetraene. Therefore, a planar form of cyclooctatetraene would, if it existed, be *antiaromatic*. As we saw earlier, cyclooctatetraene is not planar and behaves like a simple cyclic polyene.

13.8 | OTHER AROMATIC COMPOUNDS

13.8A Benzenoid Aromatic Compounds

In addition to those that we have seen so far, there are many other examples of aromatic compounds. Representatives of one broad class of **benzenoid aromatic compounds**, called **polycyclic aromatic hydrocarbons (PAH)**, are illustrated in Fig. 13.9.

- Benzenoid polycyclic **aromatic** hydrocarbons consist of molecules having two or more benzene rings *fused* together.

A close look at one example, naphthalene, will illustrate what we mean by this.

According to resonance theory, a molecule of naphthalene can be considered to be a hybrid of three Kekulé structures. One of these Kekulé structures, the most important one, is shown in Fig. 13.10. There are two carbon atoms in naphthalene (C4a and C8a) that are common to both rings. These two atoms are said to be at the points of *ring fusion*. They direct all of their bonds toward other carbon atoms and do not bear hydrogen atoms.

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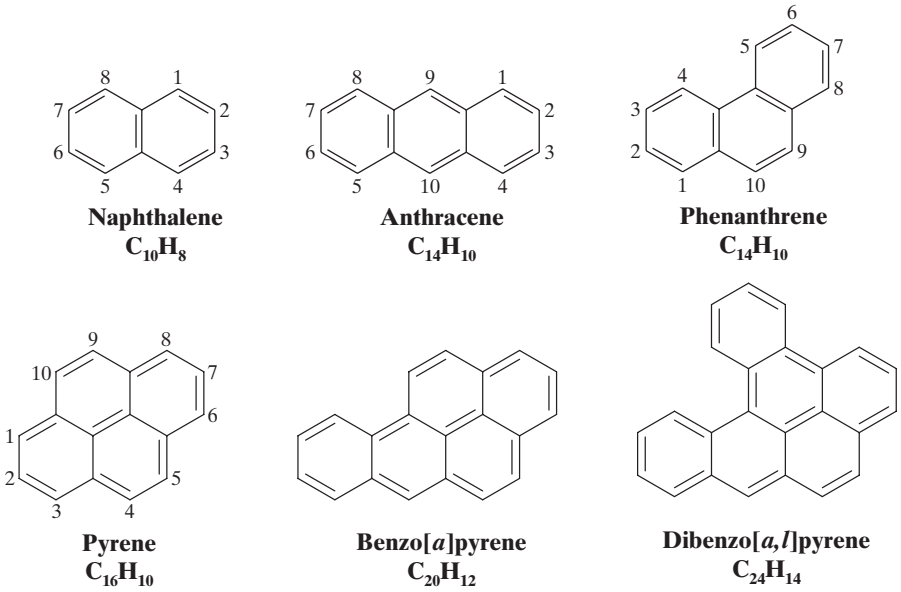

Figure 13.9 Benzenoid aromatic hydrocarbons. Some polycyclic aromatic hydrocarbons (PAHs), such as dibenzo[*a*,*l*]pyrene, are carcinogenic. (See "Important, but hidden, epoxides" at the end of Chapter 11.)

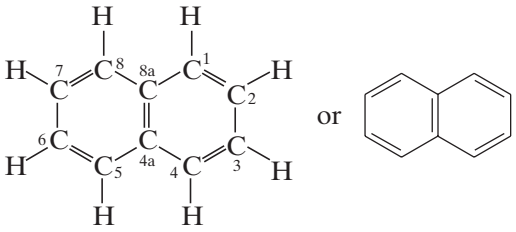

Figure 13.10 One Kekulé structure for naphthalene.

Molecular orbital calculations for naphthalene begin with the model shown in Fig. 13.11. The *p* orbitals overlap around the periphery of both rings and across the points of ring fusion.

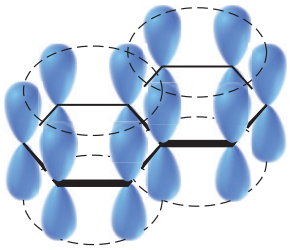

Figure 13.11 The stylized *p* orbitals of naphthalene.

When molecular orbital calculations are carried out for naphthalene using the model shown in Fig. 13.11, the results of the calculations correlate well with our experimental knowledge of naphthalene. The calculations indicate that delocalization of the 10 π electrons over the two rings produces a structure with considerably lower energy than that calculated for any individual Kekulé structure. Naphthalene, consequently, has a substantial resonance energy. Based on what we know about benzene, moreover, naphthalene's tendency to react by substitution rather than addition and to show other properties associated with aromatic compounds is understandable.

Anthracene and phenanthrene (Fig. 13.9) are isomers. In anthracene the three rings are fused in a linear way, and in phenanthrene they are fused so as to produce an angular molecule. Both of these molecules also show large resonance energies and chemical properties typical of aromatic compounds.

Pyrene (Fig. 13.12) is also aromatic. Pyrene itself has been known for a long time; a pyrene derivative, however, has been the object of research that shows another interesting application of Hückel's rule.

To understand this particular research, we need to pay special attention to the Kekulé structure for pyrene (Fig. 13.12). The total number of π electrons in pyrene is 16 (8 double bonds = 16 π electrons). Sixteen is a non-Hückel number, but **Hückel's rule is intended to be applied only to monocyclic compounds** and pyrene is clearly tetracyclic. If we disregard the internal double bond of pyrene, however, and look only at the periphery, we see that the periphery

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is a planar ring with 14 π electrons. The periphery is, in fact, very much like that of [14]annulene. Fourteen *is* a Hückel number ($4n + 2$, where $n = 3$), and one might then predict that the periphery of pyrene would be aromatic by itself, in the absence of the internal double bond.

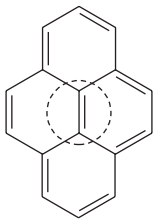
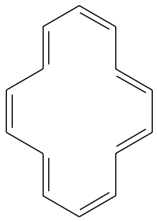
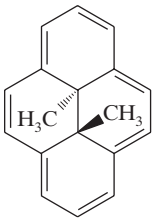


Figure 13.12 One Kekulé structure for pyrene. The internal double bond is enclosed in a dotted circle for emphasis.



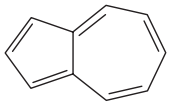
[14]Annulene



***trans*-15,16-Dimethyldihydropyrene**

This prediction was confirmed when V. Boekelheide (University of Oregon) synthesized *trans*-15,16-dimethyldihydropyrene and showed that it is aromatic.

13.8B Nonbenzenoid Aromatic Compounds



Azulene

Naphthalene, phenanthrene, and anthracene are examples of *benzenoid* aromatic compounds. On the other hand, the cyclopentadienyl anion, the cycloheptatrienyl cation, *trans*-15,16-dimethyldihydropyrene, and the aromatic annulenes (except for [6]annulene) are classified as **nonbenzenoid aromatic compounds**.

Another example of a *nonbenzenoid* aromatic hydrocarbon is the compound azulene. Azulene has a resonance energy of 205 kJ mol^{-1}. Factors related to aromaticity account for this property of azulene (see Practice Problem 13.4).

Practice Problem 13.4

Azulene has an appreciable dipole moment. Write resonance structures for azulene that explain this dipole moment and that help explain its aromaticity.

13.9 | HETEROCYCLIC AROMATIC COMPOUNDS

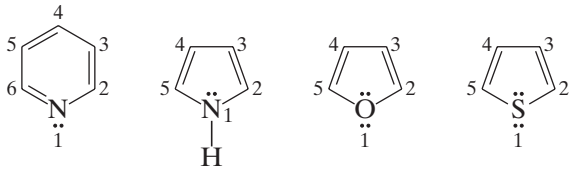
Almost all of the cyclic molecules that we have discussed so far have had rings composed solely of carbon atoms. However, in many cyclic compounds an element other than carbon is present in the ring.

- Cyclic compounds that include an element other than carbon are called **heterocyclic compounds**.

Heterocyclic molecules are quite commonly encountered in nature. For this reason, and because some of these molecules are aromatic, we shall now describe a few examples of **heterocyclic aromatic compounds**.

Heterocyclic compounds containing nitrogen, oxygen, or sulfur are by far the most common. Four important examples are given here in their Kekulé forms. *These four compounds are all aromatic:*

- Pyridine is electronically related to benzene.
- Pyrrole, furan, and thiophene are related to the cyclopentadienyl anion.



Pyridine **Pyrrole** **Furan** **Thiophene**

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The nitrogen atoms in molecules of both pyridine and pyrrole are sp^2 hybridized. In pyridine (Fig. 13.13) the sp^2-hybridized nitrogen donates one bonding electron to the π system. This electron, together with one from each of the five carbon atoms, gives pyridine a sextet of electrons like benzene. The two unshared electrons of the nitrogen of pyridine are in an sp^2 orbital that lies in the same plane as the atoms of the ring. This sp^2 orbital does not overlap with the p orbitals of the ring (it is, therefore, said to be *orthogonal* to the p orbitals). The unshared pair on nitrogen is not a part of the π system, and these electrons confer on pyridine the properties of a weak base.

In pyrrole (Fig. 13.14) the electrons are arranged differently. Because only four π electrons are contributed by the carbon atoms of the pyrrole ring, the sp^2-hybridized nitrogen must contribute two electrons to give an aromatic sextet. Because these electrons are a part of the aromatic sextet, they are not available for donation to a proton. Thus, in aqueous solution, pyrrole is not appreciably basic.

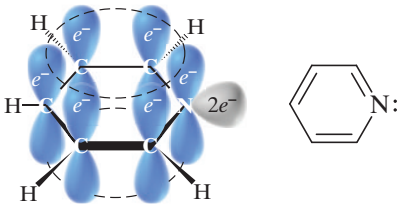


Figure 13.13 Pyridine is aromatic and weakly basic. Its nitrogen atom has an unshared electron pair in an sp^2 orbital (shown in gray) that is not part of the aromatic system.

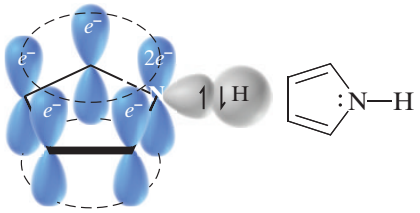
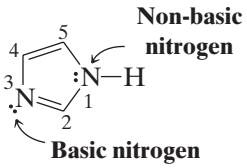


Figure 13.14 Pyrrole is aromatic but not basic. It does not have any unshared electron pairs. The electron pair on nitrogen is part of the aromatic system.

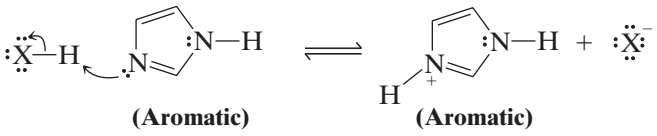
Solved Problem 13.3

Imidazole (at right) has two nitrogens. N3 is relatively basic (like the nitrogen of pyridine). N1 is relatively non-basic (like the nitrogen of pyrrole). Explain the different basicities of these two nitrogens.

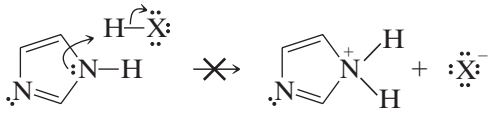


Answer

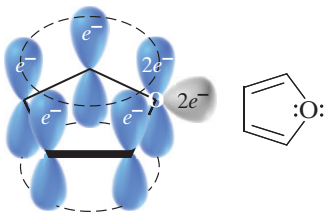
When imidazole accepts a proton at N3 the electron pair that accepts the proton is not a part of the π system of six electrons that makes imidazole aromatic. Consequently, the conjugate base that is formed is still aromatic (it is an aromatic cation) and retains its resonance energy of stabilization.



On the other hand, if imidazole were to accept a proton at N1 the resulting ion (which is not formed) would **not** be aromatic and would have much greater potential energy (its resonance stabilization would be lost). Hence, N1 is not appreciably basic.



Furan and thiophene are structurally quite similar to pyrrole. The oxygen atom in furan and the sulfur atom in thiophene are sp^2 hybridized. In both compounds the p orbital of the heteroatom donates two electrons to the π system. The oxygen and sulfur atoms of furan and thiophene carry an unshared pair of electrons in an sp^2 orbital (Fig. 13.15) that is orthogonal to the π system.



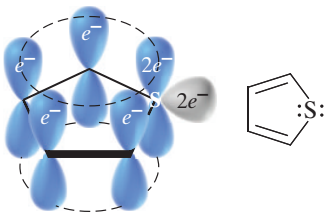


Figure 13.15 Furan and thiophene are aromatic. In each case, the heteroatom provides a pair of electrons to the aromatic system, but each also has an unshared electron pair in an sp^2 orbital that is not part of the aromatic system.

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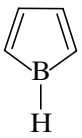
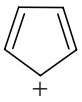
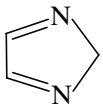
Solved Problem 13.4

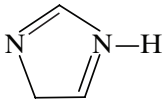
Designate whether each of the following compounds is aromatic, non-aromatic or anti-aromatic.

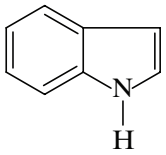
(a) 

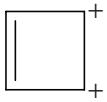
(b) 

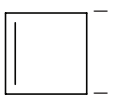
(c) 

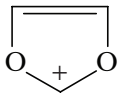
(d) 

(e) 

(f) 

(g) 

(h) 

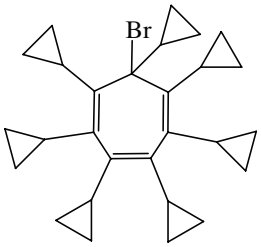
(i) 

Answer

(a) Anti-aromatic ($4\pi e$).
(b) Aromatic ($6\pi e$).
(c) Anti-aromatic ($4\pi e$).
(d) The compound is non-aromatic.
(e) The compound is aromatic.
(f) Aromatic ($10\pi e$).
(g) Aromatic ($2\pi e$).
(h) Aromatic ($6\pi e$).
(i) Aromatic ($6\pi e$).

Solved Problem 13.5

In the given compound, will Br ionize in the form of **(a)** Br^- or **(b)** Br^+.

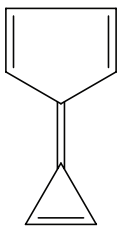


Answer

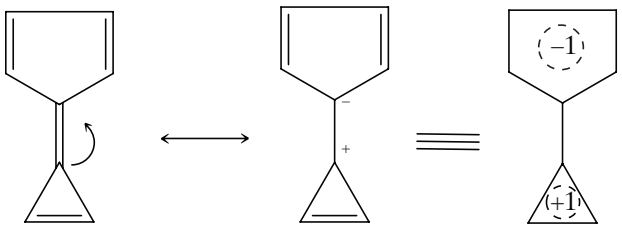
In this compound, Br will ionize in the form of Br^- so as to attain aromatic character for the molecule.

Solved Problem 13.6

The given compound has high dipole moment. Explain.



Answer



It is apparent that the given compound tends to acquire a resonance stabilized dipolar structure to gain aromaticity in each and so would have high dipole moment.

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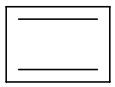
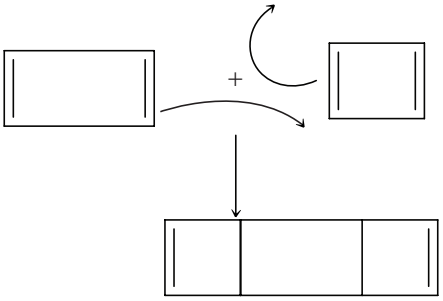
Solved Problem 13.7

Explain why the given compound undergoes dimerization at room temperature and readily reacts with active metals.

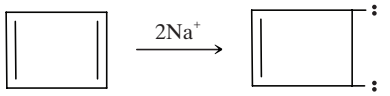


Answer

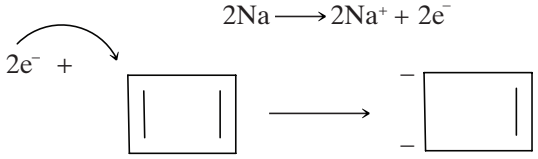
The given compound dimerizes as follows:



Here, the substrate is anti-aromatic and therefore unstable. It readily undergoes dimerization to give a product which is non-aromatic. It reacts with an active metal as follows:



The mechanism of the above reaction is believed to proceed as follows:

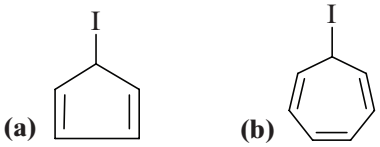


$6\pi e$, cyclic and planar system, (aromatic)

Obviously, the reaction with an a active metal converts the unstable anti-aromatic substrate into a stable aromatic system and proceeds readily.

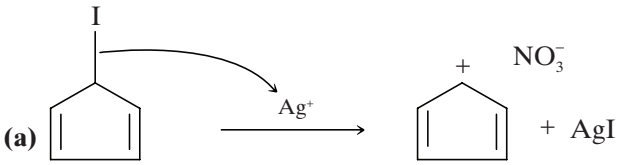
Solved Problem 13.8

Compare the rate of reaction of the following compounds with $AgNO_3$.



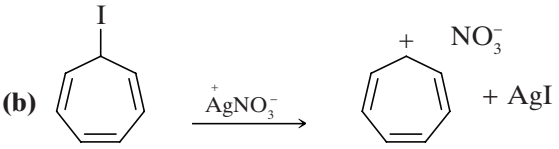
Answer

More the stability of the resultant carbocation, greater will be the rate of reaction.



Anti-aromatic system

The carbocation is an anti-aromatic system, so the rate of reaction is slow.

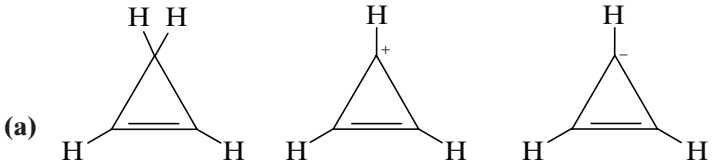


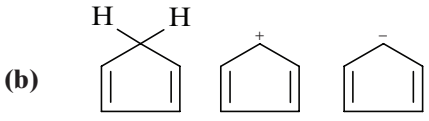
Aromatic system

The carbocation in this case is stable aromatic system and so the reaction proceeds faster.

Solved Problem 13.9

Classify each as aromatic, anti-aromatic and non-aromatic compound.





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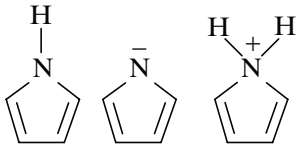
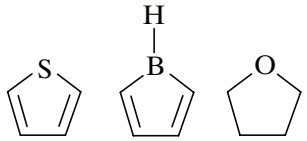
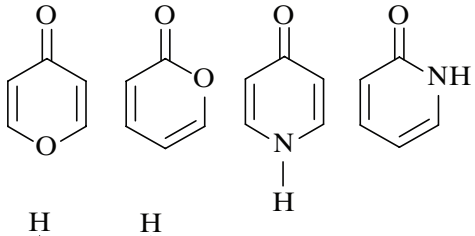
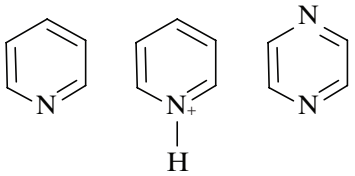
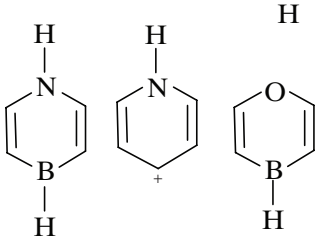
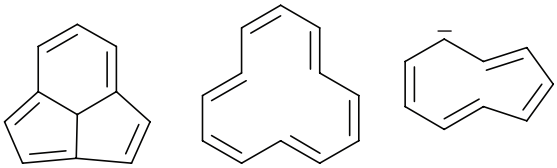
(c) 

(d) 

(e) 

(f) 

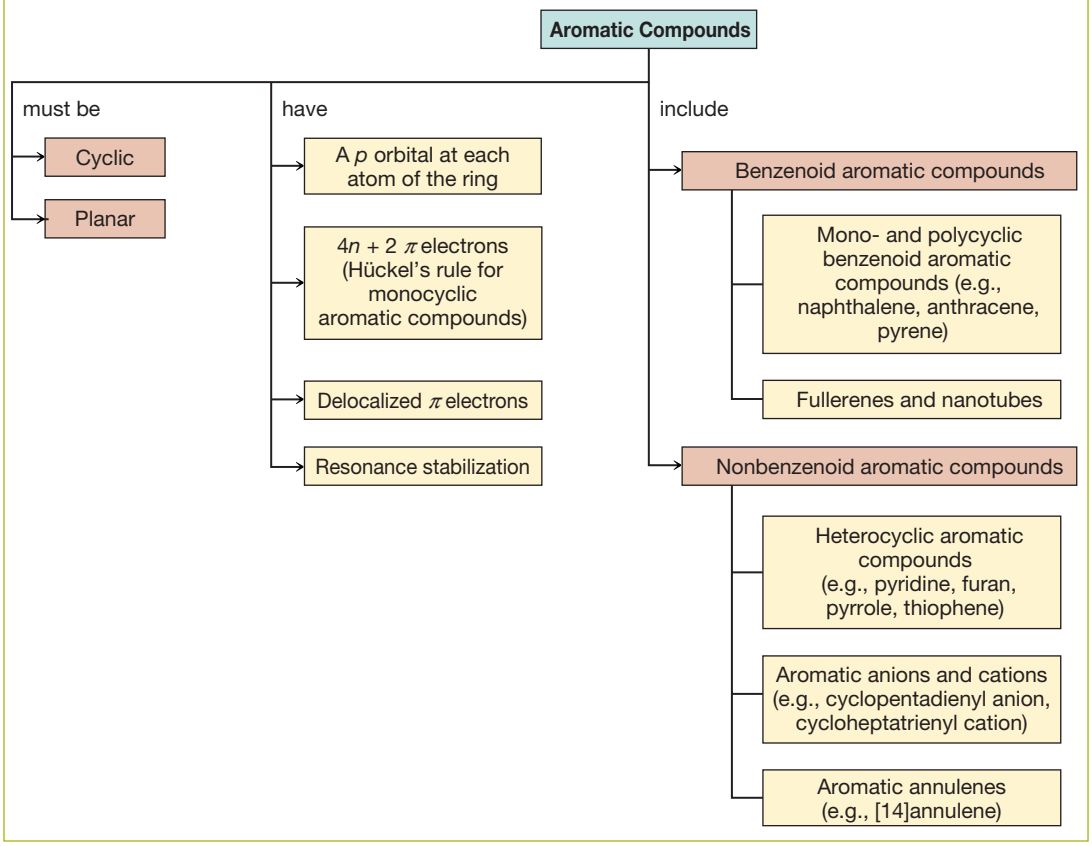
(g) 

(h) 

Answer

(a) Non-aromatic; Aromatic ($2\pi e$); Anti-aromatic ($4\pi e$).
(b) Non-aromatic; Anti-aromatic ($4\pi e$); Aromatic ($6\pi e$).
(c) Aromatic ($6\pi e$); Aromatic ($6\pi e$); Non-aromatic.
(d) Aromatic ($6\pi e$); Aromatic ($6\pi e$); Non-aromatic.
(e) All are aromatic.
(f) All are aromatic.
(g) All are aromatic.
(h) Aromatic ($10\pi e$); Anti-aromatic ($12\pi e$); Anti-aromatic ($10\pi e$).

CONCEPT MAP



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REVIEW PROBLEMS

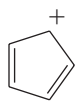
Nomenclature

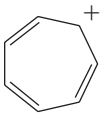
13.5 Write structural formulas for each of the following:
- **(a)** 3-Nitrobenzoic acid
- **(b)** *p*-Bromotoluene
- **(c)** *o*-Dibromobenzene
- **(d)** *m*-Dinitrobenzene
- **(e)** 3,5-Dinitrophenol
- **(f)** *p*-Nitrobenzoic acid
- **(g)** 3-Chloro-1-ethoxybenzene
- **(h)** *p*-Chlorobenzenesulfonic acid
- **(i)** Methyl *p*-toluenesulfonate
- **(j)** Benzyl bromide
- **(k)** *p*-Nitroaniline
- **(l)** *o*-Xylene
- **(m)** *tert*-Butylbenzene
- **(n)** *p*-Methylphenol
- **(o)** *p*-Bromoacetophenone
- **(p)** 3-Phenylcyclohexanol
- **(q)** 2-Methyl-3-phenyl-1-butanol
- **(r)** *o*-Chloroanisole

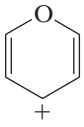
13.6 Write structural formulas and give acceptable names for all representatives of the following:
- **(a)** Tribromobenzenes
- **(b)** Dichlorophenols
- **(c)** Nitroanilines
- **(d)** Methylbenzenesulfonic acids
- **(e)** Isomers of C_6H_5—C_4H_9

Aromaticity

13.7 Which of the following molecules would you expect to be aromatic?

(a) 

(b) 

(c) 

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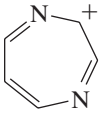
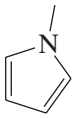
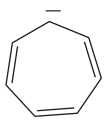
(e) 

(f) 

(g) 

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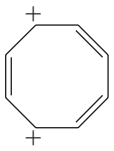
(i) 

(j) 

(k) 

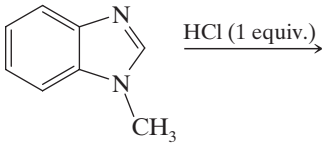
(l) 

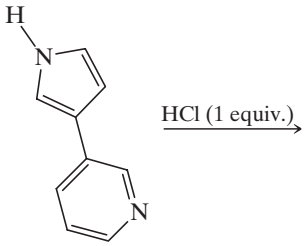
13.8 Use the polygon-and-circle method to draw an orbital diagram for each of the following compounds.

(a) 

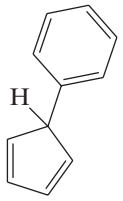
(b) 

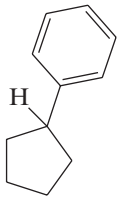
13.9 Write the structure of the product formed when each of the following compounds reacts with one molar equivalent of HCl.

(a) 

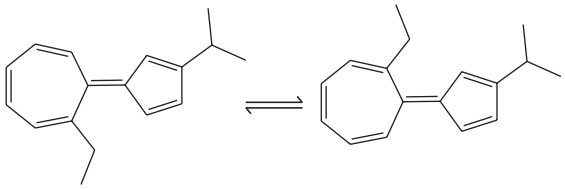
(b) 

13.10 Which of the hydrogen atoms shown below is more acidic? Explain your answer.

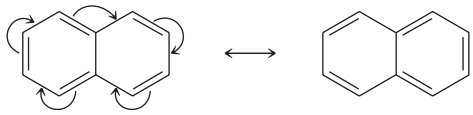
(a) 

(b) 

13.11 The rings below are joined by a double bond that undergoes cis–trans isomerization much more readily than the bond of a typical alkene. Provide an explanation.



13.12 Although Hückel's rule (Section 13.7) strictly applies only to monocyclic compounds, it does appear to have application to certain bicyclic compounds, if one assumes use of resonance structures involving only the perimeter double bonds, as shown with one resonance contributor for naphthalene below.



Both naphthalene (Section 13.8A) and azulene (Section 13.8B) have 10 π electrons and are aromatic. Pentalene (below) is apparently antiaromatic and is unstable even at –100 °C. Heptalene has been made but it adds bromine, it reacts with acids, and it is not planar. Is Hückel's rule applicable to these compounds? If so, explain their lack of aromaticity.

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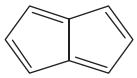
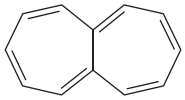
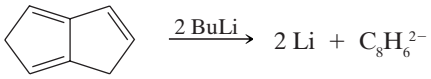


Pentalene



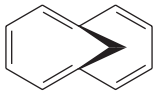
Heptalene

13.13 In 1964 Katz also showed that removing two protons from the compound below (using butyllithium as the base) leads to the formation of a stable dianion with the formula $C_8H_6^{2-}$ (as the dilithium salt).



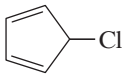
Propose a reasonable structure for the product and explain why it is stable.

13.14 Although none of the [10]annulenes given in Section 13.7B is aromatic, the following 10 π-electron system is aromatic:



What factor makes this possible?

13.15 5-Chloro-1,3-cyclopentadiene (below) undergoes S_N1 solvolysis in the presence of silver ion extremely slowly even though the chlorine is doubly allylic and allylic halides normally ionize readily (Section 14.15). Provide an explanation for this behavior.



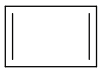
13.16 Explain the following: **(a)** Cyclononatetraenyl anion is planar (in spite of the angle strain involved) and appears to be aromatic. **(b)** Although [16]annulene is not aromatic, it adds two electrons readily to form an aromatic dianion.

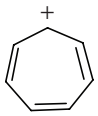
13.17 Furan possesses less aromatic character than benzene as measured by their resonance energies (96 kJ mol^{-1} for furan; 151 kJ mol^{-1} for benzene). What reaction have we studied earlier that shows that furan is less aromatic than benzene and can react in a way characteristic of some dienes?

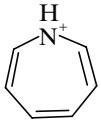
ADDITIONAL OBJECTIVE QUESTIONS

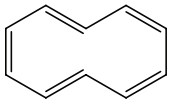
Single Correct Choice Type

1. Which of the following compounds is likely to adopt a planar conformation?

(a) 

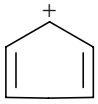
(b) 

(c) 

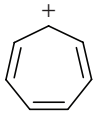
(d) 

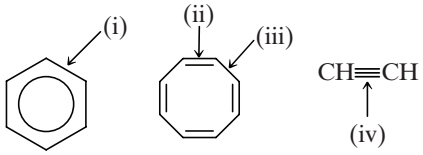
2. Find out the aromatic compound.

(a) 

(b) 

(c) 

(d) 

3. 

Correct order of bond length will be

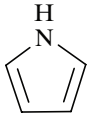
(a) (iii) > (i) > (ii) > (iv) **(b)** (iii) > (ii) > (i) > (iv)

(c) (i) > (iii) > (ii) > (iv) **(d)** (iii) < (i) < (ii) < (iv)

4. Which of the following compounds is not aromatic?

(a) 

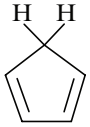
(b) 

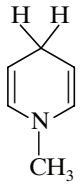
(c) 

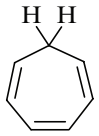
(d) 

5. Consider the highlighted protons. Which compound is predicted to have the lowest p*K*a?

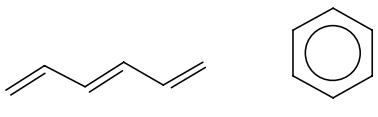
(a) 

(b) 

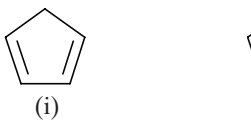
(c) 

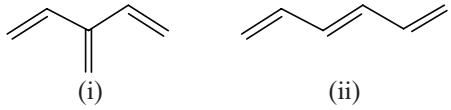
(d) 

6. In which of the following pair first compound has more resonance energy than second?

(a) 
(i) (ii)

(b) 
(i) (ii)

(c) 
(i) (ii)

(d) 
(i) (ii)

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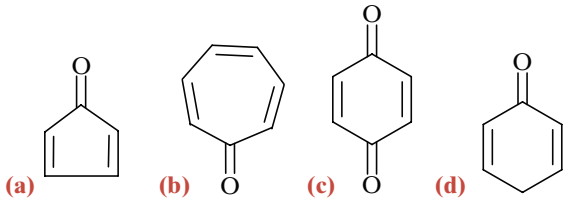
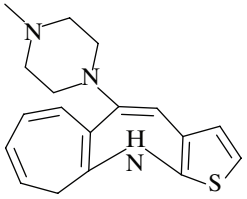
7. Which of the following compound is non-aromatic?



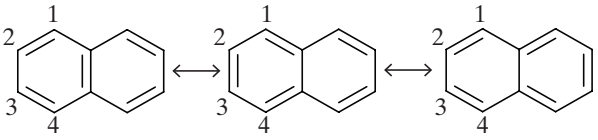
(a) **(b)** **(c)** **(d)**

8. This anti-psychotic drug is non-planar to avoid being



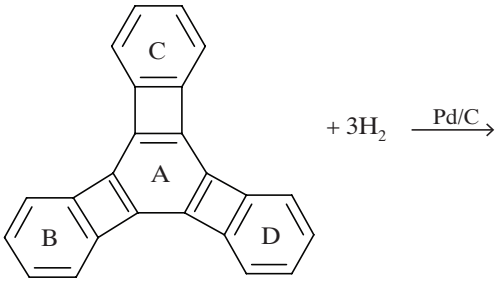
(a) resonance stabilized. **(b)** anti-aromatic.
(c) aromatic. **(d)** conjugated.

9. These are three canonical structures of naphthalene. Examine them and find correct statement among the following:



(a) All C—C bonds are of same length.
(b) C1—C2 bond is shorter than C2—C3 bond.
(c) C1—C2 bond is longer than C2—C3 bond
(d) None of these.

10. Consider the given reaction:



In this reaction which one of the given ring will undergo reduction?

(a) C **(b)** D **(c)** A **(d)** B

Linked Comprehension Type

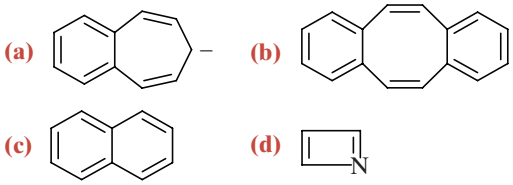
Paragraph for Questions 1 to 3

We have now learned that benzene is unusually stable, and that this stability seems to be correlated with the overlap of its carbon 2*p* orbitals to form π molecular orbitals. In 1931, Erich Huckel (1896–1980), a German chemist physicist, elucidated with molecular orbital arguments the criteria for this sort of stability, which has come to be called aromaticity.

Criteria for aromaticity:

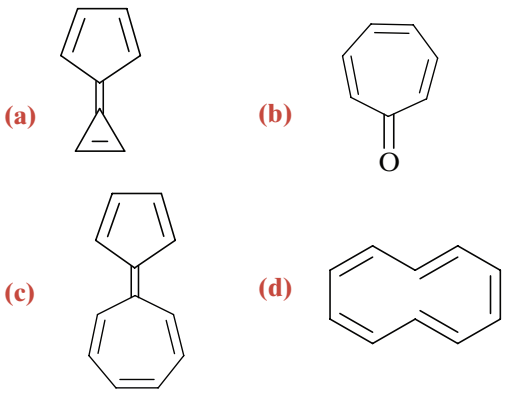
- Aromatic compounds contain one or more rings that have a cyclic arrangement of *p*-orbitals. Thus, aromaticity is a property of certain cyclic compounds.
- Every atom of an aromatic ring has a *p*-orbital.
- Aromatic rings are planar.
- The cyclic arrangements of *p*-orbitals in an aromatic compound must contain $4n + 2\pi$ electrons, where *n* is any positive integer (0, 1, 2, …). In other words, an aromatic ring must contain 2, 6, 10 π electrons.

1. Which of the following compound is not anti-aromatic?



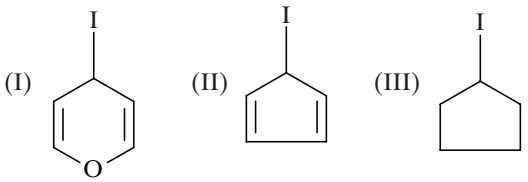
(a) **(b)** **(c)** **(d)**

2. Which of the following compound is non-aromatic?



(a) **(b)** **(c)** **(d)**

3. Compare the rate of reaction of the following with $AgNO_3$.



(I) (II) (III)

(a) I > II > III **(b)** I > III > II
(c) II > III > I **(d)** II > I > III

Integer Type

1. How many π electrons are present in $C_5H_5^-$?

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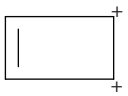
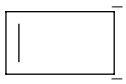
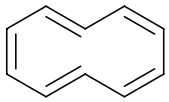
Matrix Match Type

1.

Column I	Column II	Column III
(a) 	**(p)** Aromatic	**(w)** $(4n + 2)\pi$ electron. $n = 0, 1, 2, 3$
(b) 	**(q)** Non-aromatic	**(x)** $4n$ π electron $n = 1, 2, 3$
(c) 	**(r)** Anti-aromatic	**(y)** Non-planar compound
(d) 	**(s)** Planar compound	**(z)** Readily reacts with active metal

ANSWER KEY

Single Correct Choice Type

1. (b) **2.** (d) **3.** (a) **4.** (d)
5. (b) **6.** (c) **7.** (d) **8.** (b)
9. (b) **10.** (c)

Linked Comprehension Type

1. (c) **2.** (d) **3.** (b)

Integer Type

1. (6)

Matrix Match Type

1. a → (p, s, w); b → (p, s, w); c → (q, x, y, z); d → (q, w, y)

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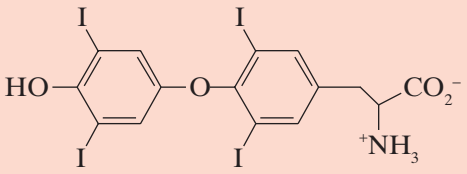
14

Reactions of Aromatic Compounds



Thyroxine
(A thyroid hormone)

Contents

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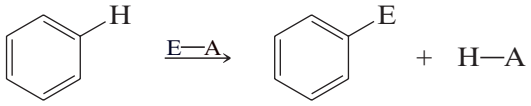
14.2 | A General Mechanism for Electrophilic Aromatic Substitution
14.3 | Halogenation of Benzene
14.4 | Nitration of Benzene
14.5 | Sulfonation of Benzene
14.6 | Friedel–Crafts Alkylation
14.7 | Friedel–Crafts Acylation
14.8 | Limitations of Friedel–Crafts Reactions
14.9 | Synthetic Applications of Friedel–Crafts Acylations: The Clemmensen and Wolff–Kishner Reductions
14.10 | Substituents Can Affect Both the Reactivity of the Ring and the Orientation of the Incoming Group
14.11 | How Substituents Affect Electrophilic Aromatic Substitution: A Closer Look
14.12 | Reactions of the Side Chain of Alkylbenzenes
14.13 | Alkenylbenzenes
14.14 | Synthetic Applications
14.15 | Allylic and Benzylic Halides in Nucleophilic Substitution Reactions
14.16 | Reduction of Aromatic Compounds

14.1 | ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS

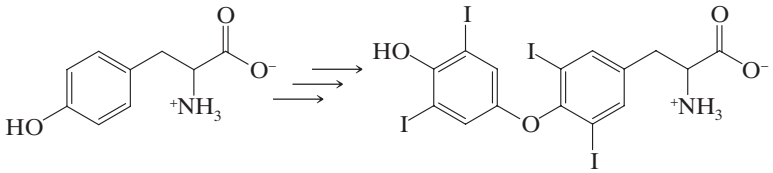
Some of the most important reactions of aromatic compounds are those in which an electrophile replaces one of the hydrogen atoms of the ring.



(E—A is an electrophilic reactant)

These reactions, called **electrophilic aromatic substitutions (EAS)**, allow the direct introduction of groups onto aromatic rings such as benzene, and they provide synthetic routes to many important compounds. Figure 14.1 outlines five different types of electrophilic aromatic substitutions that we will study in this chapter, including carbon–carbon bond-forming reactions and halogenations.

A noteworthy example of electrophilic aromatic substitution in nature, as mentioned in the introduction, is biosynthesis of the thyroid hormone thyroxine, where iodine is incorporated into benzene rings that are derived from tyrosine.



Tyrosine
(a dietary amino acid)

Thyroxine
(a thyroid hormone)

In the next section we shall learn the general mechanism for the way an electrophile reacts with a benzene ring. Then, in Sections 14.3–14.7, we shall see specific examples of electrophiles and how each is formed in a reaction mixture.

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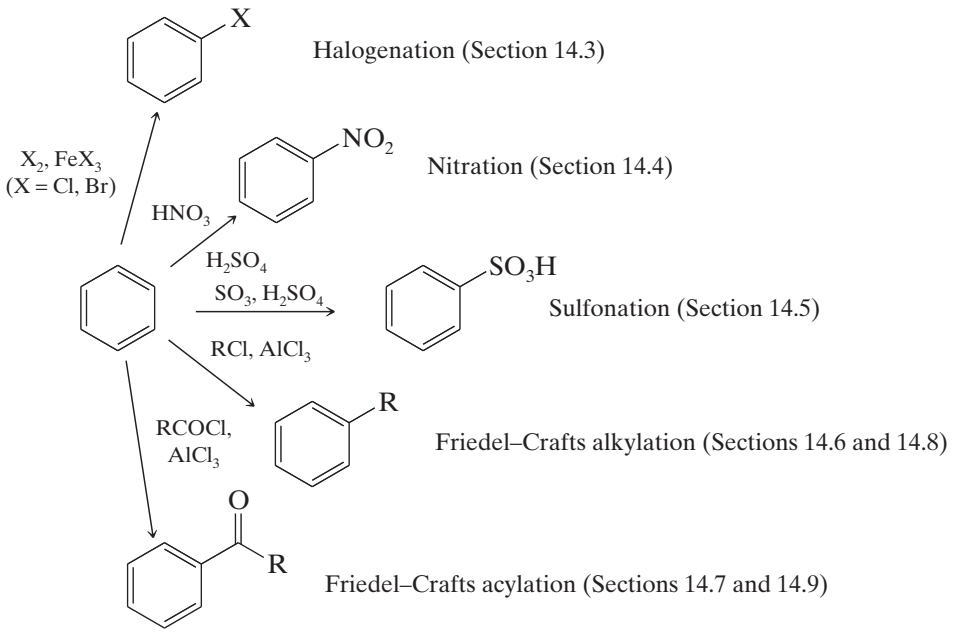
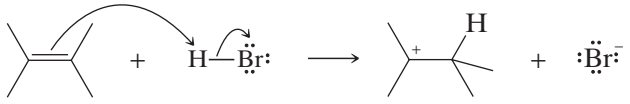


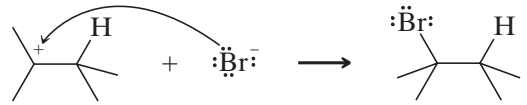
Figure 14.1 Electrophilic aromatic substitution reactions.

14.2 | A GENERAL MECHANISM FOR ELECTROPHILIC AROMATIC SUBSTITUTION

The π electrons of benzene react with strong electrophiles. In this respect, benzene has something in common with alkenes. When an alkene reacts with an electrophile, as in the addition of HBr (Section 8.2), electrons from the alkene π bond react with the electrophile, leading to a carbocation intermediate.



The carbocation formed from the alkene then reacts with the nucleophilic bromide ion to form the addition product.



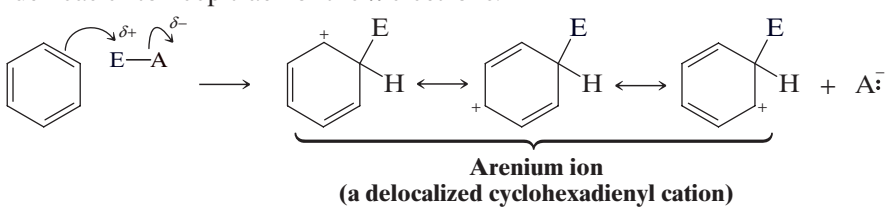
The similarity of benzene reactivity with that of an alkene ends, however, at the carbocation stage, prior to nucleophilic attack. As we saw in Chapter 12, benzene's closed shell of six π electrons give it special stability.

- Although benzene is susceptible to electrophilic attack, it undergoes *substitution reactions* rather than *addition reactions*.

Substitution reactions allow the aromatic sextet of π electrons in benzene to be regenerated after attack by the electrophile. We can see how this happens if we examine a general mechanism for **electrophilic aromatic substitution**.

Experimental evidence indicates that electrophiles attack the π system of benzene to form a ***nonaromatic cyclohexadienyl carbocation*** known as an **arenium ion**. In showing this step, it is convenient to use Kekulé structures, because these make it much easier to keep track of the π electrons:

Step 1



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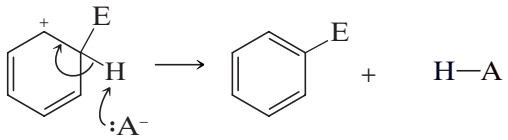
- In step 1 the electrophile takes two electrons of the six-electron π system to form a σ bond to one carbon atom of the benzene ring.

Formation of this bond interrupts the cyclic system of π electrons, because in the formation of the arenium ion the carbon that forms a bond to the electrophile becomes sp^3 hybridized and, therefore, no longer has an available p orbital. Now only five carbon atoms of the ring are sp^2 hybridized and still have p orbitals. The four π electrons of the arenium ion are delocalized through these five p orbitals.

- In step 2 a proton is removed from the carbon atom of the arenium ion that bears the electrophile, restoring aromaticity to the ring.

Step 2



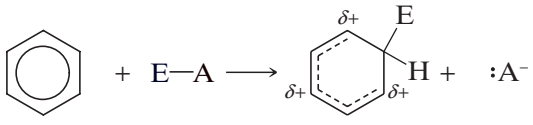
The two electrons that bonded the proton to the ring become a part of the π system. The carbon atom that bears the electrophile becomes sp^2 hybridized again, and a benzene derivative with six fully delocalized π electrons is formed. The proton is removed by any of the bases present, for example, by the anion derived from the electrophile.

Practice Problem 14.1

Show how loss of a proton can be represented using each of the three resonance structures for the arenium ion and show how each representation leads to the formation of a benzene ring with three alternating double bonds (i.e., six fully delocalized π electrons).

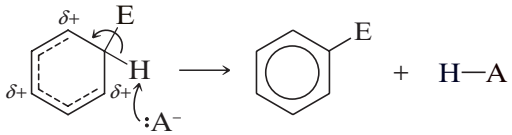
Kekulé structures are more appropriate for writing mechanisms such as electrophilic aromatic substitution because they permit the use of resonance theory, which, as we shall soon see, is invaluable as an aid to our understanding. If, for brevity, however, we wish to show the mechanism using the hybrid formula for benzene we can do it in the following way. We draw the arenium ion as a delocalized cyclohexadienyl cation:

Step 1



Arenium ion

Step 2

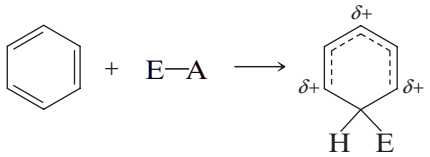


There is firm experimental evidence that the arenium ion is a true *intermediate* in electrophilic substitution reactions. It is not a transition state. This means that in a free-energy diagram (Fig. 14.2) the arenium ion lies in an energy valley between two transition states.

The free energy of activation for step 1, $\Delta G^{\ddagger}_{(1)}$, has been shown to be much greater than the free energy of activation for step 2, $\Delta G^{\ddagger}_{(2)}$, as depicted in Figure 14.2. This is consistent with what we would expect. The reaction leading from benzene and an electrophile to the arenium ion is highly endothermic, because the aromatic stability of the benzene ring is lost. The reaction leading from the arenium ion to the substituted benzene, by contrast, is highly exothermic because it restores aromaticity to the system.

Of the following two steps, step 1 (the formation of the arenium ion) is usually the rate-determining step in electrophilic aromatic substitution because of its higher free energy of activation:

Step 1



Slow, rate determining

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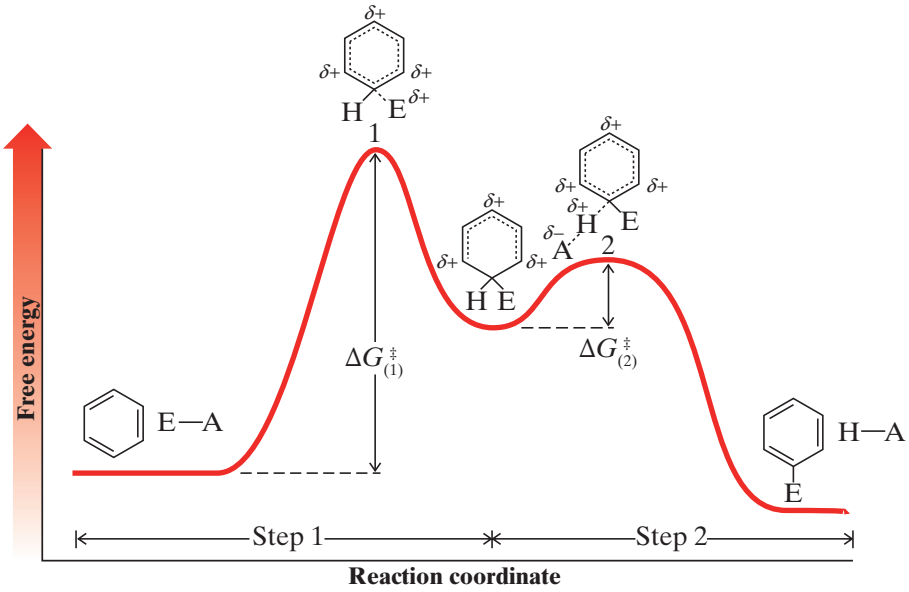
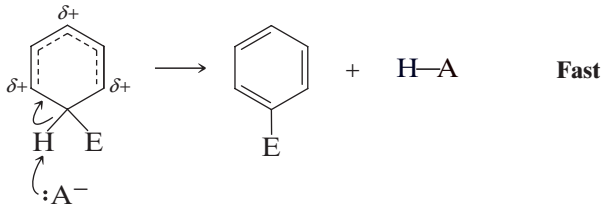


Figure 14.2 The free-energy diagram for an electrophilic aromatic substitution reaction. The arenium ion is a true intermediate lying between transition states 1 and 2. In transition state 1 the bond between the electrophile and one carbon atom of the benzene ring is only partially formed. In transition state 2 the bond between the same benzene carbon atom and its hydrogen atom is partially broken. The bond between the hydrogen atom and the conjugate base is partially formed.

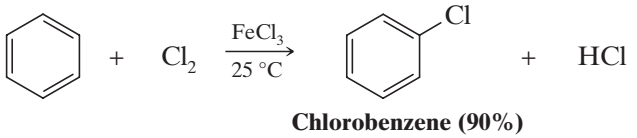
Step 2



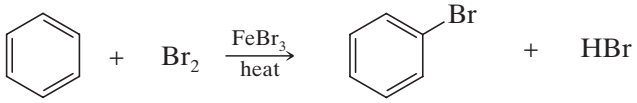
Step 2, the removal of a proton, occurs rapidly relative to step 1 and has no effect on the overall rate of reaction.

14.3 | HALOGENATION OF BENZENE

Benzene reacts with bromine and chlorine in the presence of Lewis acids to give halogenated substitution products in good yield.



Chlorobenzene (90%)



Bromobenzene (75%)

The Lewis acids typically used are aluminum chloride ($AlCl_3$) and iron chloride ($FeCl_3$) for chlorination, and iron bromide ($FeBr_3$) for bromination. The purpose of the Lewis acid is to make the halogen a stronger electrophile. A mechanism for electrophilic aromatic bromination is shown here.

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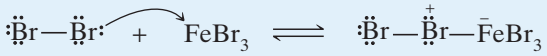
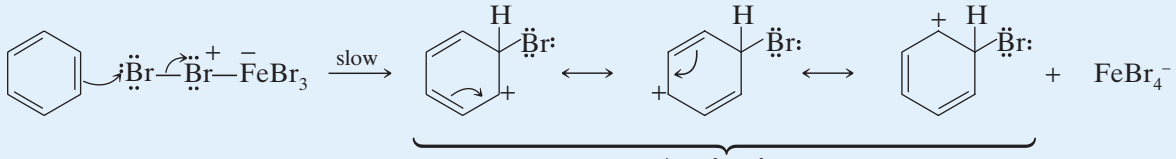
A MECHANISM FOR THE REACTION — Electrophilic Aromatic Bromination

Step 1



Bromine combines with $FeBr_3$ to form a complex.

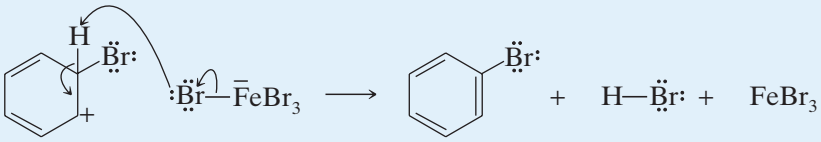
Step 2



Arenium ion

The benzene ring donates an electron pair to the terminal bromine, forming the arenium ion and neutralizing the formal positive charge on the other bromine.

Step 3

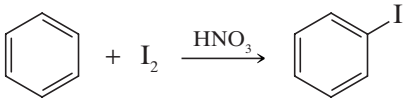


A proton is removed from the arenium ion to form bromobenzene and regenerate the catalyst.

The mechanism of the chlorination of benzene in the presence of ferric chloride is analogous to the one for bromination.

Fluorine reacts so rapidly with benzene that aromatic fluorination requires special conditions and special types of apparatus. Even then, it is difficult to limit the reaction to monofluorination. Fluorobenzene can be made, however, by an indirect method that we shall see in Section 18.7D.

Iodine, on the other hand, is so unreactive that a special technique has to be used to effect direct iodination; the reaction has to be carried out in the presence of an oxidizing agent such as nitric acid:

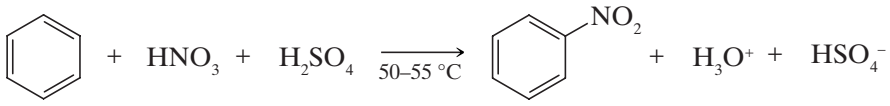


86%

Biochemical iodination, as in the biosynthesis of thyroxine, occurs with enzymatic catalysis.

14.4 | NITRATION OF BENZENE

Benzene undergoes nitration on reaction with a mixture of concentrated nitric acid and concentrated sulfuric acid.



85%

Concentrated sulfuric acid increases the rate of the reaction by increasing the concentration of the electrophile, the nitronium ion (NO_2^+), as shown in the first two steps of the following mechanism.

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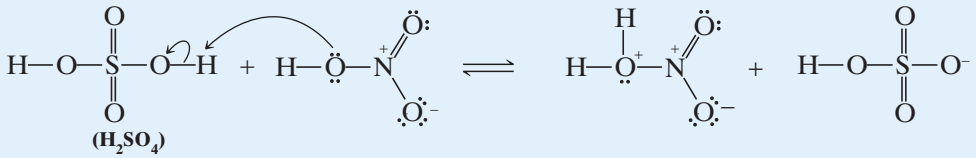
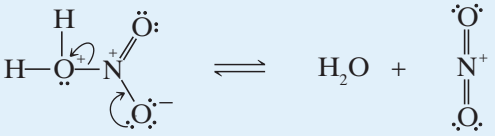
A MECHANISM FOR THE REACTION — Nitration of Benzene

Step 1



In this step nitric acid accepts a proton from the stronger acid, sulfuric acid.

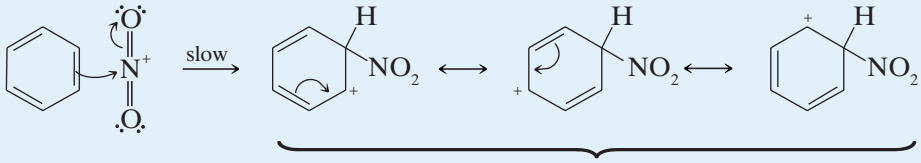
Step 2



Nitronium ion

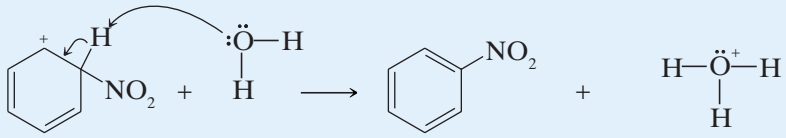
Now that it is protonated, nitric acid can dissociate to form a nitronium ion.

Step 3



The nitronium ion is the electrophile in nitration; it reacts with benzene to form a resonance-stabilized arenium ion.

Step 4



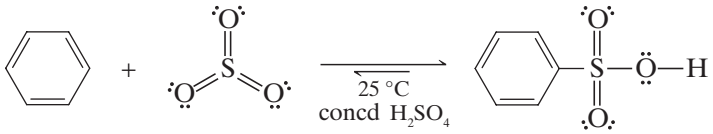
The arenium ion then loses a proton to a Lewis base and becomes nitrobenzene.

Practice Problem 14.2

Given that the pK_a of H_2SO_4 is –9 and that of HNO_3 is –1.4, explain why nitration occurs more rapidly in a mixture of concentrated nitric and sulfuric acids than in concentrated nitric acid alone.

14.5 | SULFONATION OF BENZENE

Benzene reacts with fuming sulfuric acid at room temperature to produce benzenesulfonic acid. Fuming sulfuric acid is sulfuric acid that contains added sulfur trioxide (SO_3). Sulfonation also takes place in concentrated sulfuric acid alone, but more slowly. Under either condition, the electrophile appears to be sulfur trioxide.



Sulfur trioxide — **Benzenesulfonic acid (56%)**

In concentrated sulfuric acid, sulfur trioxide is produced in an equilibrium in which H_2SO_4 acts as both an acid and a base (see step 1 of the following mechanism).

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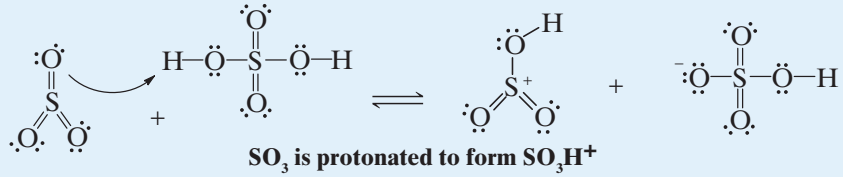
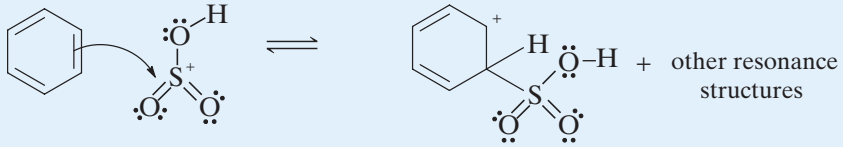
A MECHANISM FOR THE REACTION — Sulfonation of Benzene

Step 1



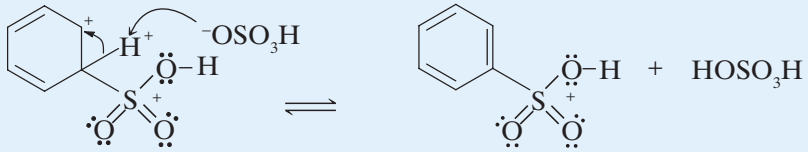
SO_3 is protonated to form SO_3H^+

Step 2



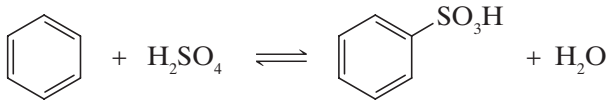
SO_3H^+ reacts as an electrophile with the benzene ring to form an arenium ion.

Step 3



Loss of a proton from the arenium ion restores aromaticity to the ring and regenerates the acid catalyst.

All of the steps in sulfonation are equilibria, which means that the overall reaction is reversible. The position of equilibrium can be influenced by the conditions we employ.



- If we want to sulfonate the ring (install a sulfonic acid group), we use concentrated sulfuric acid or—better yet—fuming sulfuric acid. Under these conditions the position of equilibrium lies appreciably to the right, and we obtain benzenesulfonic acid in good yield.
- If we want to desulfonate the ring (**remove** a sulfonic acid group), we employ dilute sulfuric acid and usually pass steam through the mixture. Under these conditions—with a high concentration of water—the equilibrium lies appreciably to the left and desulfonation occurs.

  We shall see later that sulfonation and desulfonation reactions are often used in synthetic work.
- We sometimes install a sulfonate group **as a protecting group**, to temporarily block its position from electrophilic aromatic substitution, or **as a directing group, to influence the position** of another substitution relative to it (Section 14.14). When it is no longer needed we remove the sulfonate group.

14.6 | FRIEDEL–CRAFTS ALKYLATION

Charles Friedel, a French chemist, and his American collaborator, James M. Crafts, discovered new methods for the preparation of alkylbenzenes (ArR) and acylbenzenes (ArCOR) in 1877. These reactions are now called the Friedel–Crafts **alkylation** and acylation reactions. We shall study the Friedel–Crafts alkylation reaction here and take up the **Friedel–Crafts acylation** reaction in Section 14.7.

- The following is a general equation for a **Friedel–Crafts alkylation** reaction:



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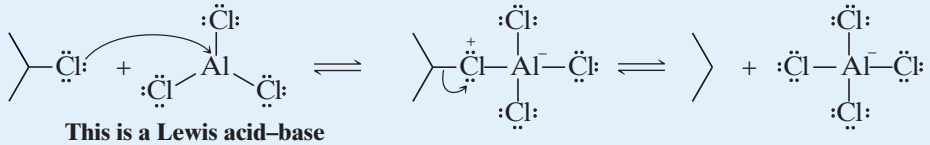
- The mechanism for the reaction starts with the formation of a carbocation.
- The carbocation then acts as an electrophile and attacks the benzene ring to form an arenium ion.
- The arenium ion then loses a proton.

This mechanism is illustrated below using 2-chloropropane and benzene.

A MECHANISM FOR THE REACTION — Friedel–Crafts Alkylation

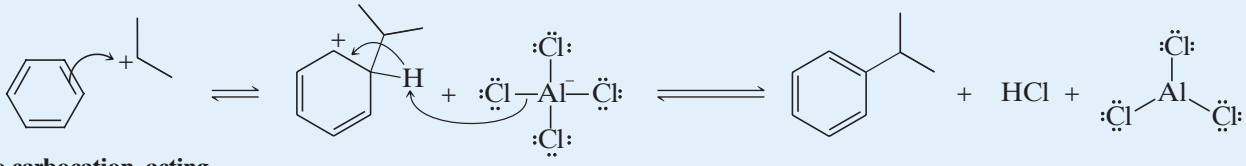
Step 1



This is a Lewis acid–base reaction (see Section 14.3).

The complex dissociates to form a carbocation and $AlCl_4^-$.

Step 2



The carbocation, acting as an electrophile, reacts with benzene to produce an arenium ion.

A proton is removed from the arenium ion to form isopropylbenzene. This step also regenerates the $AlCl_3$ and liberates HCl.

- When R—X is a primary halide, a simple carbocation probably does not form. Instead, the aluminum chloride forms a complex with the alkyl halide, and this complex acts as the electrophile.

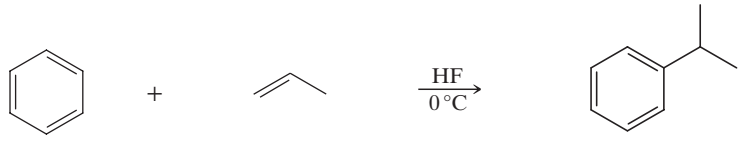
The complex is one in which the carbon–halogen bond is nearly broken—and one in which the carbon atom has a considerable positive charge:



Even though this complex is not a simple carbocation, it acts as if it were and it transfers a positive alkyl group to the aromatic ring.

- These complexes react so much like carbocations that they also undergo typical carbocation rearrangements (Section 14.8).
- Friedel–Crafts alkylations are not restricted to the use of alkyl halides and aluminum chloride. Other pairs of reagents that form carbocations (or species like carbocations) may be used in Friedel–Crafts alkylations as well.

These possibilities include the use of a mixture of an alkene and an acid:



Propene

Isopropylbenzene (cumene) (84%)



Cyclohexene

Cyclohexylbenzene (62%)

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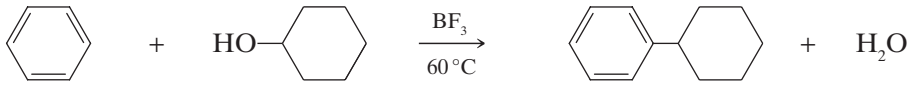
A mixture of an alcohol and an acid may also be used:



Cyclohexanol — **Cyclohexylbenzene (56%)**

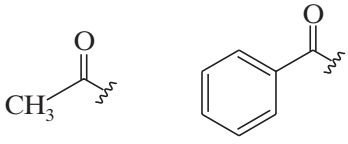
There are several important limitations of the Friedel–Crafts reaction. These are discussed in Section 14.8.

Practice Problem 14.3

Outline all steps in a reasonable mechanism for the formation of isopropylbenzene from propene and benzene in liquid HF (just shown). Your mechanism must account for the product being isopropylbenzene, not propylbenzene.

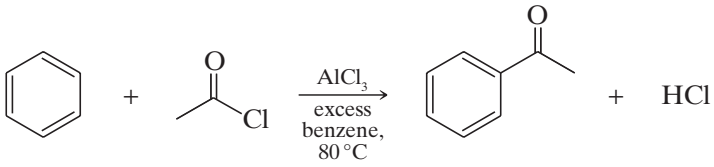
14.7 | FRIEDEL–CRAFTS ACYLATION

The  group is called an **acyl group**, and a reaction whereby an acyl group is introduced into a compound is called an **acylation** reaction. Two common acyl groups are the acetyl group and the benzoyl group. (The benzoyl group should not be confused with the benzyl group, — $CH_2C_6H_5$; see Section 13.2.)



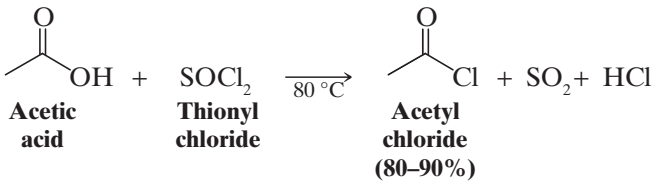
Acetyl group (ethanoyl group) — **Benzoyl group**

The **Friedel–Crafts acylation** reaction is often carried out by treating the aromatic compound with an **acyl halide** (often an acyl chloride). Unless the aromatic compound is one that is highly reactive, the reaction requires the addition of at least one equivalent of a Lewis acid (such as $AlCl_3$) as well. The product of the reaction is an aryl ketone:

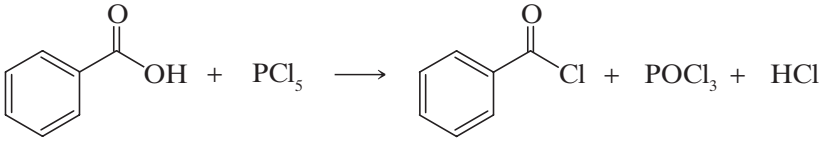


Acetyl chloride — **Acetophenone (methyl phenyl ketone) (97%)**

Acyl chlorides, also called **acid chlorides**, are easily prepared by treating carboxylic acids with thionyl chloride ($SOCl_2$) or phosphorus pentachloride (PCl_5):



Acetic acid — **Thionyl chloride** — **Acetyl chloride (80–90%)**



Benzoic acid — **Phosphorus pentachloride** — **Benzoyl chloride (90%)**

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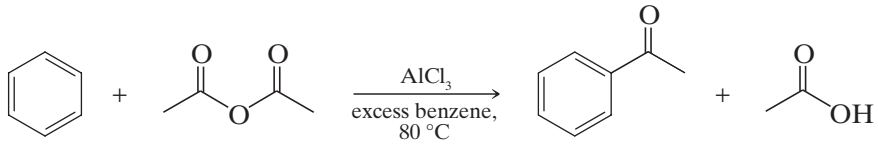
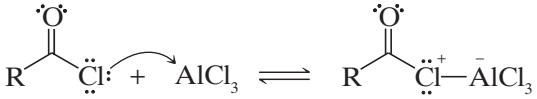
Friedel–Crafts acylations can also be carried out using carboxylic acid anhydrides. For example,



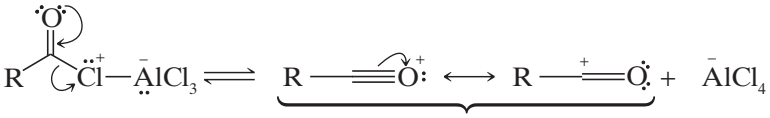
Acetic anhydride (a carboxylic acid anhydride) — **Acetophenone (82–85%)**

In most Friedel–Crafts acylations the electrophile appears to be an **acylium ion** formed from an acyl halide in the following way:

Step 1



Step 2



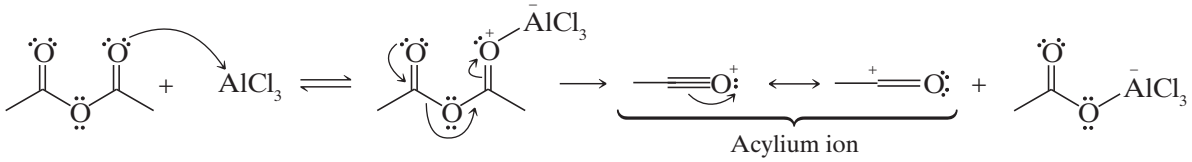
An acylium ion (a resonance hybrid)

Solved Problem 14.1

Show how an acylium ion could be formed from acetic anhydride in the presence of $AlCl_3$.

Answer

We recognize that $AlCl_3$ is a Lewis acid and that an acid anhydride, because it has multiple unshared electron pairs, is a Lewis base. A reasonable mechanism starts with a Lewis acid–base reaction and proceeds to form an acylium ion in the following way.

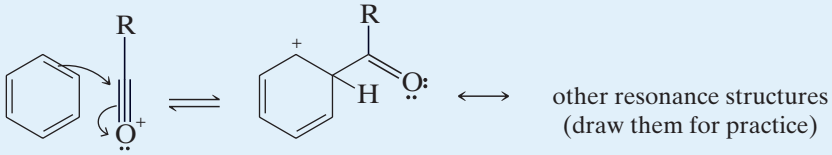


Acylium ion

The remaining steps in the Friedel–Crafts acylation of benzene are the following:

A MECHANISM FOR THE REACTION — Friedel–Crafts Acylation

Step 3



other resonance structures (draw them for practice)

The acylium ion, acting as an electrophile, reacts with benzene to form the arenium ion.

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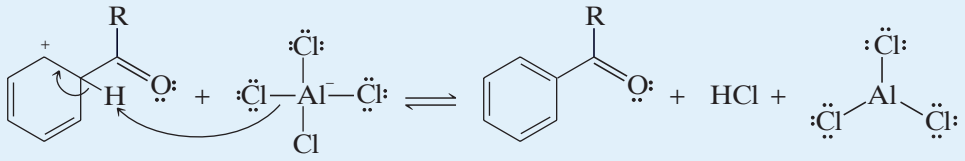
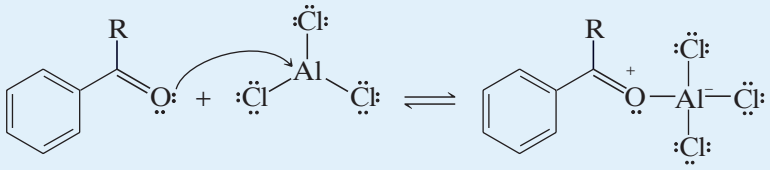
Step 4



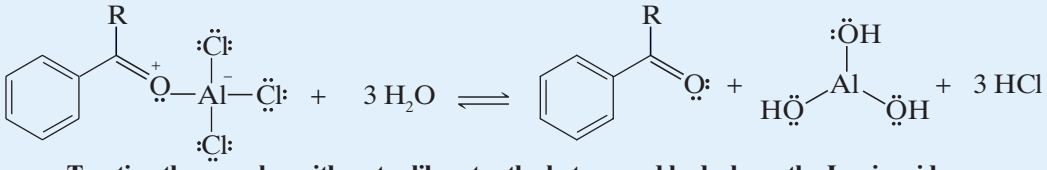
A proton is removed from the arenium ion, forming the aryl ketone.

Step 5



The ketone, acting as a Lewis base, reacts with aluminum chloride (a Lewis acid) to form a complex.

Step 6



Treating the complex with water liberates the ketone and hydrolyzes the Lewis acid.

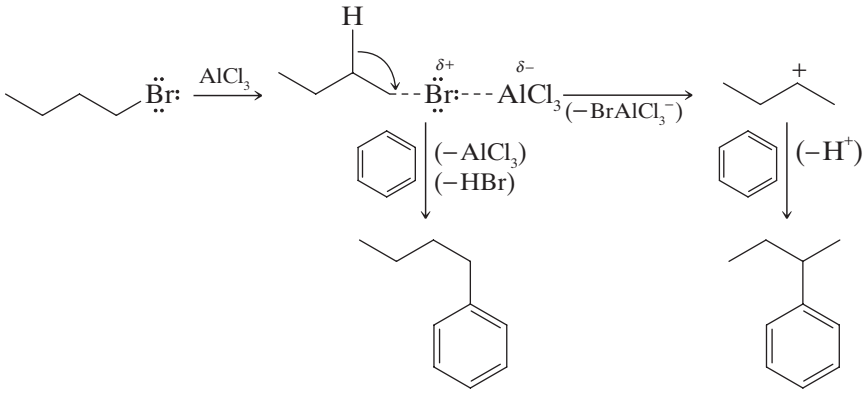
Several important synthetic applications of the Friedel–Crafts reaction are given in Section 14.9.

14.8 | LIMITATIONS OF FRIEDEL–CRAFTS REACTIONS

Several restrictions limit the usefulness of Friedel–Crafts reactions:

1. **When the carbocation formed from an alkyl halide, alkene, or alcohol can rearrange to one or more carbocations that are more stable, it usually does so, and the major products obtained from the reaction are usually those from the more stable carbocations**.

When benzene is alkylated with butyl bromide, for example, some of the developing butyl cations rearrange by a hydride shift. Some of the developing 1° carbocations (see following reactions) become more stable 2° carbocations. Then benzene reacts with both kinds of carbocations to form both butylbenzene and *sec*-butylbenzene:



Butylbenzene (32–36% of mixture)

***sec*-Butylbenzene (64–68% of mixture)**

2. **Friedel–Crafts reactions usually give poor yields when powerful electron-withdrawing groups** (Section 14.11) **are present on the aromatic ring or when the ring bears an** —NH_2, —NHR, **or** —NR_2 **group**. This applies to both alkylations and acylations.

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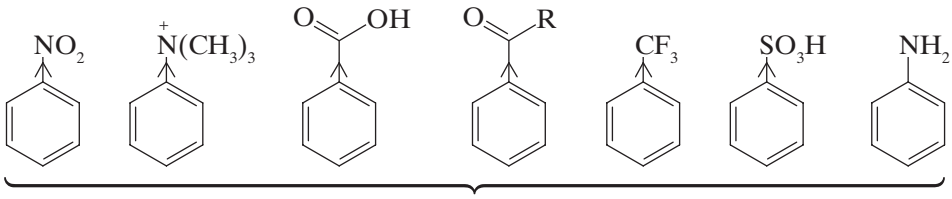
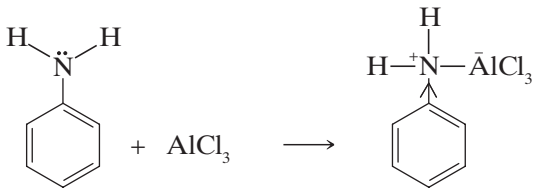


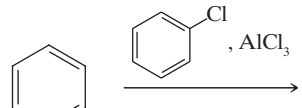
These usually give poor yields in Friedel-Crafts reactions.

We shall learn in Section 14.10 that groups present on an aromatic ring can have a large effect on the reactivity of the ring toward electrophilic aromatic substitution. **Electron-withdrawing groups make the ring less reactive by making it electron deficient**. Any substituent more electron withdrawing (or deactivating) than a halogen, that is, **any meta-directing group** (Section 14.11C), **makes an aromatic ring too electron deficient to undergo a Friedel–Crafts reaction**. The amino groups, —NH_2, —NHR, and —NR_2, are changed into powerful electron-withdrawing groups by the Lewis acids used to catalyze Friedel–Crafts reactions. For example,

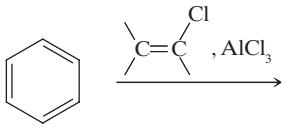


Does not undergo a Friedel–Crafts reaction

3. **Aryl and vinylic halides cannot be used as the halide component because they do not form carbocations readily** (see Section 6.14A):

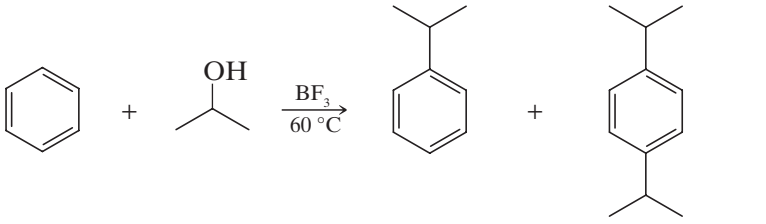


No Friedel–Crafts reaction because the halide is aryl



No Friedel–Crafts reaction because the halide is vinylic

4. **Polyalkylations often occur.** Alkyl groups are inductive electron-releasing groups, and once one is introduced into the benzene ring, it activates the ring toward further substitution (see Section 14.10):



Isopropyl-benzene (24%) **p-Diisopropylbenzene (14%)**

Polyacylations are not a problem in Friedel–Crafts acylations. The acyl group (RCO—) by itself is an electron-withdrawing group, and when it forms a complex with $AlCl_3$ in the last step of the reaction (Section 14.7), it is made even more electron withdrawing. This strongly inhibits further substitution and makes monoacylation easy.

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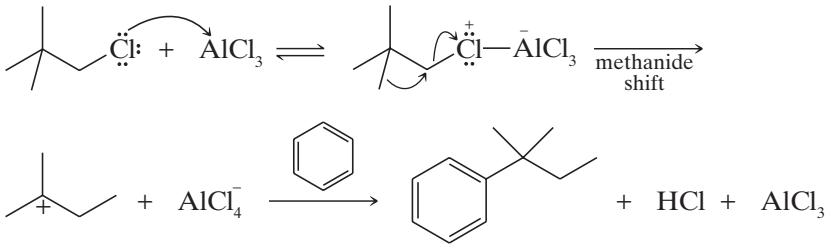
Solved Problem 14.2

When benzene reacts with 1-chloro-2,2-dimethylpropane (neopentyl chloride) in the presence of aluminum chloride, the major product is 2-methyl-2-phenylbutane, not 2,2-dimethyl-1-phenylpropane (neopentylbenzene). Explain this result.

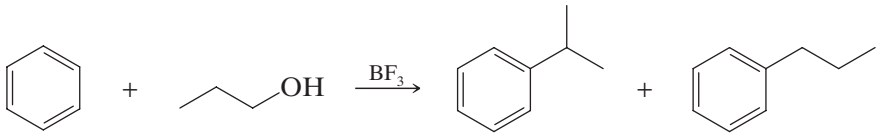
Answer

The carbocation formed by direct reaction of $AlCl_3$ with 1-chloro-2,2-dimethylpropane would be a primary carbocation; however, it rearranges to the more stable tertiary carbocation before it can react with the benzene ring.



Practice Problem 14.4

Provide a mechanism that accounts for the following result.

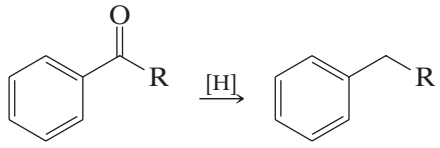


14.9 | SYNTHETIC APPLICATIONS OF FRIEDEL–CRAFTS ACYLATIONS: THE CLEMMENSEN AND WOLFF–KISHNER REDUCTIONS

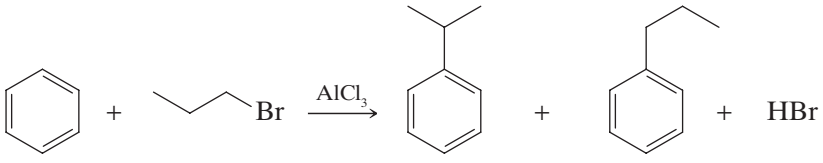
- Rearrangements of the carbon chain do not occur in Friedel–Crafts acylations.

The acylium ion, because it is stabilized by resonance, is more stable than most other carbocations. Thus, there is no driving force for a rearrangement. Because rearrangements do not occur, Friedel–Crafts acylations followed by reduction of the carbonyl group to a CH_2 group often give us much better routes to unbranched alkylbenzenes than do Friedel–Crafts alkylations.

- The carbonyl group of an aryl ketone can be reduced to a CH_2 group.



As an example, let us consider the problem of synthesizing propylbenzene. If we attempt this synthesis through a Friedel–Crafts alkylation, a rearrangement occurs and the major product is isopropylbenzene (see also Practice Problem 14.4):



Isopropylbenzene (major product) **Propylbenzene (minor product)**

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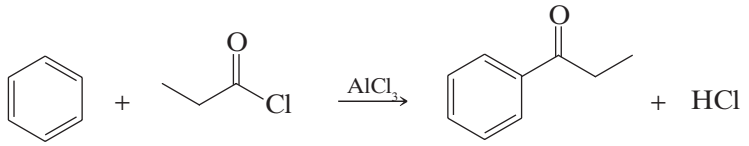
By contrast, the Friedel–Crafts acylation of benzene with propanoyl chloride produces a ketone with an unrearranged carbon chain in excellent yield:



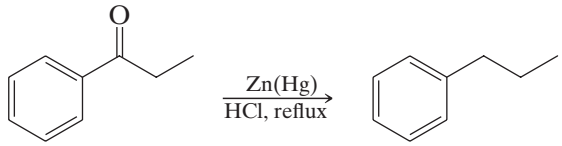
Propanoyl chloride — **Ethyl phenyl ketone (90%)**

This ketone can then be reduced to propylbenzene by several methods.

14.9A The Clemmensen Reduction

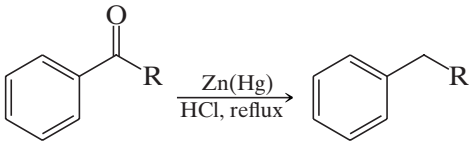
One general method for reducing a ketone to a methylene group—called the **Clemmensen reduction**—consists of refluxing the ketone with hydrochloric acid containing amalgamated zinc. [*Caution*: As we shall discuss later (Section 18.4B), zinc and hydrochloric acid will also reduce nitro groups to amino groups.]

A Clemmensen Reduction



Ethyl phenyl ketone — **Propylbenzene (80%)**

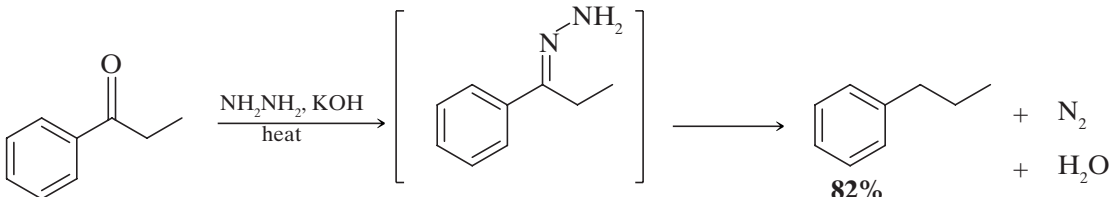
In general,



14.9B The Wolff–Kishner Reduction

Another method for reducing a ketone to a methylene group is the Wolff–Kishner reduction, which involves heating the ketone with hydrazine and base. The Wolff–Kishner reduction complements the Clemmensen reduction in that it is conducted under basic conditions, whereas the Clemmensen reduction involves acidic conditions. The Wolff–Kishner reduction proceeds via a hydrazone intermediate (Section 15.8B) that is not isolated during the reaction. Ethyl phenyl ketone can be reduced to propylbenzene by the Wolff–Kishner reduction as follows, for example.

A Wolff–Kishner Reduction



Hydrazone intermediate (see Section 15.8B) — **82%**

When cyclic anhydrides are used as one component, the Friedel–Crafts acylation provides a means of adding a new ring to an aromatic compound. One illustration is shown here. Note that only the ketone is reduced in the Clemmensen reduction step. The carboxylic acid is unaffected. The same result can be achieved using the Wolff–Kishner reduction.

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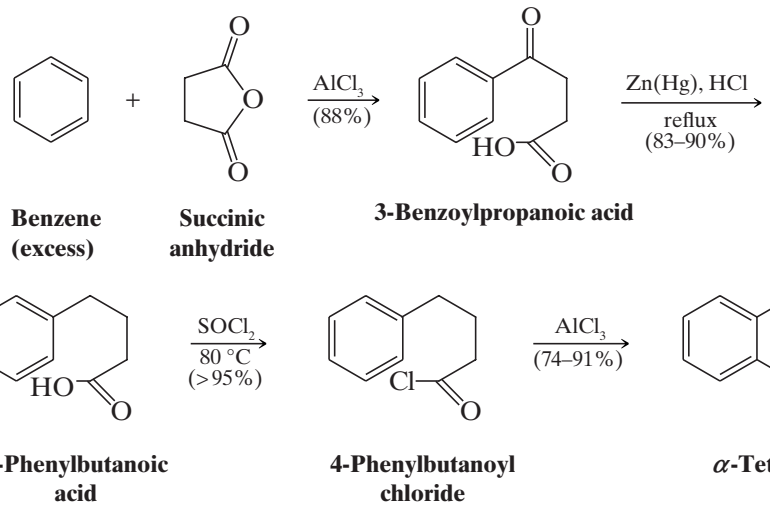


Benzene (excess) | **Succinic anhydride** | **3-Benzoylpropanoic acid**

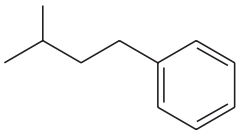
4-Phenylbutanoic acid | **4-Phenylbutanoyl chloride** | **α-Tetralone**

Practice Problem 14.5

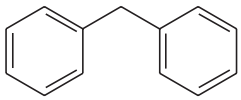
Starting with benzene and the appropriate acyl chloride or acid anhydride, outline a synthesis of each of the following:

(a) Butylbenzene

(b)

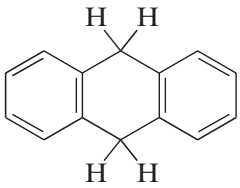


(c)



Diphenylmethane

(d)



9,10-Dihydroanthracene

14.10 | SUBSTITUENTS CAN AFFECT BOTH THE REACTIVITY OF THE RING AND THE ORIENTATION OF THE INCOMING GROUP

A **substituent group** already present on a benzene ring can affect both the **reactivity** of the ring toward electrophilic substitution and the **orientation** that the incoming group takes on the ring.

- A substituent can make the ring **more reactive** than benzene (i.e., it can make the compound react faster than benzene reacts). Such a group is called an **activating group**.
- A substituent can make the ring **less reactive** than benzene (i.e., it can make the compound react more slowly than benzene reacts). Such groups are called **deactivating groups**.

14.10A HOW DO Substituents Affect Reactivity?

Recall from Fig. 14.2 and Section 14.2 that the slow step in electrophilic aromatic substitution, the step that determines the overall rate of reaction, is the first step. In this step an electron-seeking reagent reacts by accepting an electron pair from the benzene ring.

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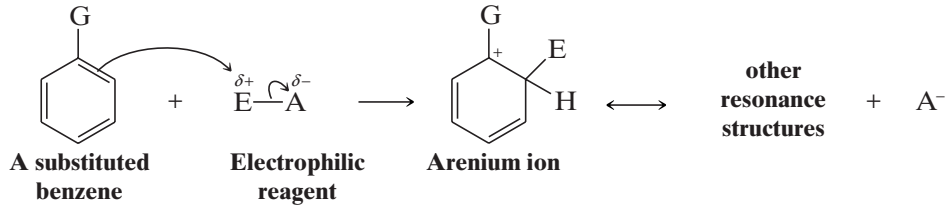
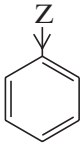
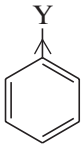


If a substituent that is already present on the ring makes the ring more electron rich by donating electrons to it, then the ring will be more nucleophilic, more reactive toward the electrophile, and the reaction will take place faster.



If Z donates electrons the ring is more electron rich and it reacts faster with an electrophile.

On the other hand, if the substituent on the ring withdraws electrons, the ring will be electron poor and an electrophile will react with the ring more slowly.

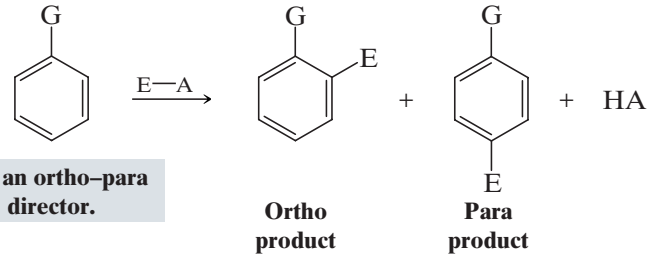


If Y withdraws electrons the ring is electron poor and it reacts more slowly with an electrophile.

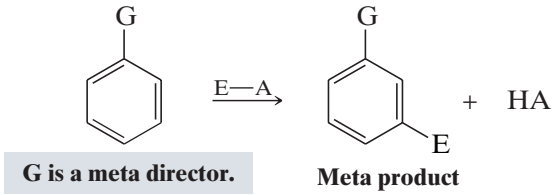
14.10B Ortho–Para-Directing Groups and Meta-Directing Groups

A substituent on the ring can also affect the **orientation** that the incoming group takes when it replaces a hydrogen atom on the ring. Substituents fall into two general classes:

- **Ortho–para directors** predominantly direct the incoming group to a position ortho or para to itself.



- **Meta directors** predominantly direct the incoming group to a position meta to itself.



14.10C Electron-Donating and Electron-Withdrawing Substituents

Whether a substituent is an activating group or a deactivating group, and whether it is an ortho–para director or a meta director, depends largely on whether the substituent donates electrons to the ring or whether it withdraws electrons.

- All electron-donating groups are activating groups and all are ortho–para directors.
- With the exception of halogen substituents, all electron-withdrawing groups are deactivating groups and all are meta directors.

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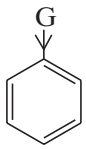
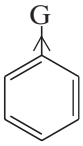
- Halogen substituents are weakly deactivating groups and are ortho–para directors.



If G donates electrons the ring is activated; it reacts faster, and at an ortho or para position.

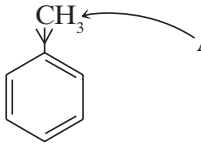


If G withdraws electrons the ring is deactivated; it reacts more slowly, and at a meta position (except when G is a halogen).

14.10D Groups: Ortho–Para Directors

- Alkyl substituents are electron-donating groups and they are **activating groups**. They are also **ortho–para directors**.

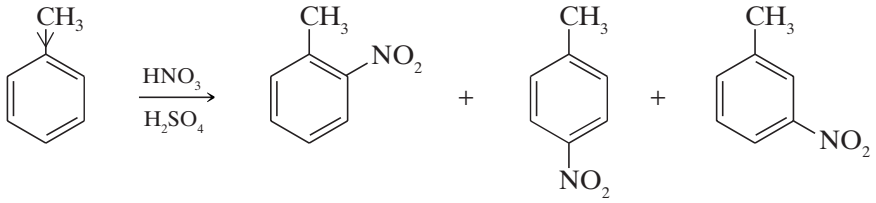
Toluene, for example, reacts considerably faster than benzene in all electrophilic substitutions:



Toluene is more reactive than benzene toward electrophilic substitution.

We observe the greater reactivity of toluene in several ways. We find, for example, that with toluene, milder conditions—lower temperatures and lower concentrations of the electrophile—can be used in electrophilic substitutions than with benzene. We also find that under the same conditions toluene reacts faster than benzene. In nitration, for example, toluene reacts 25 times as fast as benzene.

We find, moreover, that when toluene undergoes electrophilic substitution, most of the substitution takes place at its ortho and para positions. When we nitrate toluene with nitric and sulfuric acids, we get mononitrotoluenes in the following relative proportions:



***o*-Nitrotoluene (59%)** | ***p*-Nitrotoluene (37%)** | ***m*-Nitrotoluene (4%)**

Of the mononitrotoluenes obtained from the reaction, 96% (59% + 37%) have the nitro group in an ortho or para position. Only 4% have the nitro group in a meta position.

Practice Problem 14.6

Explain how the percentages just given show that the methyl group exerts an ortho–para directive effect by considering the percentages that would be obtained if the methyl group had no effect on the orientation of the incoming electrophile.

Predominant substitution of toluene at the ortho and para positions is not restricted to nitration reactions. The same behavior is observed in halogenation, sulfonation, and so forth.

- Groups that have an unshared electron pair on the atom attached to the aromatic ring, such as amino, hydroxyl, alkoxyl, and amides or esters with the oxygen or nitrogen directly bonded to the ring, are powerful activating groups and are strong ortho–para directors.

Phenol and aniline react with bromine in water (no catalyst is required) at room temperature to produce compounds in which both of the ortho positions and the para position become substituted.

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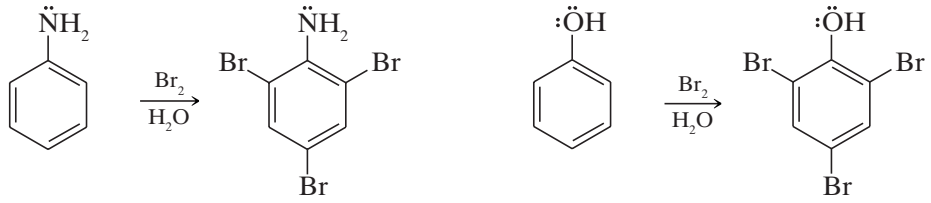
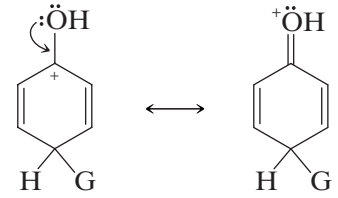


2,4,6-Tribromoaniline (~100%) **2,4,6-Tribromophenol (~100%)**

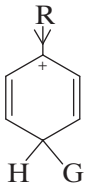
- In general, substituent groups with unshared electron pairs on the atom adjacent to the benzene ring (e.g., hydroxyl, amino) are stronger activating groups than groups without unshared electron pairs (i.e., alkyl groups).
- Contribution of electron density to the benzene ring through resonance is generally stronger than through an inductive effect.

As a corollary, even though amides and esters have an unshared electron pair on the atom adjacent to the ring, their activating effect is diminished because the carbonyl group provides a resonance structure where electron density is directed away from the benzene ring. This makes amides and esters less activating than groups where the only resonance possibilities involve donation of electron density toward the benzene ring.

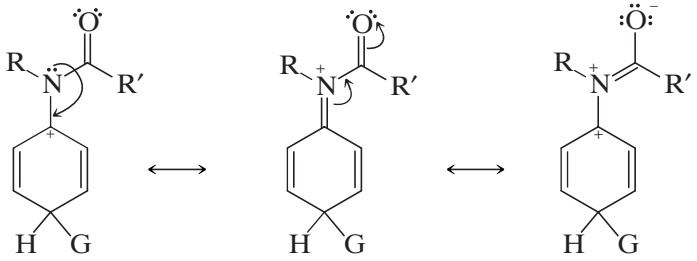
Examples of stabilization of an arenium ion by resonance and inductive effects



Electron donation through resonance



Electron donation through the inductive effect



Electron donation to the ring by resonance is reduced when there is an alternative resonance pathway away from the ring.

14.10E Deactivating Groups: Meta Directors

- The nitro group is a very strong **deactivating group** and, because of the combined electronegativities of the nitrogen and oxygen atoms, it is a powerful electron-withdrawing group.

Nitrobenzene undergoes nitration at a rate only 10^{-4} times that of benzene. The nitro group is a **meta director**. When nitrobenzene is nitrated with nitric and sulfuric acids, 93% of the substitution occurs at the meta position:

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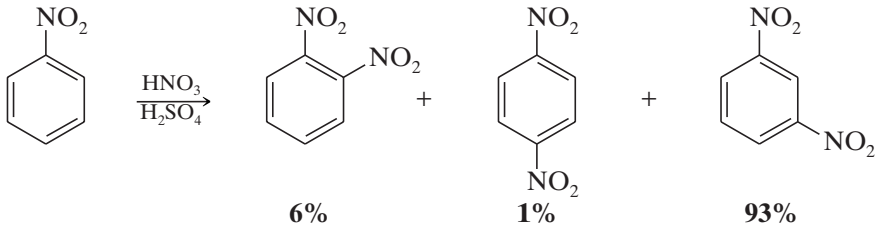

- The carboxyl group (—CO_2H), the sulfonic acid group (—SO_3H), and the trifluoromethyl group (—CF_3) are also deactivating groups; they are also meta directors.

14.10F Halo Substituents: Deactivating Ortho–Para Directors

- The chloro, bromo, and iodo groups are ortho–para directors. However, even though they contain unshared electron pairs, they are deactivating toward electrophilic aromatic substitution because of the electronegative effect of the halogens.

Chlorobenzene and bromobenzene, for example, undergo nitration at a rate approximately 30 times slower than benzene. The relative percentages of monosubstituted products that are obtained when chlorobenzene is chlorinated, brominated, nitrated, or sulfonated are shown in Table 14.1.

Table 14.1 Electrophilic Substitutions of Chlorobenzene

Reaction	Ortho Product (%)	Para Product (%)	Total Ortho and Para (%)	Meta Product (%)
Chlorination	39	55	94	6
Bromination	11	87	98	2
Nitration	30	70	100	
Sulfonation		100	100	

Similar results are obtained from electrophilic substitutions of bromobenzene.

14.10G Classification of Substituents

A summary of the effects of some substituents on reactivity and orientation is provided in Table 14.2.

Table 14.2 Effect of Substituents on Electrophilic Aromatic Substitution

Ortho–Para Directors	Meta Directors
Strongly Activating	**Moderately Deactivating**
—$\ddot{N}H_2$, —$\ddot{N}HR$, —$\ddot{N}R_2$	—C≡N
—$\ddot{O}H$, $\ddot{O}:^-$	—SO_3H
Moderately Activating	
—$\ddot{N}H$—C(=O)—R	—C(=O)—OH, —C(=O)—OR
—$\ddot{O}$—C(=O)—R, —$\ddot{O}$R	—C(=O)—H, —C(=O)—R

Continued

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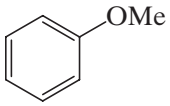
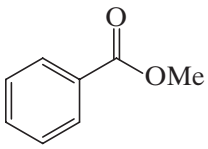
Table 14.2 Continued

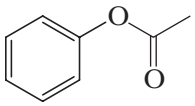
Ortho–Para Directors	Meta Directors
Weakly Activating	**Strongly Deactivating**
—R (alkyl)	—NO_2
—C_6H_5 (phenyl)	—NR_3^+
Weakly Deactivating	—CF_3, CCl_3
—F:, —Cl:, —Br:, —I:	

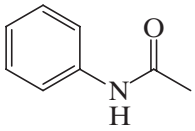
Solved Problem 14.3

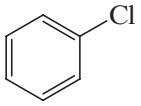
Label each of the following aromatic rings as activated or deactivated based on the substituent attached, and state whether the group is an ortho–para or meta director.

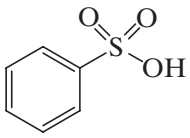
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

Answer

If a substituent donates electron density it will activate the ring and cause ortho and para substitution. If a substituent withdraws electron density it will deactivate the ring and cause meta substitution (except for halogens, which are electron withdrawing but cause ortho–para substitution). **(a)** Activated; an ether is an ortho–para director; **(b)** deactivated; the ester carbonyl is a meta director; **(c)** activated; the single-bonded oxygen of the ester is directly bonded to the ring, and therefore it is an ortho–para director; **(d)** activated; the amide nitrogen is an ortho–para director; **(e)** deactivated; however, the halogen is ortho–para director through resonance; **(f)** deactivated; the sulfonate group is a meta director.

Practice Problem 14.7

Predict the major products formed when:

(a) Toluene is sulfonated.
(b) Benzoic acid is nitrated.
(c) Nitrobenzene is brominated.
(d) Isopropylbenzene reacts with acetyl chloride and $AlCl_3$.

If the major products would be a mixture of ortho and para isomers, you should so state.

14.11 | HOW SUBSTITUENTS AFFECT ELECTROPHILIC AROMATIC SUBSTITUTION: A CLOSER LOOK

14.11A Reactivity: The Effect of Electron-Releasing and Electron-Withdrawing Groups

We can account for relative reaction rates by examining the transition state for the rate-determining steps.

- Any factor that reduces the energy of the transition state relative to that of the reactants lowers the free energy of activation and increases the relative rate of the reaction.
- Any factor that raises the energy of the transition state relative to that of the reactants increases the free energy of activation and decreases the relative rate of the reaction.

The rate-determining step in electrophilic substitutions of substituted benzenes is the step that results in the formation of the arenium ion. We can write the formula for a substituted benzene in a generalized way if we use the letter G to represent any ring substituent, including hydrogen.

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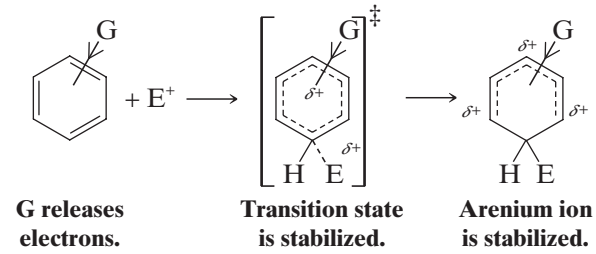
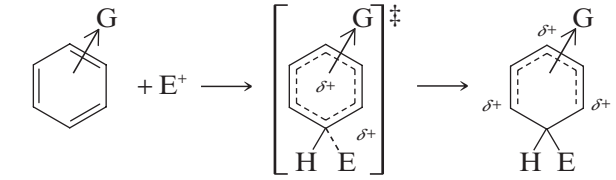
When we examine this step for a large number of reactions, we find that the relative rates of the reactions depend on whether G **releases** or **withdraws** electrons.

- If G is an electron-releasing group (relative to hydrogen), the reaction occurs faster than the corresponding reaction of benzene.
- If G is an electron-withdrawing group, the reaction is slower than that of benzene:



G releases electrons. **Transition state is stabilized.** **Arenium ion is stabilized.**

When G is electron donating, the reaction is faster.



G withdraws electrons. **Transition state is destabilized.** **Arenium ion is destabilized.**

When G is electron withdrawing, the reaction is slower.

It appears, then, that the substituent **(G)** must affect the stability of the transition state relative to that of the reactants.

- Electron-releasing groups make the transition state more stable, whereas electron-withdrawing groups make it less stable.

That this is so is entirely reasonable, because the transition state resembles the arenium ion, and the arenium ion is a delocalized *carbocation*.

This effect illustrates another application of the Hammond–Leffler postulate (Section 6.13A). The arenium ion is a high-energy intermediate, and the step that leads to it is a *highly endothermic step*. Thus, according to the Hammond–Leffler postulate, there should be a strong resemblance between the arenium ion itself and the transition state leading to it.

Since the arenium ion is positively charged, we would expect an electron-releasing group to stabilize the arenium ion *and the transition state leading to it*, for the transition state is a developing delocalized carbocation. We can make the same kind of arguments about the effect of electron-withdrawing groups. An electron-withdrawing group should make the arenium ion *less stable*, and in a corresponding way it should make the transition state leading to the arenium ion *less stable*.

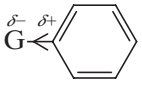
Figure 14.3 shows how the electron-withdrawing and electron-releasing abilities of substituents affect the relative free energies of activation of electrophilic aromatic substitution reactions.

14.11B Inductive and Resonance Effects: Theory of Orientation

We can account for the electron-withdrawing and electron-releasing properties of groups on the basis of two factors: *inductive effects* and *resonance effects*. We shall also see that these two factors determine orientation in aromatic substitution reactions.

Inductive Effects

The **inductive effect** of a substituent G arises from the electrostatic interaction of the polarized bond to G with the developing positive charge in the ring as it is attacked by an electrophile. If, for example, G is a more electronegative atom (or group) than carbon, then the ring will be at the positive end of the dipole:



(e.g., G = F, Cl, or Br)

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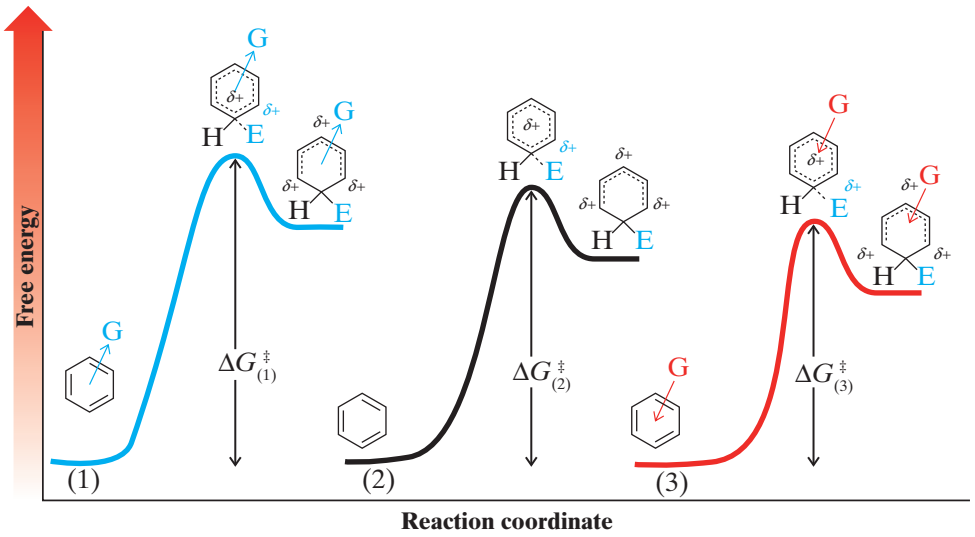
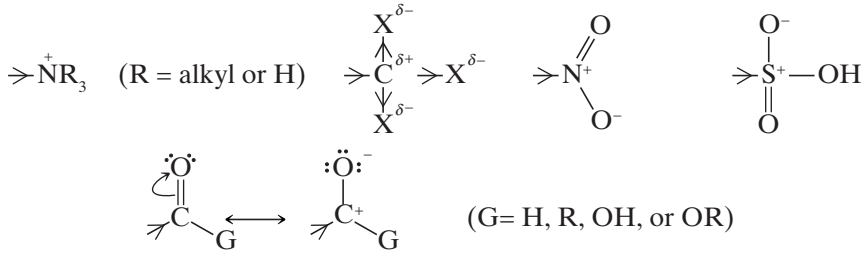


Figure 14.3 A comparison of free-energy profiles for arenium ion formation in a ring with an electron-withdrawing substituent (⊱G), no substituent, and an electron-donating substituent (≺G). In (1) (blue energy profile), the electron-withdrawing group G raises the transition state energy. The energy of activation barrier is the highest, and therefore the reaction is the slowest. Reaction (2), with no substituent, serves as a reference for comparison. In (3) (red energy profile), an electron-donating group G stabilizes the transition state. The energy of activation barrier is the lowest, and therefore the reaction is the fastest.

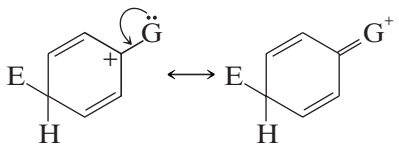
Attack by an electrophile will be slowed because this will lead to an additional full positive charge on the ring. The halogens are all more electronegative than carbon and exert an electron-withdrawing inductive effect. Other groups have an electron-withdrawing inductive effect because the atom directly attached to the ring bears a full or partial positive charge. Examples are the following:



Electron-withdrawing groups with a full or partial charge on the atom attached to the ring

Resonance Effects

The **resonance** effect of a substituent G refers to the possibility that the presence of G may increase or decrease the resonance stabilization of the intermediate arenium ion. The G substituent may, for example, cause one of the three contributors to the resonance hybrid for the arenium ion to be better or worse than the case when G is hydrogen. Moreover, when G is an atom bearing one or more nonbonding electron pairs, it may lend extra stability to the arenium ion by providing a *fourth* resonance contributor in which the positive charge resides on G:



This electron-donating resonance effect applies with decreasing strength in the following order:

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Most electron donating $-\ddot{N}H_2$, $-\ddot{N}R_2$ > $-\ddot{O}H$, $-\ddot{O}R$ > $-\ddot{X}:$ **Least electron donating**

This order also indicates the relative activating ability of these groups.

- Amino groups are highly activating, hydroxyl and alkoxyl groups are somewhat less activating, and halogen substituents are weakly deactivating.

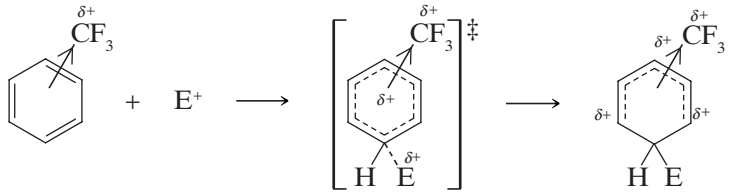
When X = F, this order can be related to the electronegativity of the atoms with the nonbonding pair. The more electronegative the atom is, the less able it is to accept the positive charge (fluorine is the most electronegative, nitrogen the least). When X = Cl, Br, or I, the relatively poor electron-donating ability of the halogens by resonance is understandable on a different basis. These atoms (Cl, Br, and I) are all larger than carbon, and, therefore, the orbitals that contain the nonbonding pairs are further from the nucleus and do not overlap well with the 2*p* orbital of carbon. This is a general phenomenon: resonance effects are not transmitted well between atoms of different rows in the periodic table.

14.11C Meta-Directing Groups

- All meta-directing groups have either a partial positive charge or a full positive charge on the atom directly attached to the ring.

As a typical example let us consider the trifluoromethyl group. The trifluoromethyl group, because of the three highly electronegative fluorine atoms, is strongly electron withdrawing. It is a strong deactivating group and a powerful meta director in electrophilic aromatic substitution reactions. We can account for both of these characteristics of the trifluoromethyl group in the following way.

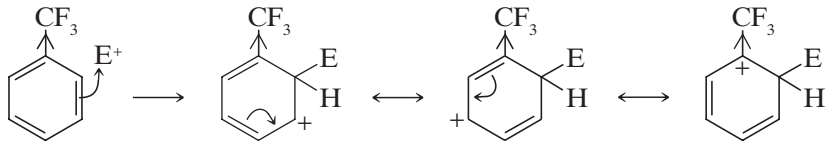
The trifluoromethyl group affects the rate of reaction by causing the transition state leading to the arenium ion to be highly unstable. It does this by withdrawing electrons from the developing carbocation, thus increasing the positive charge on the ring:



Trifluoromethylbenzene **Transition state** **Arenium ion**

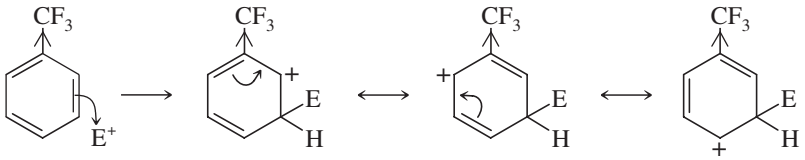
We can understand how the trifluoromethyl group affects *orientation* in electrophilic aromatic substitution if we examine the resonance structures for the arenium ion that would be formed when an electrophile attacks the ortho, meta, and para positions of trifluoromethylbenzene.

Ortho Attack

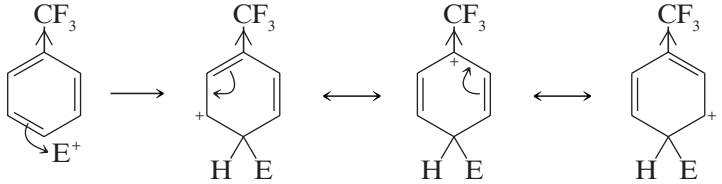


Highly unstable contributor

Meta Attack



Para Attack



Highly unstable contributor

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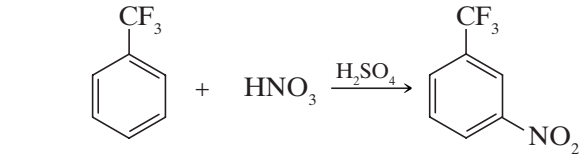
- The arenium ion arising from ortho and para attack each has *one contributing structure that is highly unstable relative to all the others because the positive charge is located on the ring carbon that bears the electron-withdrawing group*.
- The arenium ion arising from meta attack has *no* such highly unstable resonance structure.
- By the usual reasoning we would also expect the transition state leading to the meta-substituted arenium ion to be the least unstable and, therefore, that meta attack would be favored.

This is exactly what we find experimentally. The trifluoromethyl group is a powerful meta director:



Trifluoromethylbenzene **~100%**

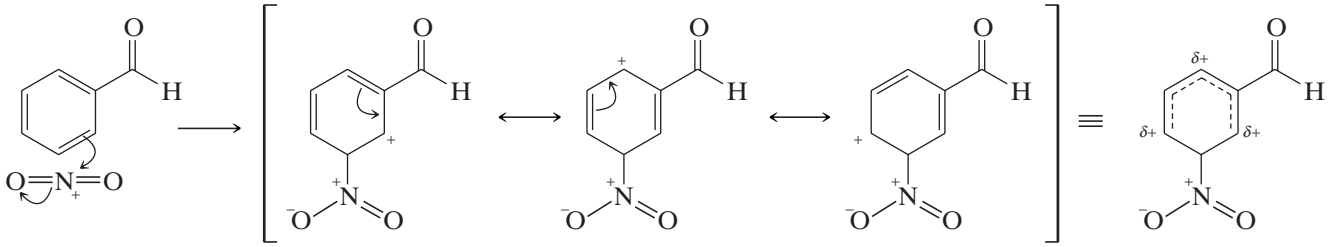
Bear in mind, however, that meta substitution is favored only in the sense that *it is the least unfavorable of three unfavorable pathways*. The free energy of activation for substitution at the meta position of trifluoromethylbenzene is less than that for attack at an ortho or para position, but it is still far greater than that for an attack on benzene. Substitution occurs at the meta position of trifluoromethylbenzene faster than substitution takes place at the ortho and para positions, but it occurs much more slowly than it does with benzene.

- The nitro group, the carboxyl group, and other meta-directing groups (see Table 14.2) are all powerful electron-withdrawing groups and act in a similar way.

Solved Problem 14.4

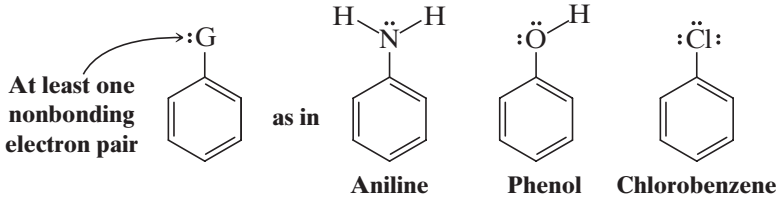
Write contributing resonance structures and the resonance hybrid for the arenium ion formed when benzaldehyde undergoes nitration at the meta position.

Answer



14.11D Ortho–Para-Directing Groups

Except for the alkyl and phenyl substituents, all of the ortho–para-directing groups in Table 14.2 are of the following general type:



This structural feature—an unshared electron pair on the atom adjacent to the ring—determines the orientation and influences reactivity in electrophilic substitution reactions.

The *directive effect* of groups with an unshared pair is predominantly caused by an electron-releasing resonance effect. The resonance effect, moreover, operates primarily in the arenium ion and, consequently, in the transition state leading to it.

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Except for the halogens, the primary effect of these groups on relative reactivity of the benzene ring is also caused by an electron-releasing resonance effect. And, again, this effect operates primarily in the transition state leading to the arenium ion.

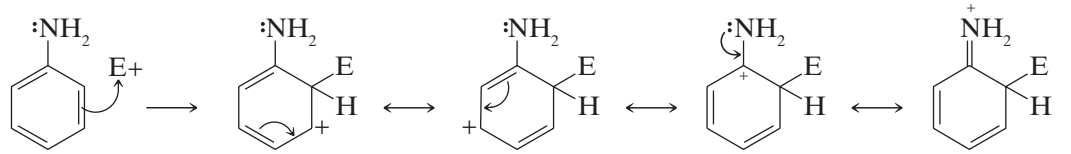
In order to understand these resonance effects, let us begin by recalling the effect of the amino group on electrophilic aromatic substitution reactions. The amino group is not only a powerful activating group, it is also a powerful ortho–para director. We saw earlier (Section 14.10D) that aniline reacts with bromine in aqueous solution at room temperature and in the absence of a catalyst to yield a product in which both ortho positions and the para position are substituted.

The inductive effect of the amino group makes it slightly electron withdrawing. Nitrogen, as we know, is more electronegative than carbon. The difference between the electronegativities of nitrogen and carbon in aniline is not large, however, because the carbon of the benzene ring is sp^2 hybridized and so it is somewhat more electronegative than it would be if it were sp^3 hybridized.

- The resonance effect of the amino group is far more important than its inductive effect in electrophilic aromatic substitution, and this resonance effect makes the amino group electron releasing.

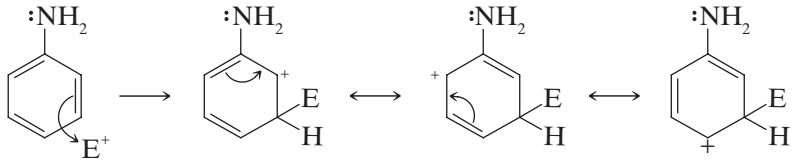
We can understand this effect if we write the resonance structures for the arenium ions that would arise from ortho, meta, and para attack on aniline:

Ortho Attack

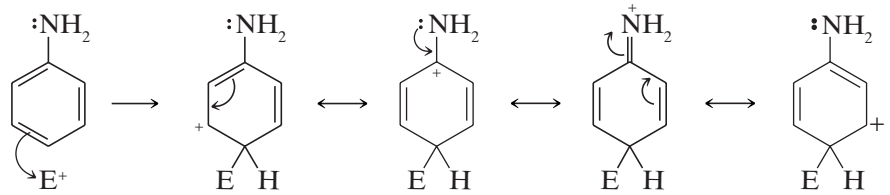


Relatively stable contributor

Meta Attack



Para Attack



Relatively stable contributor

Four reasonable resonance structures can be written for the arenium ions resulting from ortho and para attack, whereas only three can be written for the arenium ion that results from meta attack. This observation, in itself, suggests that the ortho- and para-substituted arenium ions should be more stable. Of greater importance, however, are the relatively stable structures that contribute to the hybrid for the ortho- and para-substituted arenium ions. In these structures, nonbonding pairs of electrons from nitrogen form an additional covalent bond to the carbon of the ring. This extra bond—and the fact that every atom in each of these structures has a complete outer octet of electrons—makes these structures the most stable of all of the contributors. Because these structures are unusually stable, they make a large—*and stabilizing*—contribution to the hybrid. This means, of course, that the ortho- and para-substituted arenium ions themselves are considerably more stable than the arenium ion that results from the meta attack. The transition states leading to the ortho- and para-substituted arenium ions occur at unusually low free energies. As a result, electrophiles react at the ortho and para positions very rapidly.

Practice Problem 14.8

Use resonance theory to explain why the hydroxyl group of phenol is an activating group and an ortho–para director. Illustrate your explanation by showing the arenium ions formed when phenol reacts with a Br^+ ion at the ortho, meta, and para positions.

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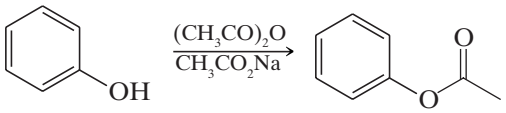
Practice Problem 14.9

Phenol reacts with acetic anhydride in the presence of sodium acetate to produce the ester phenyl acetate:



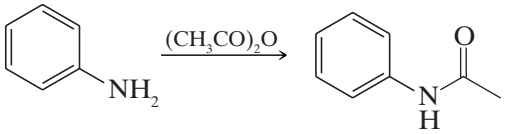
Phenol **Phenyl acetate**

The CH_3COO— group of phenyl acetate, like the —OH group of phenol (Practice Problem 14.8), is an ortho–para director.

(a) What structural feature of the CH_3COO— group explains this?

(b) Phenyl acetate, although undergoing reaction at the ortho and para positions, is less reactive toward electrophilic aromatic substitution than phenol. Use resonance theory to explain why this is so.

(c) Aniline is often so highly reactive toward electrophilic substitution that undesirable reactions take place (see Section 14.14A). One way to avoid these undesirable reactions is to convert aniline to acetanilide (below) by treating aniline with acetyl chloride or acetic anhydride:



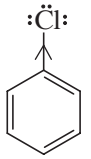
Aniline **Acetanilide**

What kind of directive effect would you expect the acetamido group (CH_3CONH—) to have?

(d) Explain why it is much less activating than the amino group, —NH_2.

The directive and reactivity effects of halo substituents may, at first, seem to be contradictory. *The halo groups are the only ortho–para directors* (in Table 14.2) *that are deactivating groups*. [Because of this behavior we have color coded halogen substituents green rather than red (electron donating) or blue (electron withdrawing).] All other deactivating groups are meta directors. We can readily account for the behavior of halo substituents, however, if we assume that their electron-withdrawing inductive effect influences *reactivity* and their electron-donating resonance effect governs *orientation*.

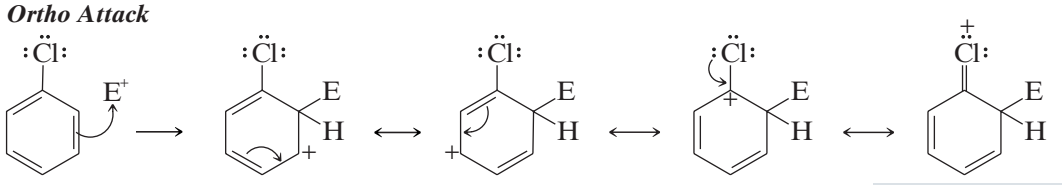
Let us apply these assumptions specifically to chlorobenzene. The chlorine atom is highly electronegative. Thus, we would expect a chlorine atom to withdraw electrons from the benzene ring and thereby deactivate it:



The inductive effect of the chlorine atom deactivates the ring.

On the other hand, when electrophilic attack does take place, the chlorine atom stabilizes the arenium ions resulting from ortho and para attack relative to that from meta attack. The chlorine atom does this in the same way as amino groups and hydroxyl groups do—***by donating an unshared pair of electrons***. These electrons give rise to relatively stable resonance structures contributing to the hybrids for the ortho- and para-substituted arenium ions.

Ortho Attack



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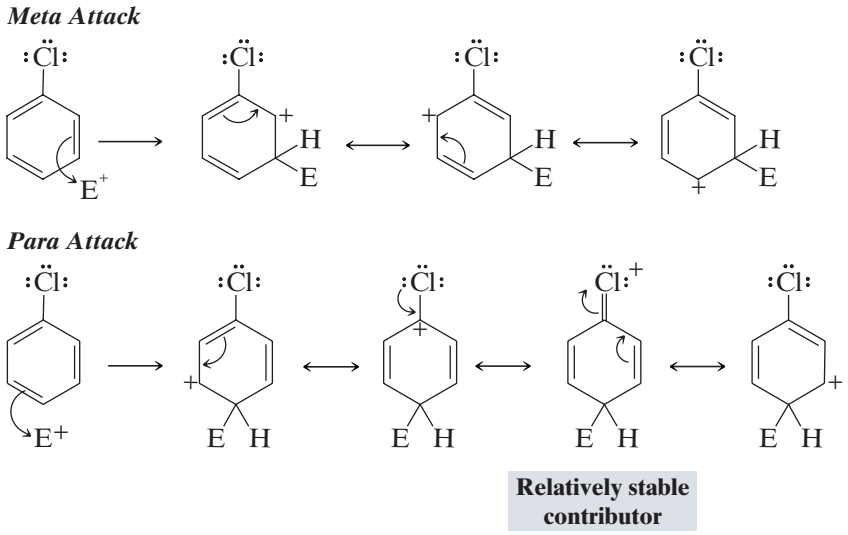


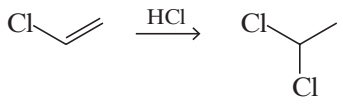
What we have said about chlorobenzene is also true of bromobenzene.
We can summarize the inductive and resonance effects of halo substituents in the following way.

- Through their electron-withdrawing inductive effect, halo groups make the ring more electron deficient than that of benzene. This causes the free energy of activation for any electrophilic aromatic substitution reaction to be greater than that for benzene, and, therefore, halo groups are deactivating.
- Through their electron-donating resonance effect, however, halo substituents cause the free energies of activation leading to ortho and para substitution to be lower than the free energy of activation leading to meta substitution. This makes halo substituents ortho–para directors.

You may have noticed an apparent contradiction between the rationale offered for the unusual effects of the halogens and that offered earlier for amino or hydroxyl groups. That is, oxygen is *more* electronegative than chlorine or bromine (and especially iodine). Yet the hydroxyl group is an activating group, whereas halogens are deactivating groups. An explanation for this can be obtained if we consider the relative stabilizing contributions made to the transition state leading to the arenium ion by resonance structures involving a group —G̈ (—G̈ = —N̈H$_2$, —Ö—H, —F̈:, —C̈l:, —B̈r:, —Ï:) that is directly attached to the benzene ring in which G donates an electron pair. If —G̈ is —Ö—H, or —N̈H$_2$, these resonance structures arise because of the overlap of a 2*p* orbital of carbon with that of oxygen or nitrogen. Such overlap is favorable because the atoms are almost the same size. With chlorine, however, donation of an electron pair to the benzene ring requires overlap of a carbon 2*p* orbital with a chlorine 3*p* orbital. Such overlap is less effective; the chlorine atom is much larger and its 3*p* orbital is much further from its nucleus. With bromine and iodine, overlap is even less effective. Justification for this explanation can be found in the observation that fluorobenzene (G = —F̈:) is the most reactive halobenzene in spite of the high electronegativity of fluorine and the fact that —F̈: is the most powerful ortho–para director of the halogens. With fluorine, donation of an electron pair arises from overlap of a 2*p* orbital of fluorine with a 2*p* orbital of carbon (as with —N̈H$_2$, and —Ö—H). This overlap is effective because the orbitals of =C< and —F̈: are of the same relative size.

Practice Problem 14.10

Chloroethene adds hydrogen chloride more slowly than ethene, and the product is 1,1-dichloroethane. How can you explain this using resonance and inductive effects?



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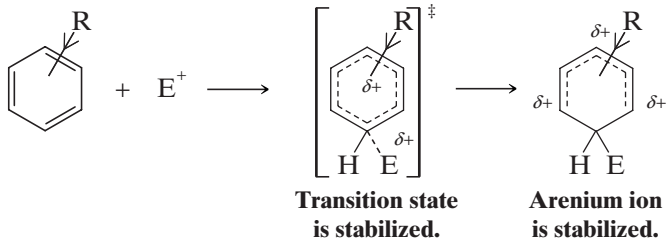
14.11E Ortho–Para Direction and Reactivity of Alkylbenzenes

Alkyl groups are better electron-releasing groups than hydrogen. Because of this, they can activate a benzene ring toward electrophilic substitution by stabilizing the transition state leading to the arenium ion:

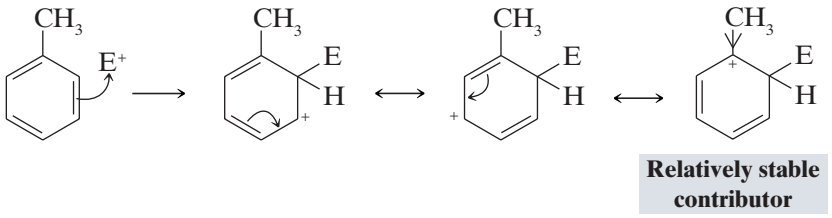


For an alkylbenzene the free energy of activation of the step leading to the arenium ion (just shown) is lower than that for benzene, and alkylbenzenes react faster.

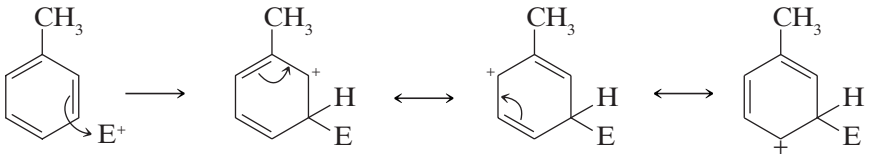
Alkyl groups are ortho–para directors. We can also account for this property of alkyl groups on the basis of their ability to release electrons—an effect that is particularly important when the alkyl group is attached directly to a carbon that bears a positive charge. (Recall the ability of alkyl groups to stabilize carbocations that we discussed in Section 6.11 and in Fig. 6.8.)

If, for example, we write resonance structures for the arenium ions formed when toluene undergoes electrophilic substitution, we get the results shown below:

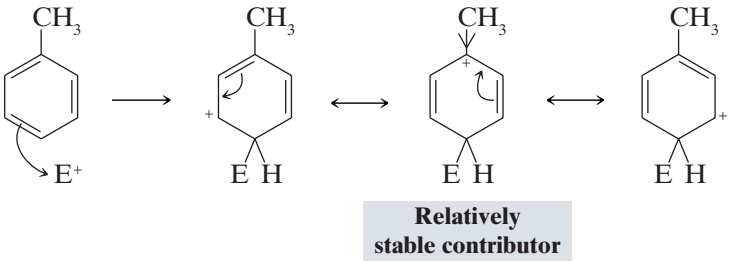
Ortho Attack



Meta Attack



Para Attack



In ortho attack and para attack we find that we can write resonance structures in which the methyl group is directly attached to a positively charged carbon of the ring. These structures are more *stable* relative to any of the others because in them the stabilizing influence of the methyl group (by inductive electron release) is most effective. These structures, therefore, make a large (stabilizing) contribution to the overall hybrid for ortho- and para-substituted arenium ions. No such relatively stable structure contributes to the hybrid for the meta-substituted arenium ion, and as a result it is less stable than the ortho- or para-substituted arenium ions. Since the ortho- and para-substituted arenium ions are more stable, the transition states leading to them occur at lower energy and ortho and para substitutions take place most rapidly.

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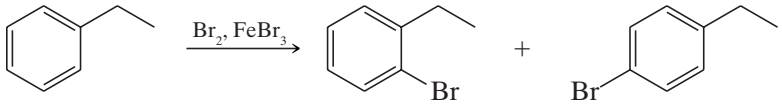
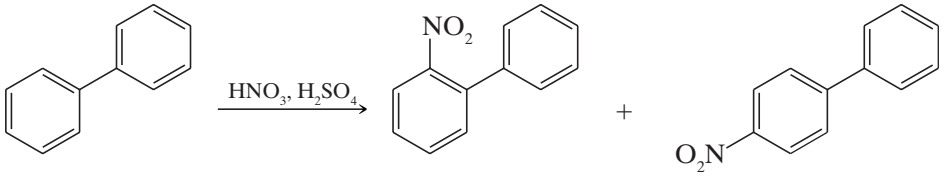
Practice Problem 14.11

Write resonance structures for the arenium ions formed when ethylbenzene reacts with a Br^+ ion (as formed from Br_2/$FeBr_3$) to produce the following ortho and para products.



Practice Problem 14.12

Provide a mechanism for the following reaction and explain why it occurs faster than nitration of benzene.

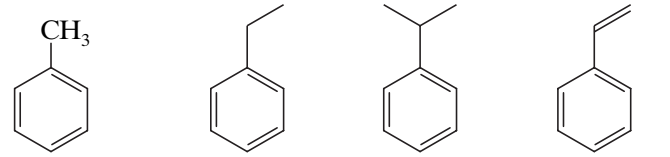


14.11F Summary of Substituent Effects on Orientation and Reactivity

With a theoretical understanding now in hand of **substituent effects** on orientation and reactivity, we refer you back to Table 14.2 for a summary of specific groups and their effects.

14.12 | REACTIONS OF THE SIDE CHAIN OF ALKYLBENZENES

Hydrocarbons that consist of both aliphatic and aromatic groups are also known as **arenes**. Toluene, ethylbenzene, and isopropylbenzene are **alkylbenzenes**:

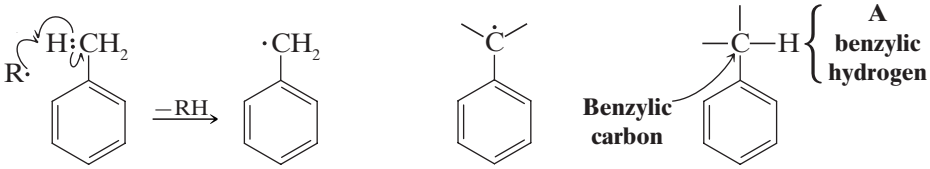


Methylbenzene (toluene) | **Ethylbenzene** | **Isopropyl-benzene (cumene)** | **Phenylethene (styrene or vinylbenzene)**

Phenylethene, usually called styrene, is an example of an **alkenylbenzene**. The aliphatic portion of these compounds is commonly called the **side chain**.

14.12A Benzylic Radicals and Cations

Hydrogen abstraction from the methyl group of methylbenzene (toluene) produces a radical called the **benzyl radical**:



Methylbenzene (toluene) | **The benzyl radical** | **A benzylic radical**

The name benzyl radical is used as a specific name for the radical produced in this reaction. The general name **benzylic radical** applies to all radicals that have an unpaired electron on the side-chain carbon atom that is directly attached

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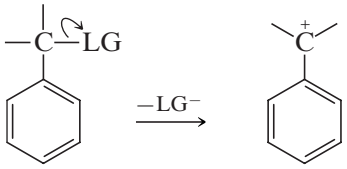
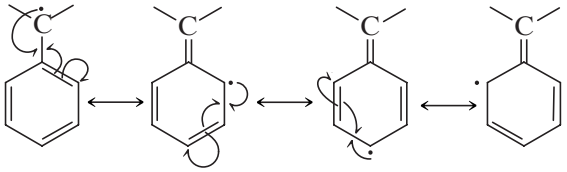
to the benzene ring (Section 10.9). The hydrogen atoms of the carbon atom directly attached to the benzene ring are called **benzylic hydrogen atoms**. A group bonded at a benzylic position is called a **benzylic substituent**.

Departure of a leaving group (LG) from a benzylic position produces a **benzylic cation**:

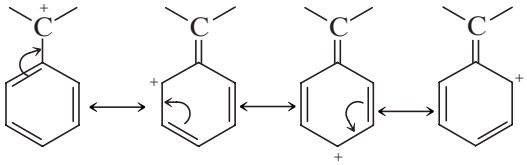


A benzylic cation

Benzylic radicals and benzylic cations are *conjugated unsaturated systems* and *both are unusually stable*. They have approximately the same stabilities as allylic radicals (Section 9.8) and allylic cations. This exceptional stability of benzylic radicals and cations can be explained by resonance theory. In the case of each entity, resonance structures can be written that place either the unpaired electron (in the case of the radical) or the positive charge (in the case of the cation) on an ortho or para carbon of the ring (see the following structures). Thus resonance delocalizes the unpaired electron or the charge, and this delocalization causes the radical or cation to be highly stabilized.



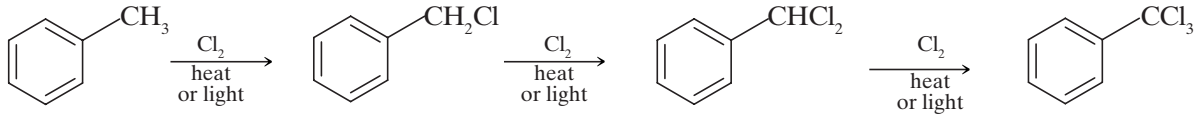
Benzylic radicals are stabilized by resonance.



Benzylic cations are stabilized by resonance.

14.12B Benzylic Halogenation of the Side Chain

We have already seen in this chapter that we can substitute bromine and chlorine for hydrogen atoms on the benzene ring of toluene and other alkylaromatic compounds using electrophilic aromatic substitution reactions. We can also substitute bromine and chlorine for hydrogen atoms on the **benzylic** carbons of alkyl side chains by radical reactions in the presence of heat, light, or a radical initiator like a peroxide, as we first saw in Chapter 9, (Section 9.8). This is made possible by the special stability of the benzylic radical intermediate (Section 14.12A). For example, benzylic chlorination of toluene takes place in the gas phase at 400–600 °C or in the presence of UV light, as shown here. Multiple substitutions occur with an excess of chlorine.

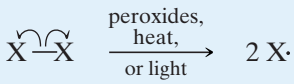


Benzyl chloride | **Dichloromethylbenzene** | **Trichloromethylbenzene**

A MECHANISM FOR THE REACTION — Benzylic Halogenation

Chain Initiation

Step 1



Peroxides, heat, or light cause halogen molecules to cleave into radicals.

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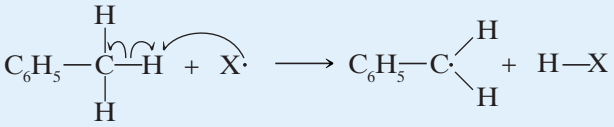
Chain Propagation

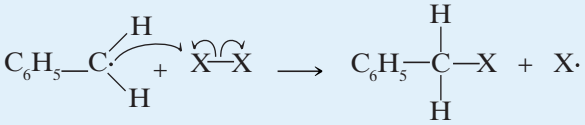
Step 2



Benzyl radical

A halogen radical abstracts a benzylic hydrogen atom, forming a benzylic radical and a molecule of the hydrogen halide.

Step 3

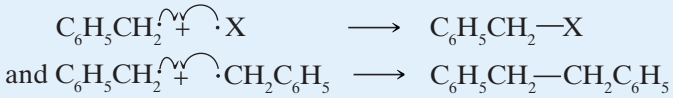


Benzyl radical **Benzyl halide**

The benzylic radical reacts with a halogen molecule to form the benzylic halide product and a halogen radical that propagates the chain.

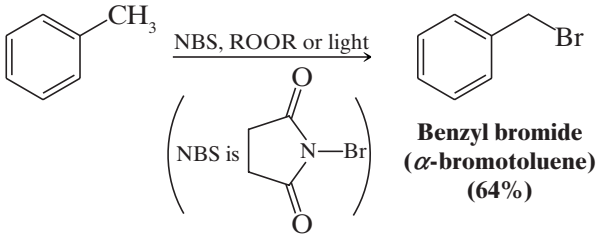
Chain Termination

Step 4



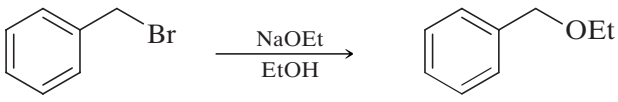
Various radical coupling reactions terminate the chain.

NBS (*N*-bromosuccinimide, Section 9.8) is often used in benzylic brominations because it provides a stoichiometric amount of bromine in low concentration.



Benzyl bromide (*α*-bromotoluene) (64%)

Benzylic halogenation provides a useful way to introduce a leaving group when a leaving group may be needed for subsequent nucleophilic substitution or elimination reactions. For example, if we wished to synthesize benzyl ethyl ether from toluene, benzyl bromide could be prepared from toluene as above, and then benzyl bromide could be allowed to react with sodium ethoxide as follows.



Benzyl ethyl ether

14.13 | ALKENYLBENZENES

14.13A Stability of Conjugated Alkenylbenzenes

- Alkenylbenzenes that have their side-chain double bond conjugated with the benzene ring are more stable than those that do not:

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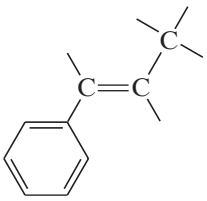
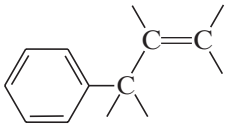


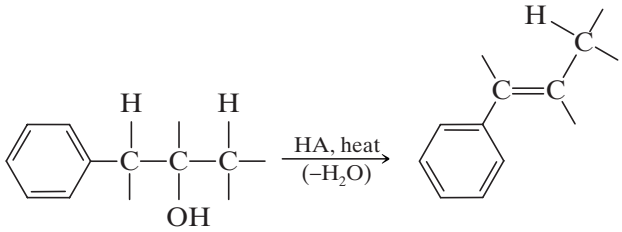
Conjugated system

is more stable than



Nonconjugated system

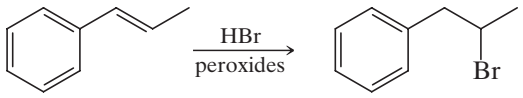
Part of the evidence for this comes from acid-catalyzed alcohol dehydrations, which are known to yield the most stable alkene (Section 7.8A). For example, dehydration of an alcohol such as the one that follows yields exclusively the conjugated system:



Because conjugation always lowers the energy of an unsaturated system by allowing the π electrons to be delocalized, this behavior is just what we would expect.

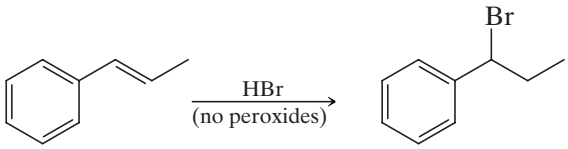
14.13B Additions to the Double Bond of Alkenylbenzenes

In the presence of peroxides, HBr adds to the double bond of 1-phenylpropene to give 2-bromo-1-phenylpropane as the major product:



1-Phenylpropene **2-Bromo-1-phenylpropane**

In the absence of peroxides, HBr adds in just the opposite way:



1-Phenylpropene **1-Bromo-1-phenylpropane**

The addition of hydrogen bromide to 1-phenylpropene proceeds through a benzylic radical in the presence of peroxides and through a benzylic cation in their absence (see Practice Problem 14.15 and Section 9.8).

Practice Problem 14.13

Write mechanisms for the reactions whereby HBr adds to 1-phenylpropene **(a)** in the presence of peroxides and **(b)** in the absence of peroxides. In each case account for the regiochemistry of the addition (i.e., explain why the major product is 2-bromo-1-phenylpropane when peroxides are present and why it is 1-bromo-1-phenylpropane when peroxides are absent).

Practice Problem 14.14

(a) What would you expect to be the major product when 1-phenylpropene reacts with HCl?
(b) What product would you expect when it is subjected to oxymercuration–demercuration?

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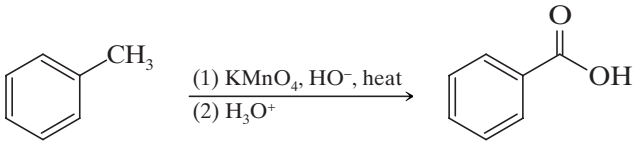
14.13C Oxidation of the Side Chain

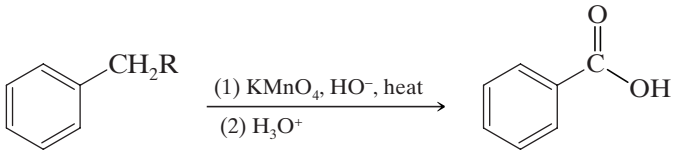
Strong oxidizing agents oxidize toluene to benzoic acid. The oxidation can be carried out by the action of hot alkaline potassium permanganate. This method gives benzoic acid in almost quantitative yield:



Benzoic acid (~100%)

An important characteristic of side-chain oxidations is that oxidation takes place initially at the benzylic carbon.

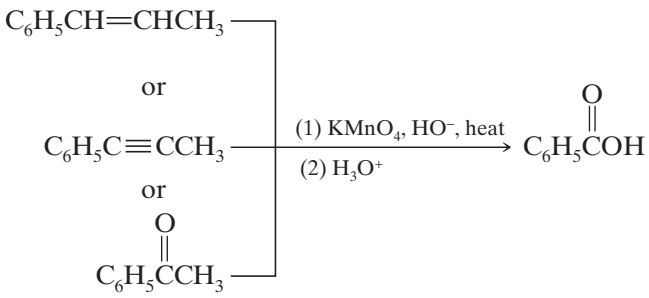
- Alkylbenzenes with alkyl groups longer than methyl are ultimately degraded to benzoic acids:



An alkylbenzene **Benzoic acid**

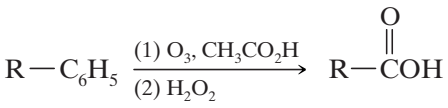
Side-chain oxidations are similar to benzylic halogenations, because in the first step the oxidizing agent abstracts a benzylic hydrogen. Once oxidation is begun at the benzylic carbon, it continues at that site. Ultimately, the oxidizing agent oxidizes the benzylic carbon to a carboxyl group, and, in the process, it cleaves off the remaining carbon atoms of the side chain. (*tert*-Butylbenzene is resistant to side-chain oxidation. Why?)

- Side-chain oxidation is not restricted to alkyl groups. Alkenyl, alkynyl, and acyl groups are also oxidized by hot alkaline potassium permanganate.



14.13D Oxidation of the Benzene Ring

The benzene ring carbon where an alkyl group is bonded can be converted to a carboxyl group by ozonolysis, followed by treatment with hydrogen peroxide.



14.14 | SYNTHETIC APPLICATIONS

The substitution reactions of aromatic rings and the reactions of the side chains of alkyl- and alkenylbenzenes, when taken together, offer us a powerful set of reactions for organic synthesis. By using these reactions skillfully, we shall be able to synthesize a large number of benzene derivatives.

- Part of the skill in planning a synthesis is deciding in what order to carry out the reactions.

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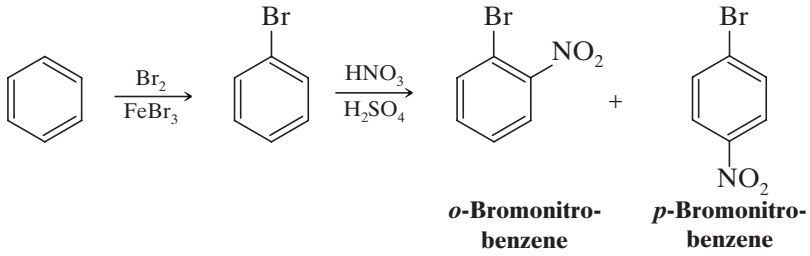
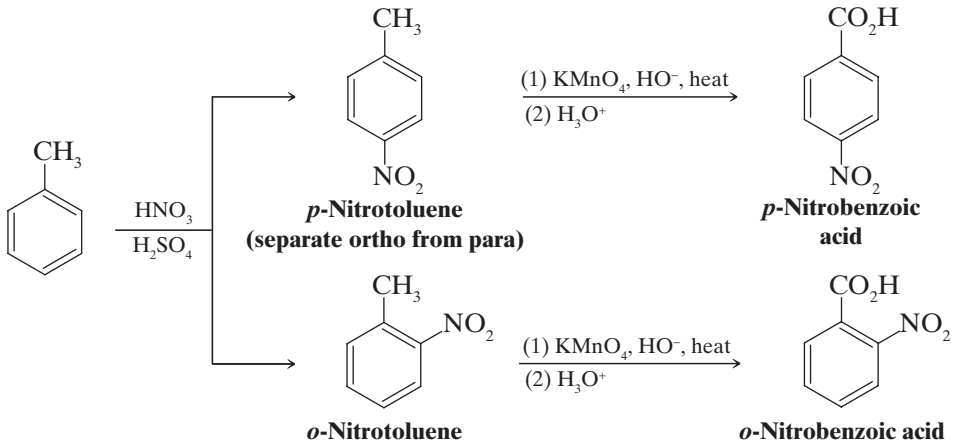
Let us suppose, for example, that we want to synthesize *o*-bromonitrobenzene. We can see very quickly that we should introduce the bromine into the ring first because it is an ortho–para director:

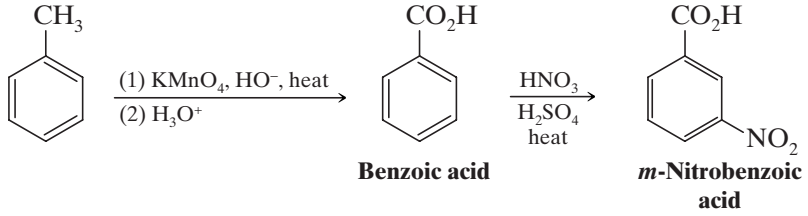


The ortho and para products can be separated by various methods because they have different physical properties. However, had we introduced the nitro group first, we would have obtained *m*-bromonitrobenzene as the major product.

Other examples in which choosing the proper order for the reactions is important are the syntheses of the *ortho*-, *meta*-, and *para*-nitrobenzoic acids. Because the methyl group of toluene is an electron-donating group (shown in red below), we can synthesize the *ortho*- and *para*-nitrobenzoic acids from toluene by nitrating it, separating the *ortho*- and *para*-nitrotoluenes, and then oxidizing the methyl groups to carboxyl groups:



We can synthesize *m*-nitrobenzoic acid by reversing the order of the reactions. We oxidize the methyl group to a carboxylic acid, then use the carboxyl as an electron-withdrawing group (shown in blue) to direct nitration to the meta position.



Solved Problem 14.5

Starting with toluene, outline a synthesis of **(a)** 1-bromo-2-trichloromethylbenzene, **(b)** 1-bromo-3-trichloromethylbenzene, and **(c)** 1-bromo-4-trichloromethylbenzene.

Answer

Compounds **(a)** and **(c)** can be obtained by ring bromination of toluene followed by benzylic radical chlorination of the side chain using three molar equivalents of chlorine:

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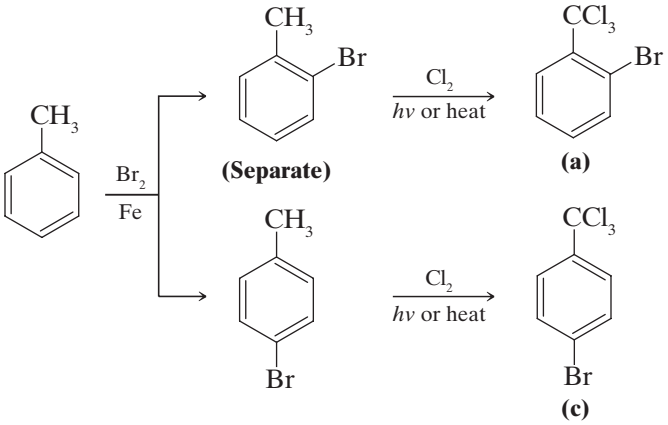
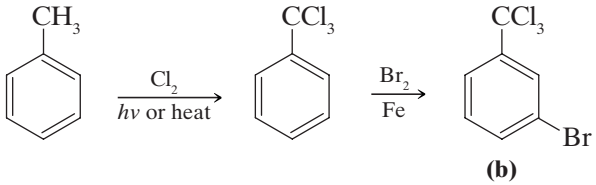
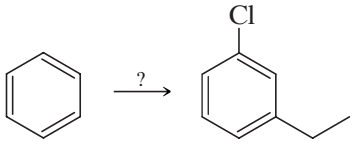


To make compound **(b)**, we reverse the order of the reactions. By converting the side chain to a —CCl_3 group first, we create a meta director, which causes the bromine to enter the desired position:



Practice Problem 14.15

Suppose you needed to synthesize *m*-chloroethylbenzene from benzene.



You could begin by chlorinating benzene and then follow with a Friedel–Crafts alkylation using chloroethane and $AlCl_3$, or you could begin with a Friedel–Crafts alkylation followed by chlorination. Neither method will give the desired product, however.

(a) Why will neither method give the desired product?

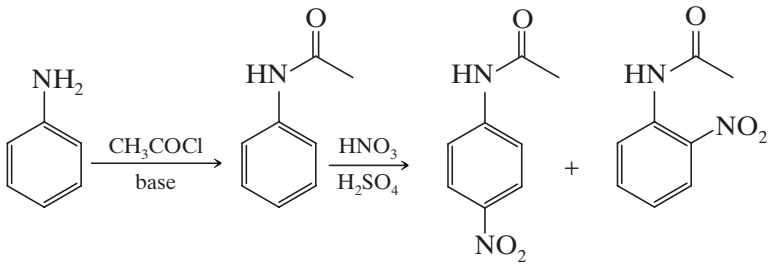
(b) There is a three-step method that will work if the steps are done in the right order. What is this method?

14.14A Use of Protecting and Blocking Groups

- Very powerful activating groups such as amino groups and hydroxyl groups cause the benzene ring to be so reactive that undesirable reactions may take place.

Some reagents used for electrophilic substitution reactions, such as nitric acid, are also strong *oxidizing agents*. Both electrophiles and oxidizing agents seek electrons. Thus, amino groups and hydroxyl groups not only activate the ring toward electrophilic substitution but also activate it toward oxidation. Nitration of aniline, for example, results in considerable destruction of the benzene ring because it is oxidized by the nitric acid. Direct nitration of aniline, consequently, is not a satisfactory method for the preparation of *o*- and *p*-nitroaniline.

Treating aniline with acetyl chloride, CH_3COCl, or acetic anhydride, $(CH_3CO)_2O$, converts the amino group of aniline to an amide (specifically an acetamido group, —$NHCOCH_3$), forming acetanilide. An amide group is only moderately activating, and it does not make the ring highly susceptible to oxidation during nitration (see Practice Problem 14.9). Thus, with the amino group of aniline blocked in acetanilide, direct nitration becomes possible:



Aniline | **Acetanilide** | ***p*-Nitroacetanilide (90%)** | ***o*-Nitroacetanilide (trace)**

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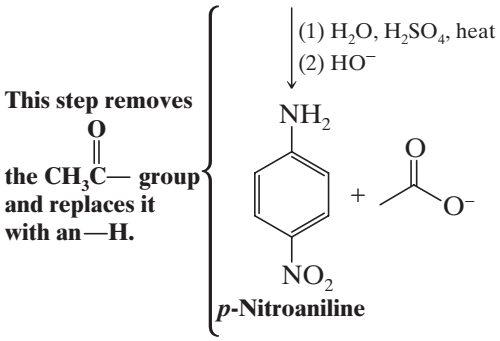
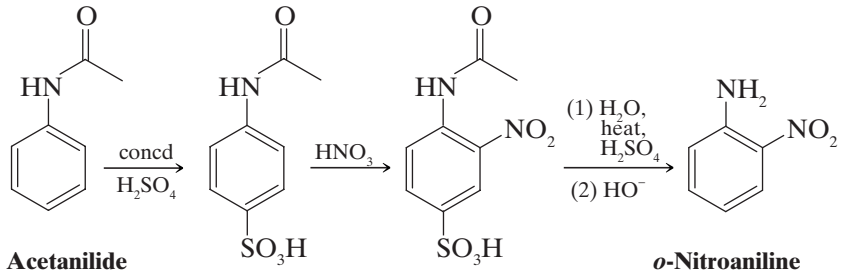


Nitration of acetanilide gives *p*-nitroacetanilide in excellent yield with only a trace of the ortho isomer. Acidic hydrolysis of *p*-nitroacetanilide (Section 17.8F) removes the acetyl group and gives *p*-nitroaniline, also in good yield.

Suppose, however, that we need *o*-nitroaniline. The synthesis that we just outlined would obviously not be a satisfactory method, for only a trace of *o*-nitroacetanilide is obtained in the nitration reaction. (The acetamido group is purely a para director in many reactions. Bromination of acetanilide, for example, gives *p*-bromoacetanilide almost exclusively.)

We can synthesize *o*-nitroaniline, however, through the reactions that follow:

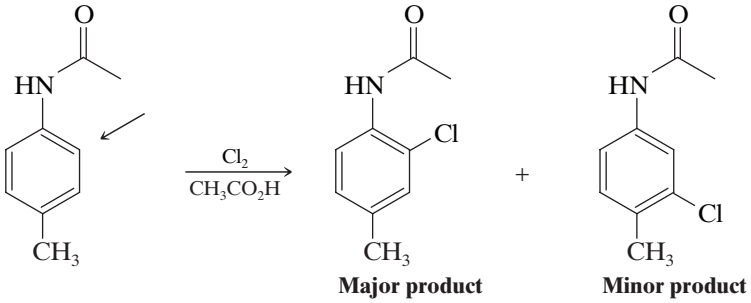


Here we see how a sulfonic acid group can be used as a "blocking group." We can remove the sulfonic acid group by desulfonation at a later stage. In this example, the reagent used for desulfonation (dilute H_2SO_4) also conveniently removes the acetyl group that we employed to "protect" the benzene ring from oxidation by nitric acid.

14.14B Orientation in Disubstituted Benzenes

- When two different groups are present on a benzene ring, the more powerful activating group (Table 14.2) generally determines the outcome of the reaction.

Let us consider, as an example, the orientation of electrophilic substitution of *p*-methylacetanilide. The amide group is a much stronger activating group than the methyl group. The following example shows that the amide group determines the outcome of the reaction. Substitution occurs primarily at the position ortho to the amide group:



- An ortho–para director takes precedence over a meta director in determining the position of substitution because all ortho–para-directing groups are more activating than meta directors.

Steric effects are also important in aromatic substitutions.

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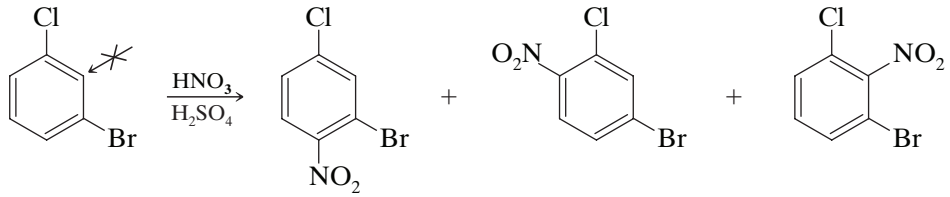
- Substitution does not occur to an appreciable extent between meta substituents if another position is open.

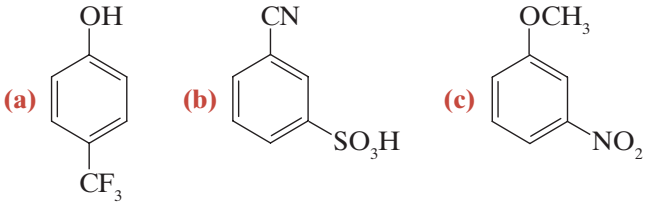
A good example of this effect can be seen in the nitration of *m*-bromochlorobenzene:



Only 1% of the mononitro product has the nitro group between the bromine and chlorine.

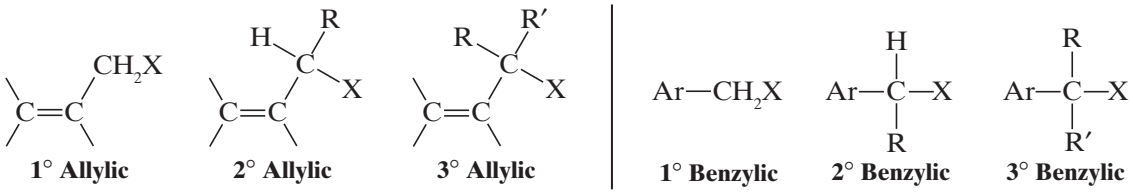
Practice Problem 14.16

Predict the major product (or products) that would be obtained when each of the following compounds is nitrated:



14.15 | ALLYLIC AND BENZYLIC HALIDES IN NUCLEOPHILIC SUBSTITUTION REACTIONS

Allylic and benzylic halides can be classified in the same way that we have classified other organic halides:



All of these compounds undergo nucleophilic substitution reactions. As with other tertiary halides (Section 6.13A), the steric hindrance associated with having three bulky groups on the carbon bearing the halogen prevents tertiary allylic and tertiary benzylic halides from reacting by an S_N2 mechanism. They react with nucleophiles only by an S_N1 mechanism.

Primary and secondary allylic and benzylic halides can react either by an S_N2 mechanism or by an S_N1 mechanism in ordinary nonacidic solvents. We would expect these halides to react by an S_N2 mechanism because they are structurally similar to primary and secondary alkyl halides. (Having only one or two groups attached to the carbon bearing the halogen does not prevent S_N2 attack.) But primary and secondary allylic and benzylic halides can also react by an S_N1 mechanism because they can form relatively stable **allylic carbocations** and **benzylic carbocations**, and in this regard they differ from primary and secondary alkyl halides.*

- Overall we can summarize the effect of structure on the reactivity of alkyl, allylic, and benzylic halides in the ways shown in Table 14.3.

*There is some dispute as to whether 2° alkyl halides react by an S_N1 mechanism to any appreciable extent in ordinary nonacidic solvents such as mixtures of water and alcohol or acetone, but it is clear that reaction by an S_N2 mechanism is, for all practical purposes, the more important pathway.

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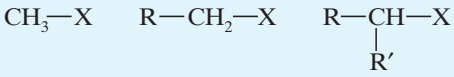
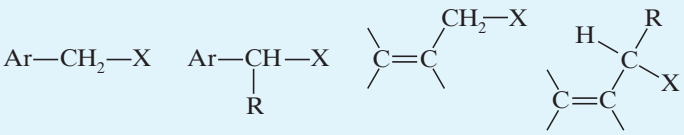
Table 14.3 A Summary of Alkyl, Allylic, and Benzylic Halides in S_N Reactions

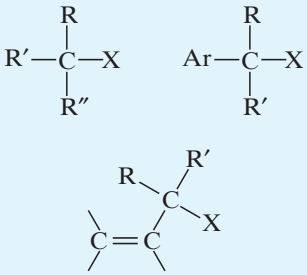
These halides give mainly S_N2 reactions.



These halides may give either S_N1 or S_N2 reactions.



These halides give mainly S_N1 reactions.

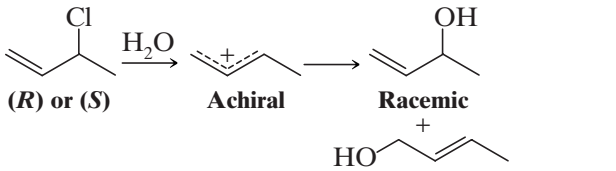


Solved Problem 14.6

When either enantiomer of 3-chloro-1-butene [(*R*) or (*S*)] is subjected to hydrolysis, the products of the reaction are optically inactive. Explain these results.

Answer

The solvolysis reaction is S_N1. The intermediate allylic cation is achiral and therefore reacts with water to give the enantiomeric 3-buten-2-ols in equal amounts and to give some of the achiral 2-buten-1-ol:



(*R*) or (*S*) **Achiral** **Racemic**

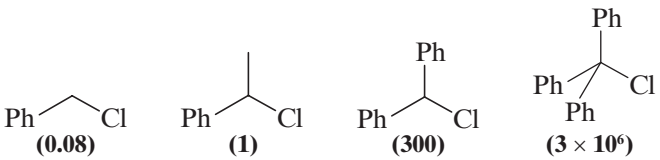
Achiral
(but two diastereomers are possible)

Practice Problem 14.17

Primary halides of the type $ROCH_2X$ apparently undergo S_N1-type reactions, whereas most primary halides do not. Can you propose a resonance explanation for the ability of halides of the type $ROCH_2X$ to undergo S_N1 reactions?

Practice Problem 14.18

The following chlorides (Ph = phenyl) undergo solvolysis in ethanol at the relative rates given in parentheses. How can you explain these results?



(0.08) **(1)** **(300)** **(3×10^6)**

14.16 | REDUCTION OF AROMATIC COMPOUNDS

Hydrogenation of benzene under pressure using a metal catalyst such as nickel results in the addition of three molar equivalents of hydrogen and the formation of cyclohexane (Section 13.3). The intermediate cyclohexadienes and cyclohexene cannot be isolated because these undergo catalytic hydrogenation faster than benzene does.

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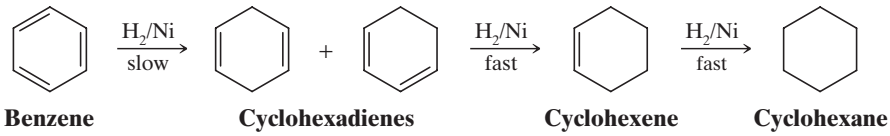
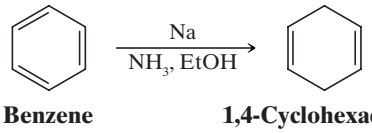


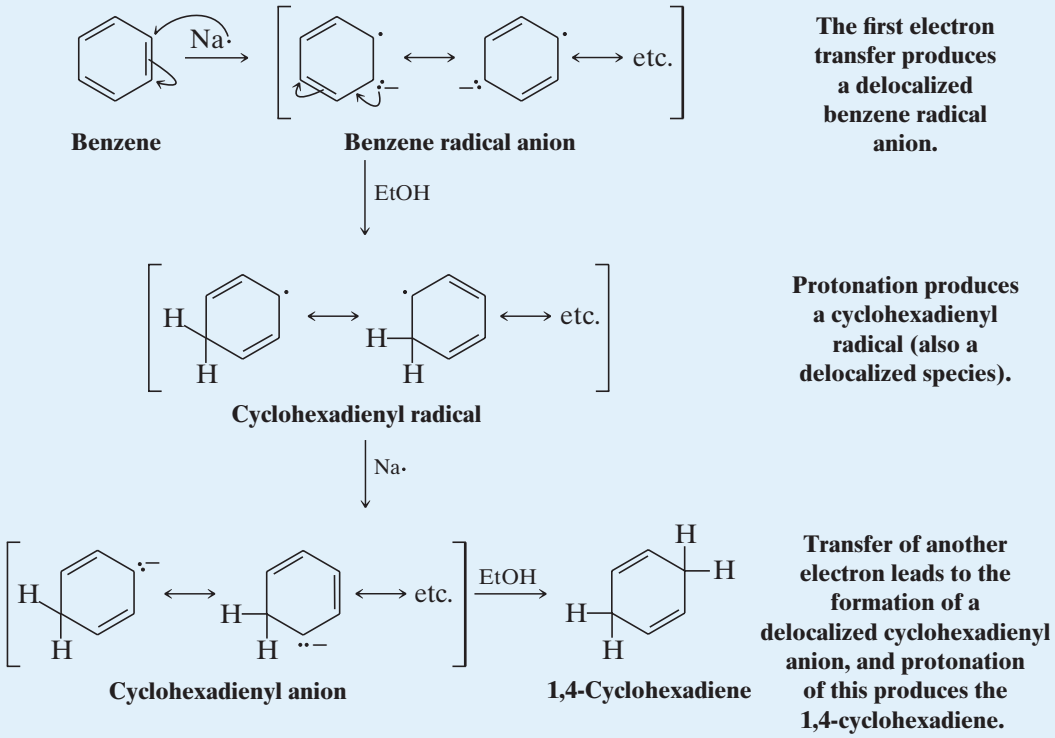
14.16A The Birch Reduction

Benzene can be reduced to 1,4-cyclohexadiene by treating it with an alkali metal (sodium, lithium, or potassium) in a mixture of liquid ammonia and an alcohol. This reaction is called the **Birch reduction**, after A. J. Birch, the Australian chemist who developed it.



The Birch reduction is a dissolving metal reduction, and the mechanism for it resembles the mechanism for the reduction of alkynes that we studied in Section 7.15B. A sequence of electron transfers from the alkali metal and proton transfers from the alcohol takes place, leading to a 1,4-cyclohexadiene. The reason for formation of a 1,4-cyclohexadiene in preference to the more stable conjugated 1,3-cyclohexadiene is not understood.

A MECHANISM FOR THE REACTION — Birch Reduction



Substituent groups on the benzene ring influence the course of the reaction. Birch reduction of methoxybenzene (anisole) leads to the formation of 1-methoxy-1,4-cyclohexadiene, a compound that can be hydrolyzed by dilute acid to 2-cyclohexenone. This method provides a useful synthesis of 2-cyclohexenones:

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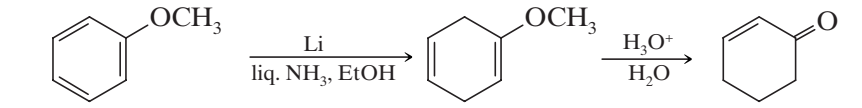
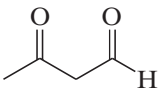
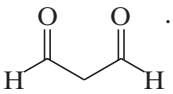


Methoxybenzene (anisole) → **1-Methoxy-1,4-cyclohexadiene (84%)** → **2-Cyclohexenone**

Practice Problem 14.19

Birch reduction of toluene leads to a product with the molecular formula C_7H_{10}. On ozonolysis followed by reduction with dimethyl sulfide, the product is transformed into  and  . What is the structure of the Birch reduction product?

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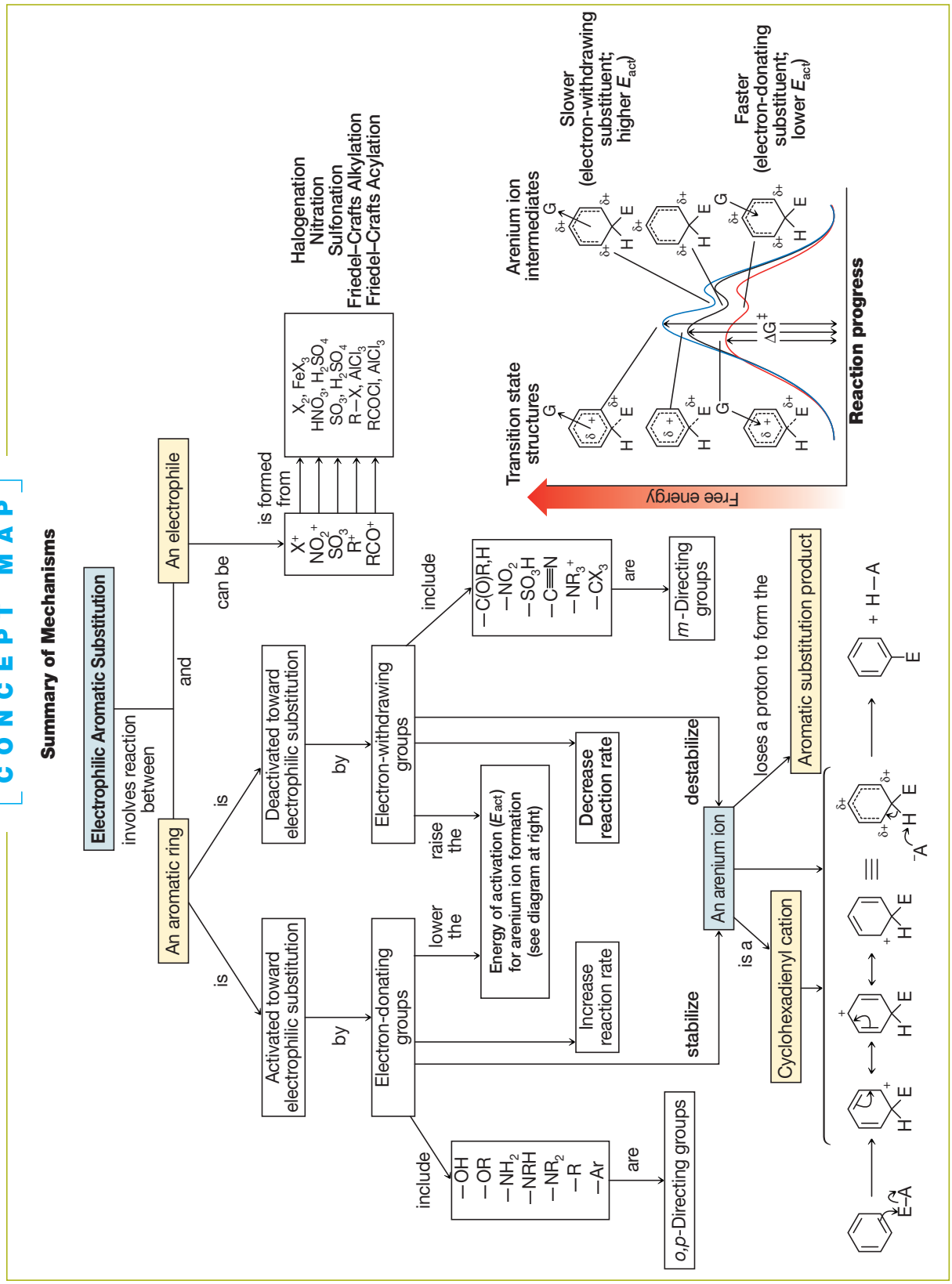

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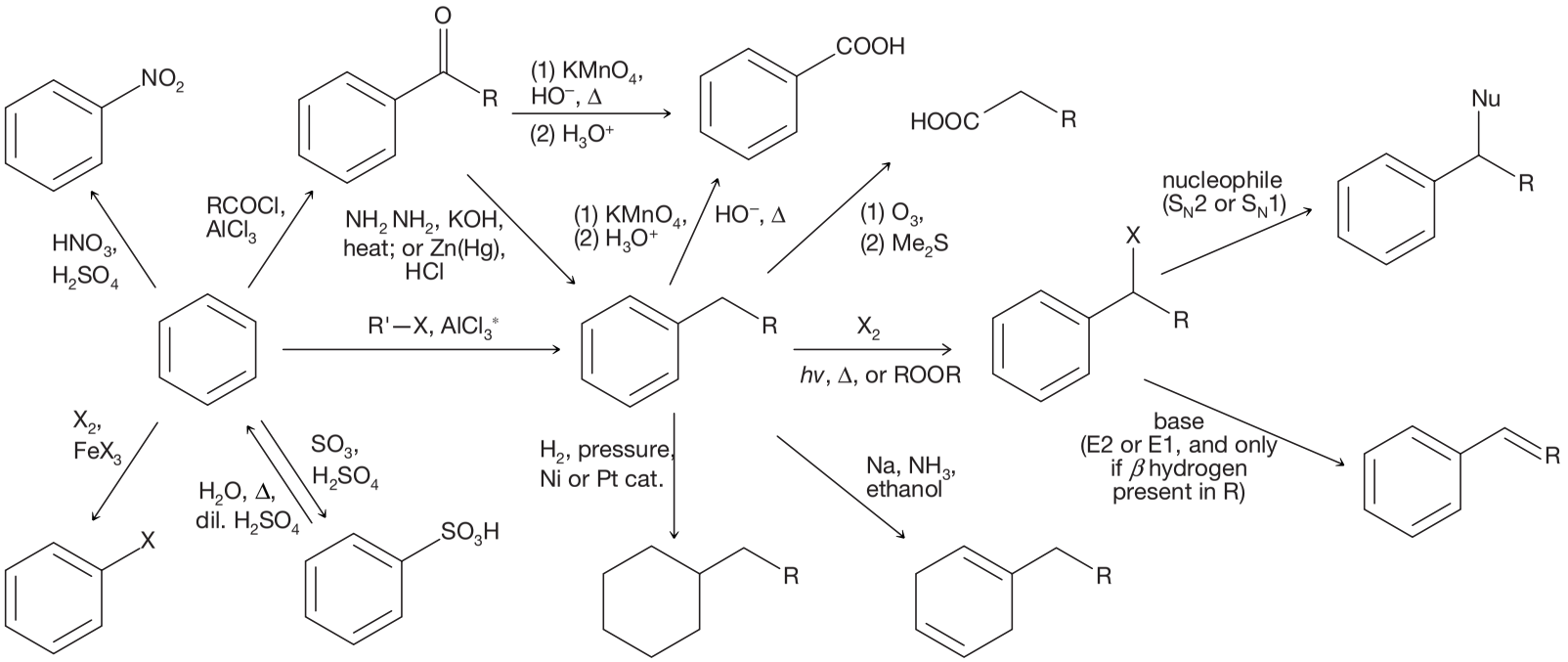
CONCEPT MAP

Some Synthetic Connections of Benzene and Aryl Derivatives

- Nitration
- Halogenation
- Sulfonation/desulfonation
- Friedel–Crafts alkylation
- Friedel–Crafts acylation
- Wolff–Kishner or Clemmensen reduction
- Side-chain oxidation
- Ring oxidation
- Catalytic hydrogenation of ring
- Birch reduction
- Benzylic radical halogenation
- Benzylic substitution/elimination



*In the Friedel–Crafts alkylation example shown here, R′ is a primary alkyl halide. If carbocation rearrangements are likely, then Friedel–Crafts acylation followed by Wolff–Kishner or Clemmensen reduction should be used to incorporate a primary alkyl group.

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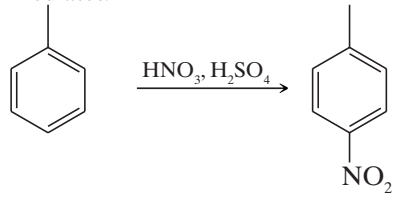
REVIEW PROBLEMS

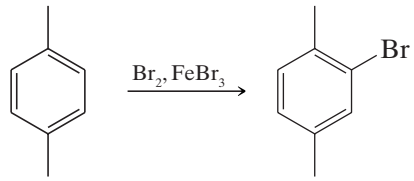
Mechanisms

14.20 Provide a detailed mechanism for each of the following reactions. Include contributing resonance structures and the resonance hybrid for the arenium ion intermediates.

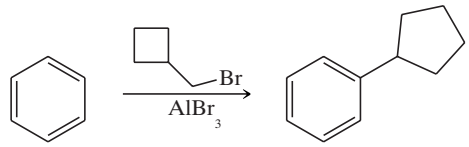
(a)



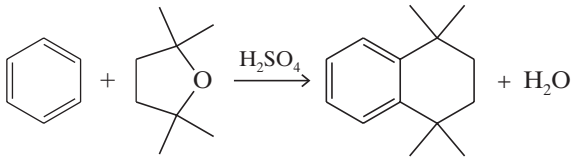
(b)



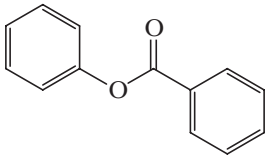
(c)



14.21 Provide a detailed mechanism for the following reaction.

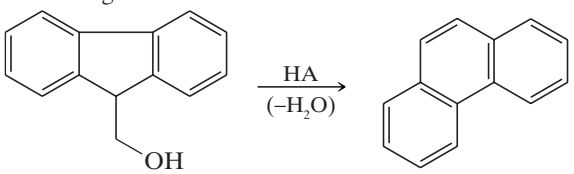


14.22 One ring of phenyl benzoate undergoes electrophilic aromatic substitution much more readily than the other. **(a)** Which one is it? **(b)** Explain your answer.

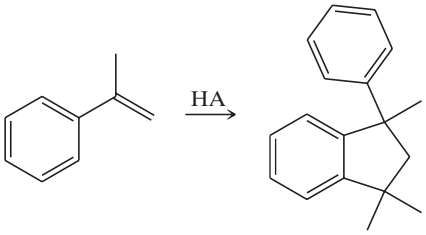


14.23 Write mechanisms that account for the products of the following reactions:

(a)



(b)



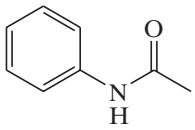
Reactions and Synthesis

14.24 Predict the major product (or products) formed when each of the following reacts with Cl_2 and $FeCl_3$:

(a) Ethylbenzene
(b) Anisole (methoxybenzene)
(c) Fluorobenzene
(d) Benzoic acid
(e) Nitrobenzene
(f) Chlorobenzene
(g) Biphenyl (C_6H_5—C_6H_5)
(h) Ethyl phenyl ether

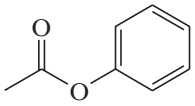
14.25 Predict the major product (or products) formed when each of the following reacts with a mixture of concentrated HNO_3 and H_2SO_4.

(a)



Acetanilide

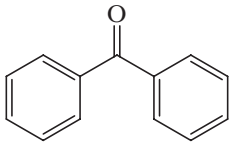
(b)



Phenyl acetate

(c) 4-Chlorobenzoic acid
(d) 3-Chlorobenzoic acid

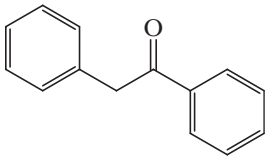
(e)



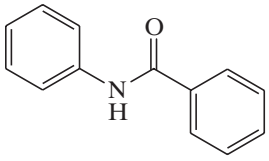
Benzophenone

14.26 What monobromination product (or products) would you expect to obtain when the following compounds undergo ring bromination with Br_2 and $FeBr_3$?

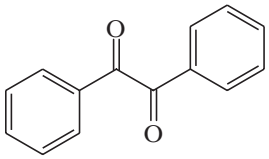
(a)



(b)

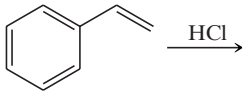


(c)



14.27 Predict the major products of the following reactions:

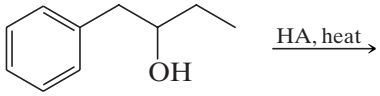
(a)



Styrene

(b) 2-Bromo-1-phenylpropane $\xrightarrow{EtONa}$

(c)



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(d) Product of (c) + HBr $\xrightarrow{\text{peroxides}}$

(e) Product of (c) + H_2O $\xrightarrow[\text{heat}]{\text{HA}}$

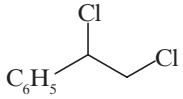
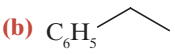
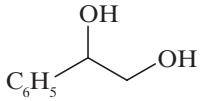
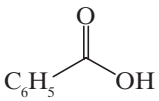
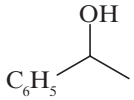
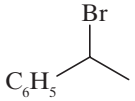
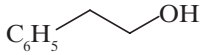
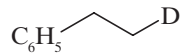
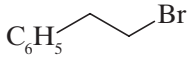
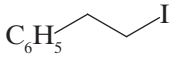
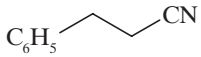
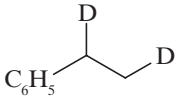
(f) Product of (c) + H_2 (1 molar equivalent) $\xrightarrow[25\ ^\circ C]{Pt}$

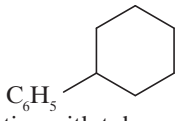
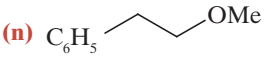
(g) Product of (f) $\xrightarrow[(2)H_3O^+]{(1)\ KMnO_4,\ HO^-,\ \text{heat}}$

14.28 Starting with benzene, outline a synthesis of each of the following:

(a) Isopropylbenzene
(b) *tert*-Butylbenzene
(c) Propylbenzene
(d) Butylbenzene
(e) 1-*tert*-Butyl-4-chlorobenzene
(f) 1-Phenylcyclopentene
(g) *trans*-2-Phenylcyclopentanol
(h) *m*-Dinitrobenzene
(i) *m*-Bromonitrobenzene
(j) *p*-Bromonitrobenzene
(k) *p*-Chlorobenzenesulfonic acid
(l) *o*-Chloronitrobenzene
(m) *m*-Nitrobenzenesulfonic acid

14.29 Starting with styrene, outline a synthesis of each of the following:

(a) 
(b) 
(c) 
(d) 
(e) 
(f) 
(g) 
(h) 
(i) 
(j) 
(k) 
(l) 

(m) 
(n) 

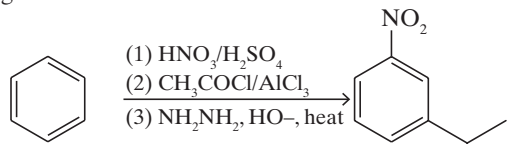
14.30 Starting with toluene, outline a synthesis of each of the following:

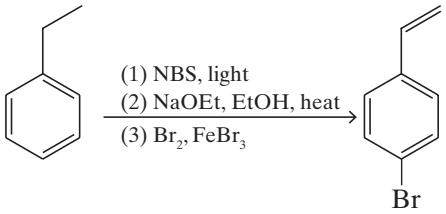
(a) *m*-Chlorobenzoic acid
(b) *p*-Methylacetophenone
(c) 2-Bromo-4-nitrotoluene
(d) *p*-Bromobenzoic acid
(e) 1-Chloro-3-trichloromethylbenzene
(f) *p*-Isopropyltoluene (*p*-cymene)
(g) 1-Cyclohexyl-4-methylbenzene
(h) 2,4,6-Trinitrotoluene (TNT)
(i) 4-Chloro-2-nitrobenzoic acid
(j) 1-Butyl-4-methylbenzene

14.31 Starting with aniline, outline a synthesis of each of the following:

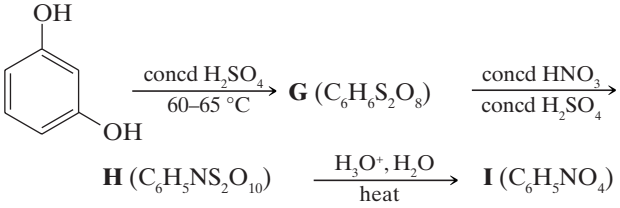
(a) *p*-Bromoaniline **(b)** *o*-Bromoaniline
(c) 2-Bromo-4-nitroaniline **(d)** 4-Bromo-2-nitroaniline
(e) 2,4,6-Tribromoaniline

14.32 Both of the following syntheses will fail. Explain what is wrong with each one.

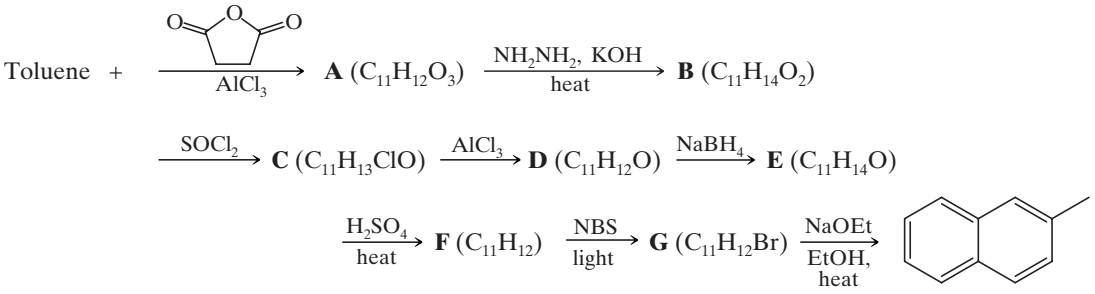
(a) 

(b) 

14.33 Propose structures for compounds **G–I:**



14.34 2-Methylnaphthalene can be synthesized from toluene through the following sequence of reactions. Write the structure of each intermediate.



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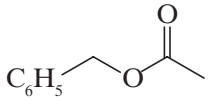
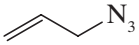
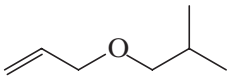
General Problems

14.35 Show how you might synthesize each of the following compounds starting with either benzyl bromide or allyl bromide:

(a) $C_6H_5CH_2CN$ **(b)** $C_6H_5CH_2OMe$

(c)  **(d)** $C_6H_5CH_2I$

(e)  **(f)** 

14.36 Provide structures for compounds **A** and **B**:

$$\text{Benzene} \xrightarrow[\text{liq. } NH_3, \text{EtOH}]{\text{Na}} \mathbf{A}\ (C_6H_8) \xrightarrow{\text{NBS}} \mathbf{B}\ (C_6H_7Br)$$

14.37 Ring nitration of a dimethylbenzene (a xylene) results in the formation of only one dimethylnitrobenzene. Which dimethylbenzene isomer was the reactant?

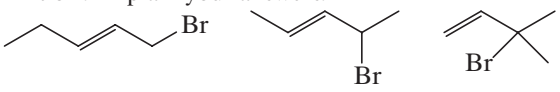
14.38 Treating cyclohexene with acetyl chloride and $AlCl_3$ leads to the formation of a product with the molecular formula $C_8H_{13}ClO$. Treating this product with a base leads to the formation of 1-acetylcyclohexene. Propose mechanisms for both steps of this sequence of reactions.

14.39 When toluene is sulfonated (concentrated H_2SO_4) at room temperature, predominantly (about 95% of the total) ortho and para substitution occurs. If elevated temperatures (150–200 °C) and longer reaction times are employed, meta (chiefly) and para substitution account for some 95% of the products. Account for these differences in terms of kinetic and thermodynamic pathways. (*Hint: m*-Toluenesulfonic acid is the most stable isomer.)

14.40 A C—D bond is harder to break than a C—H bond, and, consequently, reactions in which C—D bonds are broken proceed more slowly than reactions in which C—H bonds are broken. What mechanistic information comes from the observation that perdeuterated benzene, C_6D_6, is nitrated at the same rate as normal benzene, C_6H_6?

14.41 Heating 1,1,1-triphenylmethanol with ethanol containing a trace of a strong acid causes the formation of 1-ethoxy-1,1,1-triphenylmethane. Write a plausible mechanism that accounts for the formation of this product.

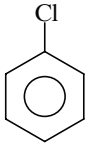
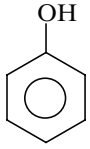
14.42 **(a)** Which of the following halides would you expect to be most reactive in an S_N2 reaction? **(b)** In an S_N1 reaction? Explain your answers.

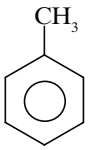
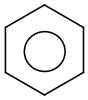


ADDITIONAL OBJECTIVE QUESTIONS

Single Correct Choice Type

1. Which of the following will be most easily attacked by an electrophile?

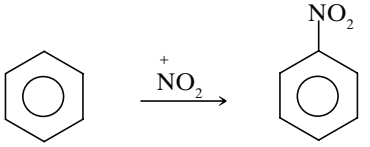
(a)  **(b)** 

(c)  **(d)** 

2. Presence of a nitro group in a benzene ring
- **(a)** activates the ring towards electrophilic substitution.
- **(b)** renders the ring basic.
- **(c)** deactivates the ring towards nucleophilic substitution.
- **(d)** deactivates the ring towards electrophilic substitution.

3. The chlorination of toluene in presence of ferric chloride gives predominantly
- **(a)** benzyl chloride. **(b)** *m*-chlorotoluene.
- **(c)** benzal chloride. **(d)** *o*-and *p*-chlorotoluene.

4. The following reaction is known as

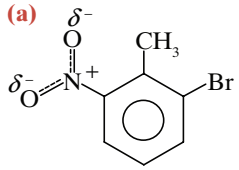
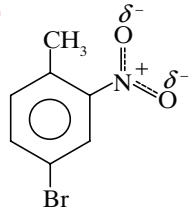


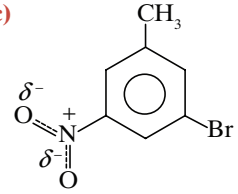
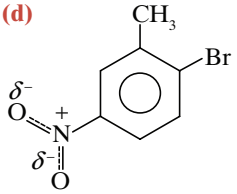
- **(a)** nucleophilic addition reaction.
- **(b)** electrophilic addition reaction.
- **(c)** nucleophilic substitution reaction.
- **(d)** electrophilic substitution reaction.

5. Arrange in order of decreasing trend towards S_E (Substitution electrophilic) reactions:

(I) Chlorobenzene (II) Benzene
(III) Anilinium chloride (IV) Toluene
- **(a)** II > I > III > IV **(b)** III > I > II > IV
- **(c)** IV > II > I > III **(d)** I > II > III > IV

6. In the reaction of 2-nitroluene with bromine in the presence of iron which of the products shown below is the most abundant in the mixture?

(a)  **(b)** 

(c)  **(d)** 

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7. Among the following statements on the nitration of aromatic compounds, the incorrect one is

(a) The rate of nitration of benzene is almost the same as that of hexadeuterobenzene.

(b) The rate of nitration of toluene is greater than that of benzene.

(c) The rate of nitration of benzene is greater than that of hexadeuterobenzene.

(d) Nitration is an electrophilic substitution reaction.

8. $CaC_2 \xrightarrow{H_2O} (A) \xrightarrow[\text{tube}]{\text{hot Fe}} (B) \xrightarrow[AlCl_3]{CH_3-Cl} (C)$

The product C is

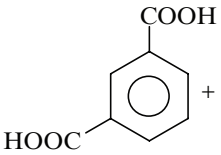
(a) toluene. **(b)** propyne.

(c) ethyl benzene. **(d)** propene.

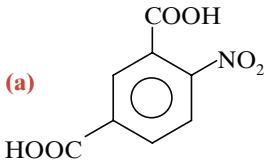
9. Nitrobenzene can be prepared from benzene by using a mixture of cone. HNO_3 and conc. H_2SO_4. In the nitrating mixture HNO_3 acts as a

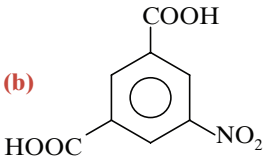
(a) base. **(b)** acid.

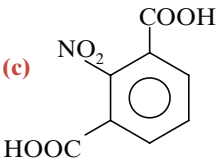
(c) reducing agent. **(d)** catalyst.

10.  $+ HNO_3 \xrightarrow{H_2SO_4} X$ (major product),

(X) will be

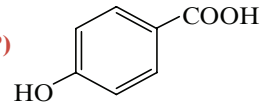
(a) 

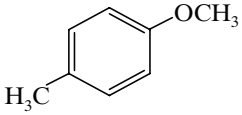
(b) 

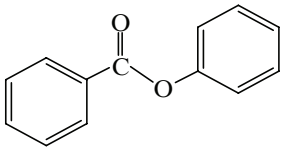
(c) 

(d) Mixture of (a) and (c)

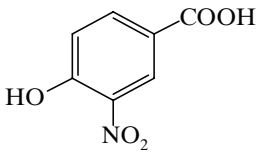
11. The compounds P, Q and S

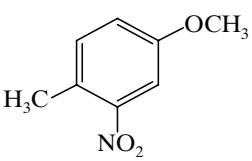
(P) 

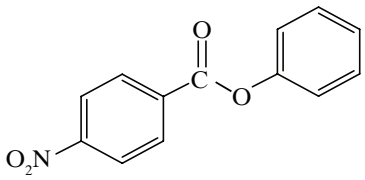
(Q) 

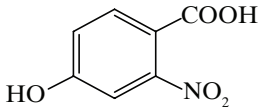
(S) 

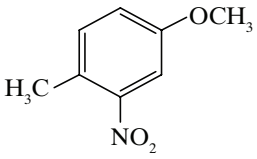
were separately subjected to nitration using HNO_3/H_2SO_4 mixture. The major product formed in each case, respectively, is

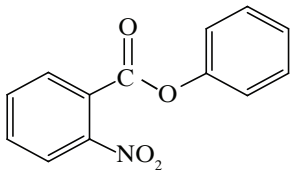
(a) 

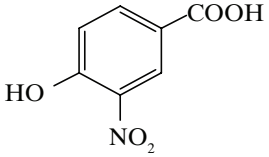


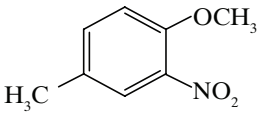


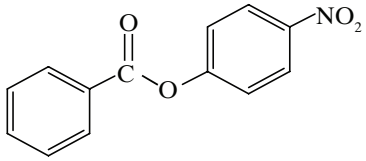
(b) 

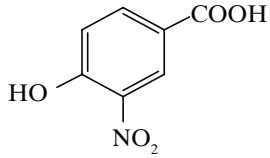


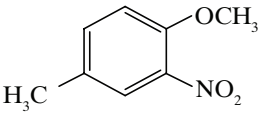


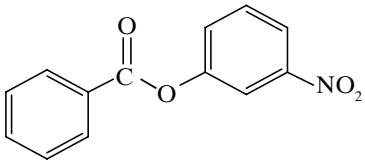
(c) 



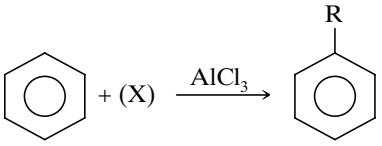


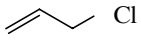
(d) 

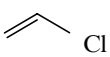


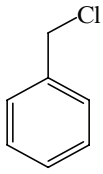


12. In the following reaction, X cannot be



(a) 

(b) 

(c) 

(d) 

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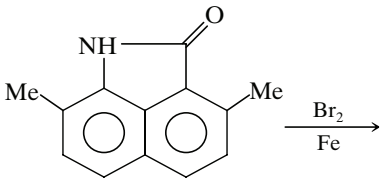
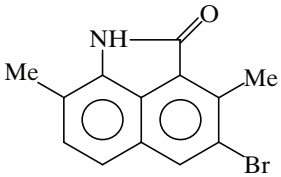
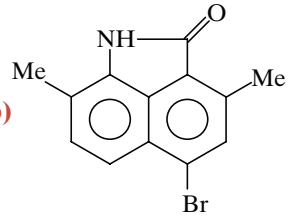
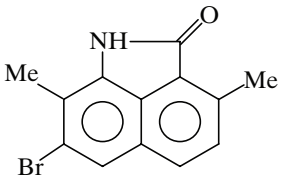
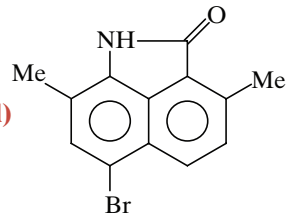
13. The major product of the below reaction is



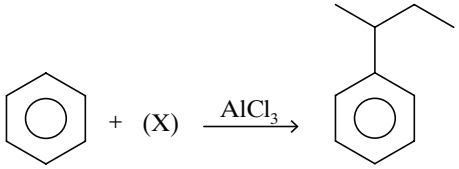
(a)


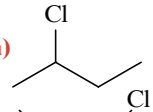
(b)


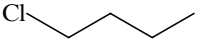
(c)


(d)


14. In the following reaction, X can be



(a)


(b)


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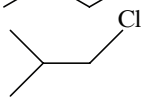
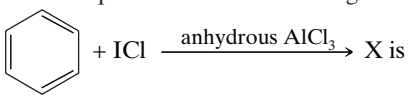
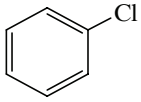
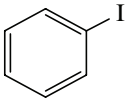


(d) (a) and (b) both

15. The compound X in the following reaction is



(a)


(b)


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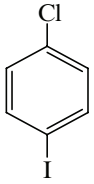
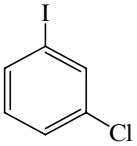
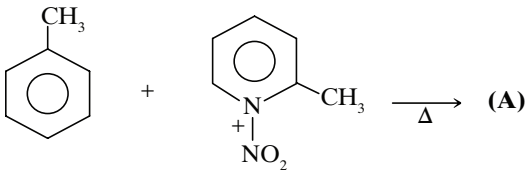
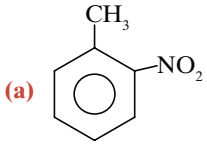


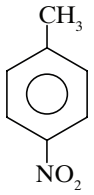
(d)


16. The product A in the below reaction is



(A)

(a)


(b)


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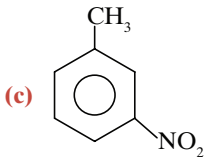
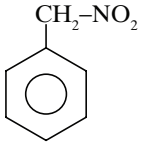


(d)


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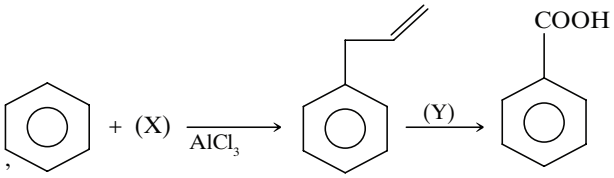
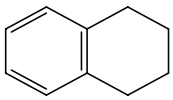


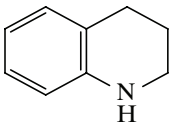
(X) and (Y) will be

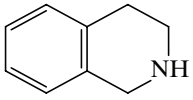
(a) Cl and $KMnO_4$, H^+, Δ **(b)** Cl and $KMnO_4$, H^+, Δ

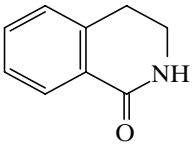
(c) Cl and $KMnO_4$, H^+, Δ **(d)** None of these

18. Which one of the following compounds undergoes bromination on its aromatic ring (electrophilic aromatic substitution) at the fastest rate?

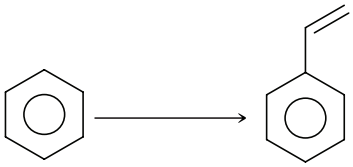
(a)


(b)


(c)


(d)


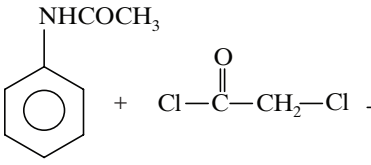
19. The following conversion can be achieved by



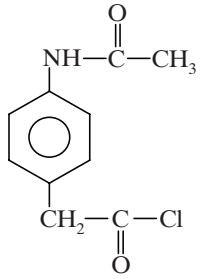
(a) Cl + $AlCl_3$ **(b)** Cl + $AlCl_3$

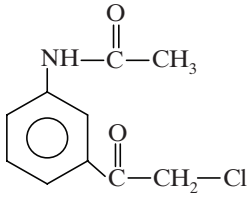
(c) Cl + $AlCl_3$, NBS + Δ, alc. KOH **(d)** None

20. The product (P) in the below reaction is



(79–83%)

(a)


(b)


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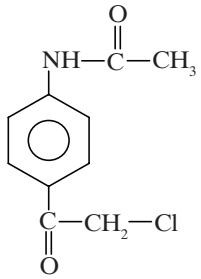
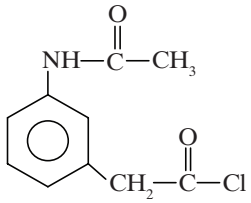
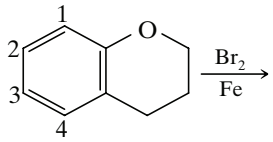
(c) 

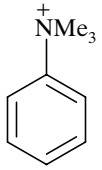
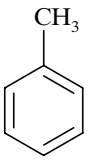
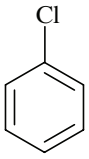
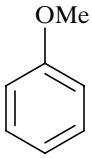
(d) 

21. In the following reaction, the substitution takes place at which position?



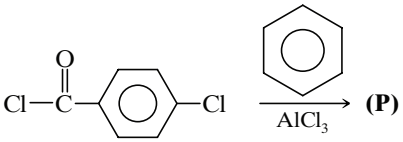
(a) 1 **(b)** 2 **(c)** 3 **(d)** both (a) and (b)

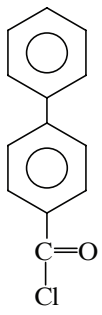
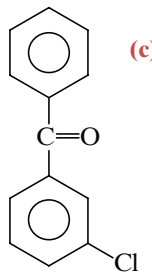
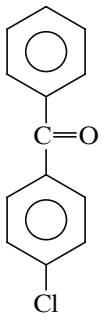
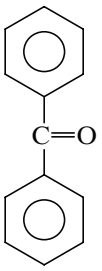
22. Rank the following compounds in order of decreasing reactivity towards electrophilic aromatic substitution reaction

(I)  (II)  (III)  (IV) 

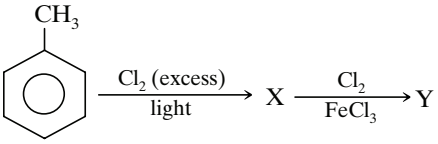
(a) IV > II > III > I **(b)** IV > II > I > III
(c) II > IV > III > I **(d)** IV > I > III > II

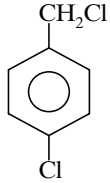
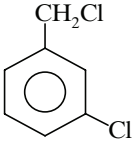
23. The unknown P in the following reaction is

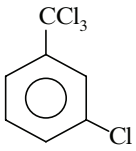


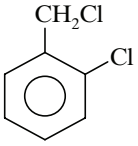
(a)  **(b)**  **(c)**  **(d)** 

24. The product Y in the following reaction is



(a)  **(b)** 

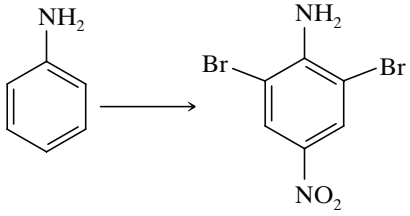
(c) 

(d) 

25. The function of anhydrous $AlCl_3$ in the Friedel-Craft's reaction is to

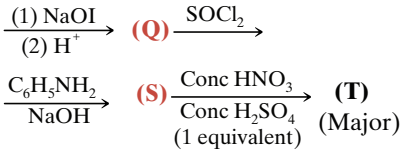
(a) absorb water. **(b)** absorb HCl.
(c) to produce electrophile. **(d)** to produce nucleophile.

26. What is the correct order of reagents to achieve the following synthesis?

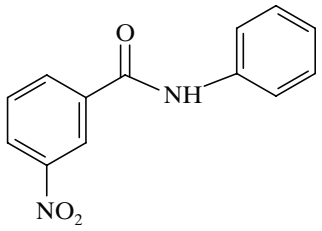


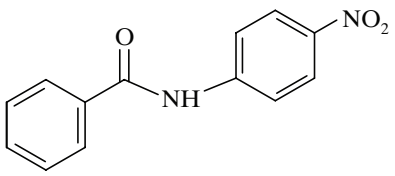
(a) 1) $Br_2/FeBr_3$ (twice) 2) HNO_3/H_2SO_4
(b) 1) CH_3COCl, NaOH 2) H_2SO_4(conc.) 3) $Br_2/FeBr_3$ (twice) 4) H_2SO_4, H_2O, heat 5) OH^- 6) HNO_3/H_2SO_4
(c) 1) CH_3COCl, NaOH 2) $Br_2/FeBr_3$ (twice) 3) H_2SO_4(conc.) 4) HNO_3/H_2SO_4 5) H_2SO_4, H_2O, heat 6) OH–
(d) 1) CH_3COCl, NaOH 2) $Br_2/FeBr_3$ (twice) 3) HNO_3/H_2SO_4

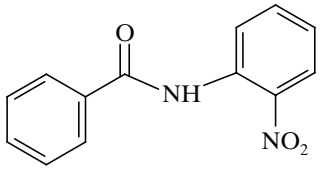
27.

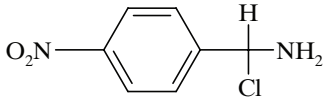


In the above reaction sequence, (T) can be:

(a) 

(b) 

(c) 

(d) 

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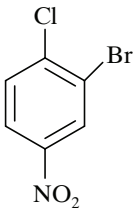
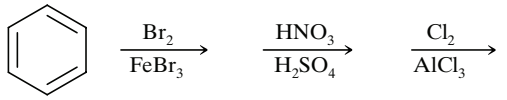
28. Which of the following synthetic schemes would be the best for the synthesis of the compound, 2-bromo-1-chloro-4-nitrobenzene?



(a) 

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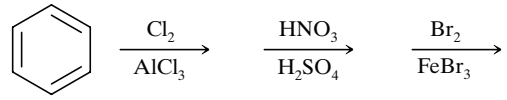
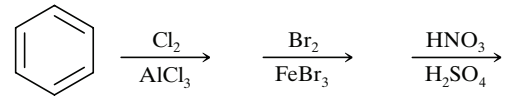
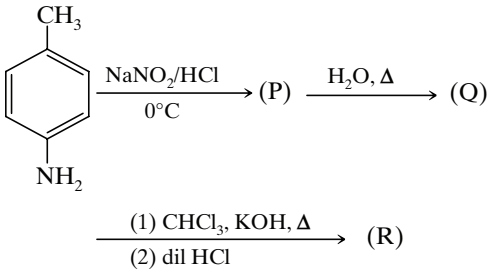
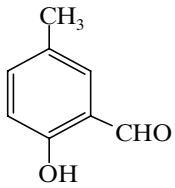
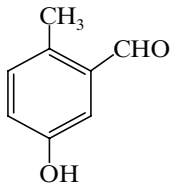
(c) 

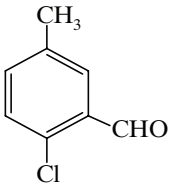
(d) 

29. Identify R in the reaction

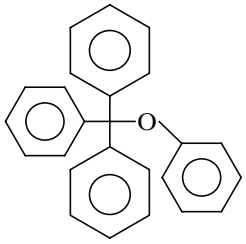


(a) 

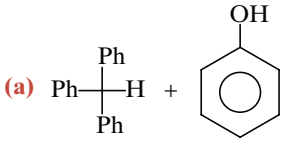
(b) 

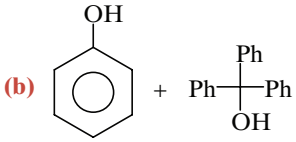
(c) 

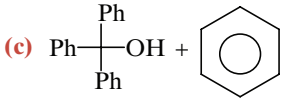
(d) None of these

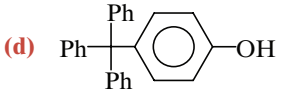
30. 

The product of this reaction is

(a) 

(b) 

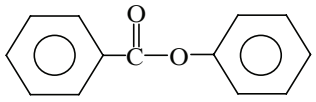
(c) 

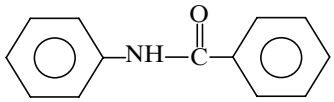
(d) 

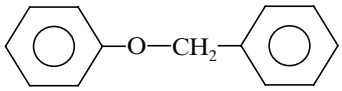
Multiple Correct Choice Type

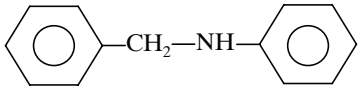
1. Toluene, when treated with Br_2/Fe, gives *p*-bromotoluene as the major product, because the CH_3 group
- **(a)** is para directing.
- **(b)** is meta directing.
- **(c)** activates the ring by hyperconjugation.
- **(d)** deactivates the ring.

2. In which of following reactions, electrophilic aromatic substitution take place on left hand side phenyl ring?

(a) 

(b) 

(c) 

(d) 

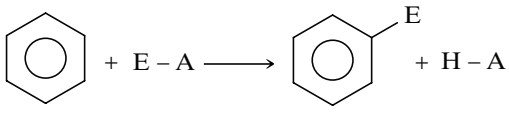
Linked Comprehension Type

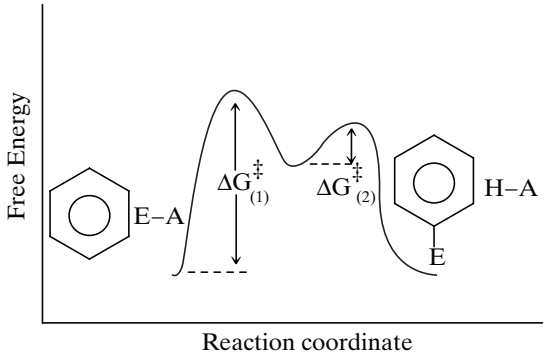
Paragraph for Questions 1 to 3

The most characteristic reactions of benzenoid arenes are the substitution reactions that occur when they react with electrophilic reagents. These reactions are of the general type shown below.

$$Ar - H + E - A \rightarrow Ar - E + H - A$$

Or





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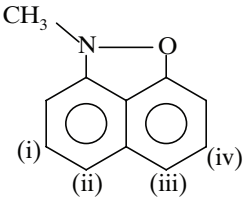
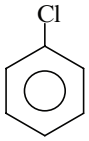
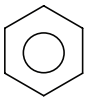
1. Identify the position where electrophilic aromatic substitution reaction takes place.

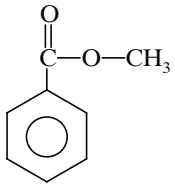


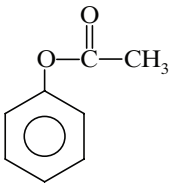
(a) i **(b)** ii **(c)** iii **(d)** iv

2. Compare the rate of electrophilic aromatic substitution.

(i) 

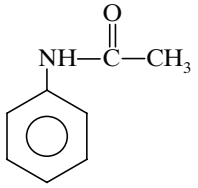
(ii) 

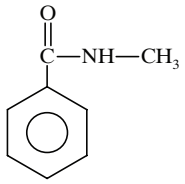
(iii) 

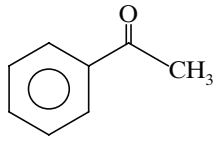
(iv) 

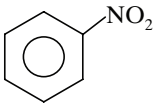
(a) (i) > (ii) > (iii) > (iv) **(b)** (ii) > (i) > (iii) > (iv)
(c) (iv) > (ii) > (iii) > (i) **(d)** (iv) > (ii) > (i) > (iii)

3. Which of the following is ortho/para director for electrophilic aromatic substitution?

(a) 

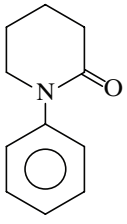
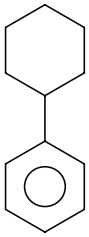
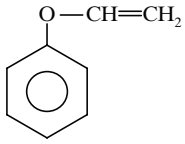
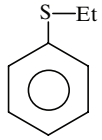
(b) 

(c) 

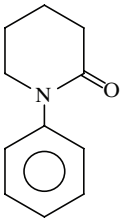
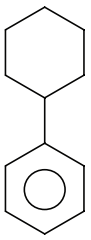
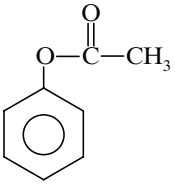
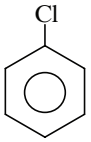
(d) 

Matrix Match Type

1.

Column I (Group)	Column II (Effect on phenyl group)
(a) 	**(p)** Activating group
(a) 	**(q)** Deactivating group
(c) 	**(r)** *ortho*/*para*-director
(d) 	**(s)** *Meta*-director

2. Match the substituted benzene ring with its properties.

Column I	Column II
(a) 	**(p)** Group attached is ortho/para director
(b) 	**(q)** Group attached is meta director
(c) 	**(r)** Rate of electrophilic aromatic substitution is greater than benzene
(d) 	**(s)** Rate of electrophilic aromatic substitution is less than benzene
	(t) Rate of electrophilic aromatic substitution is equal to benzene.

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ANSWER KEY

Single Correct Choice Type

1. (b) **2.** (d) **3.** (d) **4.** (d)
5. (c) **6.** (b) **7.** (c) **8.** (a)
9. (a) **10.** (b) **11.** (c) **12.** (b)
13. (d) **14.** (d) **14.** (b) **16.** (b)
17. (a) **18.** (b) **19.** (c) **20.** (c)
21. (c) **22.** (a) **23.** (c) **24.** (c)
25. (c) **26.** (b) **27.** (b) **28.** (c)
29. (a) **30.** (d)

Multiple Correct Choice Type

1. (a), (c) **2.** (b), (c)

Linked Comprehension Type

1. (b) **2.** (d) **3.** (a)

Matrix Match Type

1. $a \rightarrow (p, r); b \rightarrow (p, r); c \rightarrow (p, r); d \rightarrow (p, r)$
2. $a \rightarrow (p, r); b \rightarrow (p, r); c \rightarrow (p, r); d \rightarrow (p, s)$

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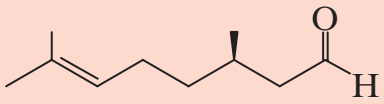
15

Aldehydes and Ketones I. Nucleophilic Addition to the Carbonyl Group



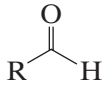
Citronellal (the scent of lemon in certain plants)

Contents

15.1 | Introduction
15.2 | Nomenclature of Aldehydes and Ketones
15.3 | Physical Properties
15.4 | Synthesis of Aldehydes
15.5 | Synthesis of Ketones
15.6 | Nucleophilic Addition to the Carbon–Oxygen Double Bond
15.7 | The Addition of Alcohols: Hemiacetals and Acetals
15.8 | The Addition of Primary and Secondary Amines
15.9 | The Addition of Hydrogen Cyanide: Cyanohydrins
15.10 | The Addition of Ylides: The Wittig Reaction
15.11 | Oxidation of Aldehydes
15.12 | The Baeyer–Villiger Oxidation
15.13 | Chemical Analyses for Aldehydes and Ketones

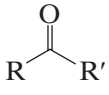
15.1 | INTRODUCTION

- Aldehydes have a **carbonyl group** bonded to a carbon atom on one side and a hydrogen atom on the other side. (Formaldehyde is an exception because it has hydrogen atoms on both sides.)
- Ketones have a carbonyl group bonded to carbon atoms on both sides.



RCHO

General formulas for aldehydes



RCOR′

General formulas for ketones

Although earlier chapters have given us some insight into the chemistry of carbonyl compounds, we shall now consider their chemistry in detail. The reason: the chemistry of the carbonyl group is central to the chemistry of most of the chapters that follow.

In this chapter we focus our attention on the preparation of aldehydes and ketones, their physical properties, and especially *nucleophilic addition reactions at their carbonyl groups*.

15.2 | NOMENCLATURE OF ALDEHYDES AND KETONES

- Aliphatic aldehydes are named substitutively in the IUPAC system by replacing the final **-e** of the name of the corresponding alkane with **-al**.

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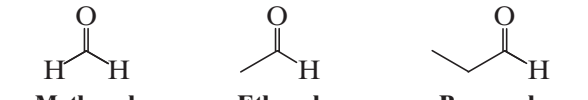
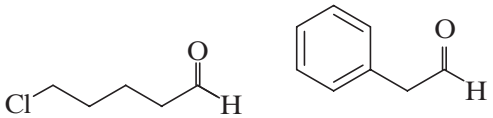
Since the aldehyde group must be at an end of the carbon chain, there is no need to indicate its position. When other substituents are present the carbonyl group carbon is assigned position 1. Many aldehydes also have common names; these are given below in parentheses. These common names are derived from the common names for the corresponding carboxylic acids (Section 17.2A), and some of them are retained by the IUPAC as acceptable names.

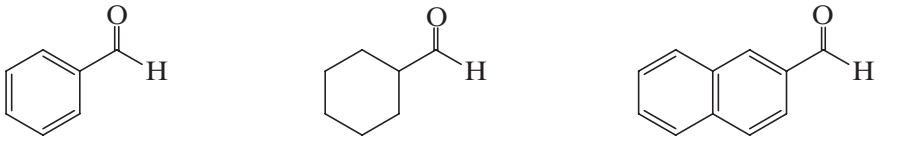


Methanal (formaldehyde) **Ethanal (acetaldehyde)** **Propanal (propionaldehyde)**



5-Chloropentanal **Phenylethanal (phenylacetaldehyde)**

- Aldehydes in which the —CHO group is attached to a ring system are named substitutively by adding the suffix **carbaldehyde**. Several examples follow:

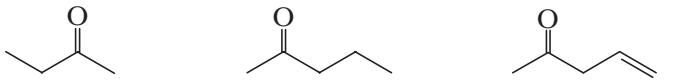


Benzenecarbaldehyde (benzaldehyde) **Cyclohexanecarbaldehyde** **2-Naphthalenecarbaldehyde**

The common name *benzaldehyde* is far more frequently used than benzenecarbaldehyde for C_6H_5CHO, and it is the name we shall use in this text.

- Aliphatic ketones are named substitutively by replacing the final **-e** of the name of the corresponding alkane with **-one**.

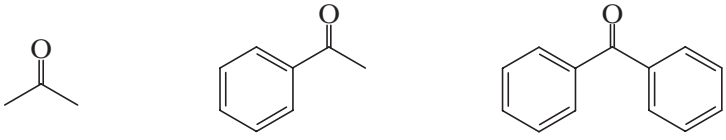
The chain is then numbered in the way that gives the carbonyl carbon atom the lower possible number, and this number is used to designate its position.



Butanone (ethyl methyl ketone) **2-Pentanone (methyl propyl ketone)** **Pent-4-en-2-one (not 1-penten-4-one) (allyl methyl ketone)**

Common functional group names for ketones (in parentheses above) are obtained simply by separately naming the two groups attached to the carbonyl group and adding the word **ketone** as a separate word.

Some ketones have common names that are retained in the IUPAC system:



Acetone (propanone) **Acetophenone (1-phenylethanone or methyl phenyl ketone)** **Benzophenone (diphenylmethanone or diphenyl ketone)**

When it is necessary to name the  group as a prefix, it is the **methanoyl** or **formyl group**. The  group is called the **ethanoyl** or **acetyl group** (often abbreviated as Ac). When  R groups are named as substituents, they are called **alkanoyl** or **acyl groups**.

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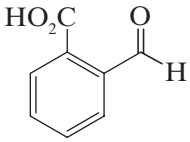
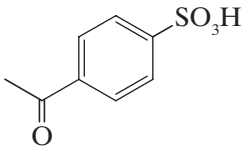


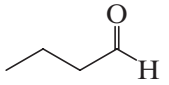
2-Methanoylbenzoic acid
(*o*-formylbenzoic acid)



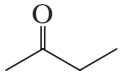
4-Ethanoylbenzenesulfonic acid
(*p*-acetylbenzenesulfonic acid)

Solved Problem 15.1

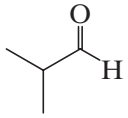
Write bond-line formulas for three isomeric compounds that contain a carbonyl group and have the molecular formula C_4H_8O. Then give their IUPAC names.



Butanal



Butanone



2-Methylpropanal

Answer

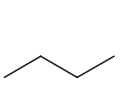
Write the formulas and then name the compounds.

Practice Problem 15.1

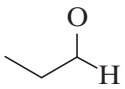
(a) Give IUPAC substitutive names for the seven isomeric aldehydes and ketones with the formula $C_5H_{10}O$. **(b)** Give structures and names (common or IUPAC substitutive names) for all the aldehydes and ketones that contain a benzene ring and have the formula C_8H_8O.

15.3 | PHYSICAL PROPERTIES

The carbonyl group is a polar group; therefore, aldehydes and ketones have higher boiling points than hydrocarbons of the same molecular weight. However, since aldehydes and ketones cannot have strong hydrogen bonds *between their molecules*, they have lower boiling points than the corresponding alcohols. The following compounds that have similar molecular weights exemplify this trend:



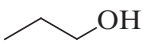
Butane
bp –0.5 °C
(MW = 58)



Propanal
bp 49 °C
(MW = 58)



Acetone
bp 56.1 °C
(MW = 58)



1-Propanol
bp 97.2 °C
(MW = 60)

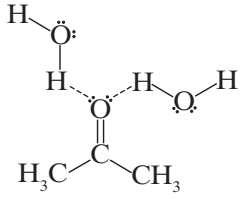
Practice Problem 15.2

Which compound in each of the following pairs has the higher boiling point? (Answer this problem without consulting tables.)

(a) Pentanal or 1-pentanol
(b) 2-Pentanone or 2-pentanol
(c) Pentane or pentanal
(d) Acetophenone or 2-phenylethanol
(e) Benzaldehyde or benzyl alcohol

The carbonyl oxygen atom allows molecules of aldehydes and ketones to form strong hydrogen bonds to molecules of water. As a result, low-molecular-weight aldehydes and ketones show appreciable solubilities in water. Acetone and acetaldehyde are soluble in water in all proportions.

Table 15.1 lists the physical properties of a number of common aldehydes and ketones.



Hydrogen bonding between water molecules and acetone

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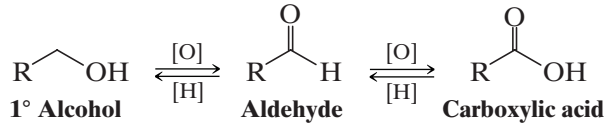
Table 15.1 Physical Properties of Aldehydes and Ketones

Formula	Name	mp (°C)	bp (°C)	Solubility in Water
HCHO	Formaldehyde	–92	–21	Very soluble
CH_3CHO	Acetaldehyde	–125	21	∞
CH_3CH_2CHO	Propanal	–81	49	Very soluble
$CH_3(CH_2)_2CHO$	Butanal	–99	76	Soluble
$CH_3(CH_2)_3CHO$	Pentanal	–92	102	Slightly soluble
$CH_3(CH_2)_4CHO$	Hexanal	–51	131	Slightly soluble
C_6H_5CHO	Benzaldehyde	–26	178	Slightly soluble
$C_6H_5CH_2CHO$	Phenylacetaldehyde	33	193	Slightly soluble
CH_3COCH_3	Acetone	–95	56.1	∞
$CH_3COCH_2CH_3$	Butanone	–86	80	Very soluble
$CH_3COCH_2CH_2CH_3$	2-Pentanone	–78	102	Soluble
$CH_3CH_2COCH_2CH_3$	3-Pentanone	–39	102	Soluble
$C_6H_5COCH_3$	Acetophenone	21	202	Insoluble
$C_6H_5COC_6H_5$	Benzophenone	48	306	Insoluble

15.4 | SYNTHESIS OF ALDEHYDES

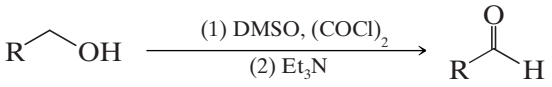
15.4A Aldehydes by Oxidation of 1° Alcohols

- The oxidation state of an aldehyde lies between that of a 1° alcohol and a carboxylic acid (Section 11.4A).

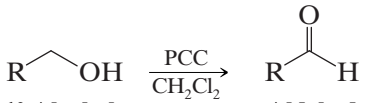


1° Alcohol **Aldehyde** **Carboxylic acid**

Aldehydes can be prepared from 1° alcohols by the Swern oxidation (Section 11.4B) and oxidation with pyridinium chlorochromate ($C_5H_5\overset{+}{N}HCrO_3Cl^-$, or PCC, Section 11.4D):



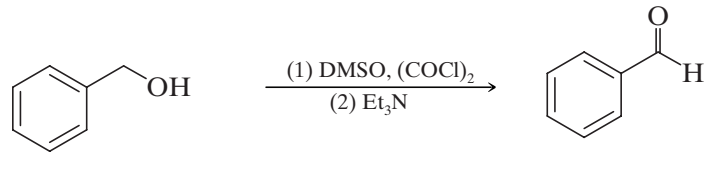
Swern oxidation of a 1° alcohol to an aldehyde.



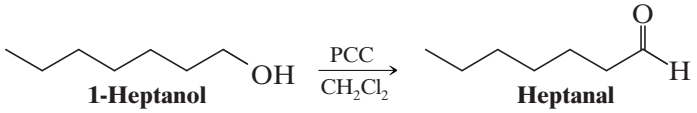
1° Alcohol **Aldehyde**

PCC oxidation of a 1° alcohol to an aldehyde

The following are examples of the use of the Swern oxidation and PCC in the synthesis of aldehydes.



Benzyl alcohol **Benzaldehyde**



1-Heptanol **Heptanal**

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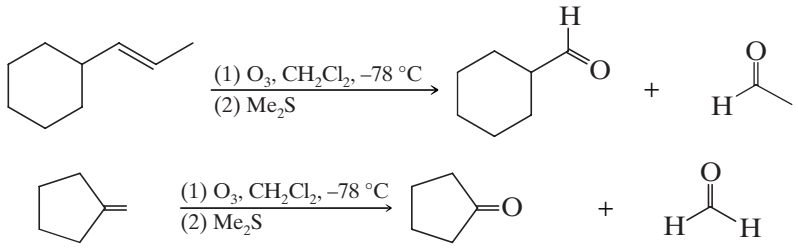
15.4B Aldehydes by Ozonolysis of Alkenes

- Alkenes can be cleaved by ozonolysis of their double bond (Section 8.17B). The products are aldehydes and ketones.

In Chapter 8 we also saw how this procedure has utility in structure determination. The following examples illustrate the synthesis of aldehydes by ozonolysis of alkenes.

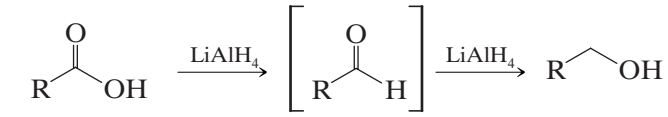


15.4C Aldehydes by Reduction of Acyl Chlorides, Esters, and Nitriles

Theoretically, it ought to be possible to prepare aldehydes by reduction of carboxylic acids. In practice, this is not possible with the reagent normally used to reduce a carboxylic acid, lithium aluminum hydride ($LiAlH_4$ or LAH).

- When any carboxylic acid is treated with LAH, it is reduced all the way to the 1° alcohol.
- This happens because LAH is a very powerful reducing agent and aldehydes are very easily reduced.

Any aldehyde that might be formed in the reaction mixture is immediately reduced by LAH to the 1° alcohol. (It does not help to use a stoichiometric amount of LAH, because as soon as the first few molecules of aldehyde are formed in the mixture, there will still be much unreacted LAH present and it will reduce the aldehyde.)



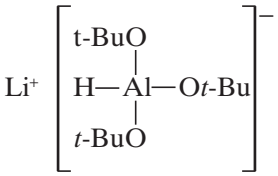
Carboxylic acid **Aldehyde** **1° Alcohol**

The secret to success here is not to use a carboxylic acid itself, but to use a derivative of a carboxylic acid that is more easily reduced, and an aluminum hydride derivative that is less reactive than LAH.

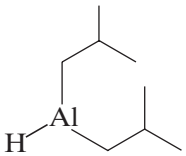
- Acyl chlorides (RCOCl), esters (RCO_2R'), and nitriles (RCN) are all easily prepared from carboxylic acids (Chapter 17), and they all are more easily reduced.

(Acyl chlorides, esters, and nitriles all also have the same oxidation state as carboxylic acids. Convince yourself of this by applying the principles that you learned in Section 11.2A).

- Two derivatives of aluminum hydride that are less reactive than LAH, in part because they are much more sterically hindered, are **lithium tri-*tert*-butoxy-aluminum hydride** and **diisobutylaluminum hydride (DIBAL-H):**



Lithium tri-*tert*-butoxy-aluminum hydride



Diisobutylaluminum hydride (abbreviated *i*-Bu_2AlH or DIBAL-H)

- The following scheme summarizes how lithium tri-*tert*-butoxyaluminum hydride and DIBAL-H can be used to synthesize aldehydes from acid derivatives:

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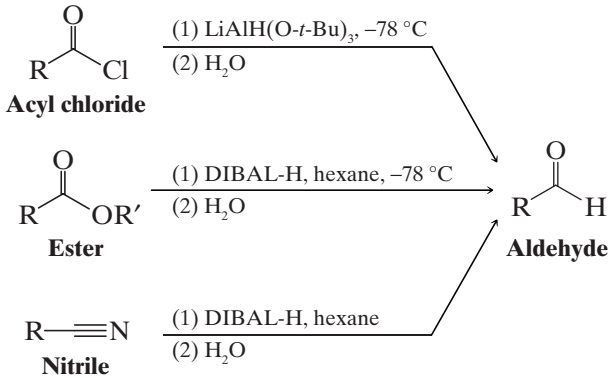
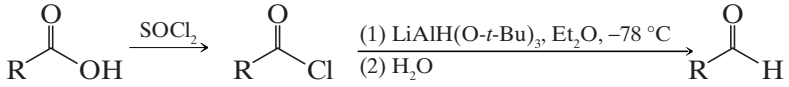


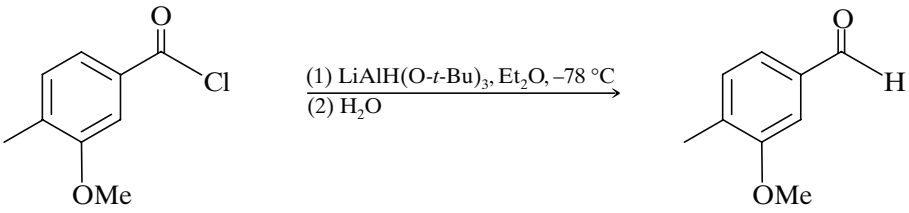
We now examine each of these aldehyde syntheses in more detail.

Aldehydes from Acyl Chlorides: RCOCl → RCHO

- Acyl chlorides can be reduced to aldehydes by treating them with $LiAlH[OC(CH_3)_3]_3$, lithium tri-*tert*-butoxyaluminum hydride, at –78 °C.
- Carboxylic acids can be converted to acyl chlorides by using $SOCl_2$ (see Section 17.5).



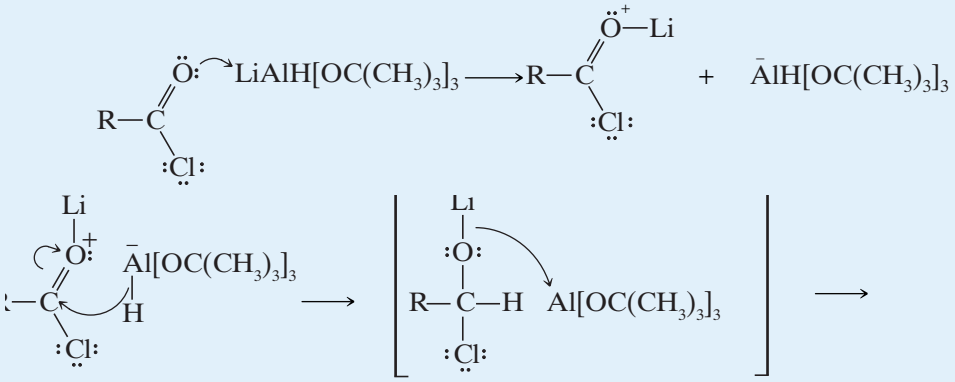
The following is a specific example:



3-Methoxy-4-methylbenzoyl chloride **3-Methoxy-4-methylbenzaldehyde**

Mechanistically, the reduction is brought about by the transfer of a hydride ion from the aluminum atom to the carbonyl carbon of the acyl chloride (see Section 11.3). Subsequent hydrolysis frees the aldehyde.

A MECHANISM FOR THE REACTION — Reduction of an Acyl Chloride to an Aldehyde



ransfer of a hydride ion to the arbonyl carbon brings about the reduction.

Acting as a Lewis acid, the aluminum atom accepts an electron pair from oxygen.

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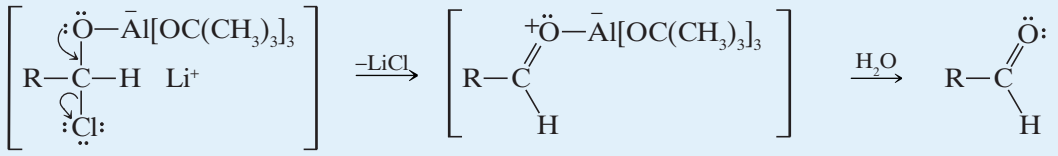
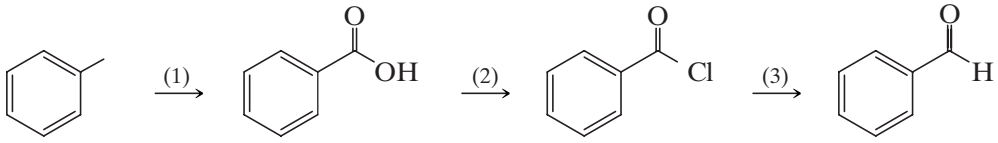


This intermediate loses a chloride ion as an electron pair from the oxygen assists.

The addition of water causes hydrolysis of this aluminum complex to take place, producing the aldehyde. (Several steps are involved.)

Solved Problem 15.2

Provide the reagents for transformations (1), (2), and (3).



Answer

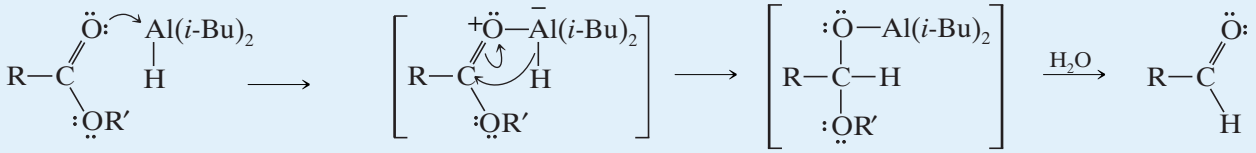
In (1), we must oxidize methylbenzene to benzoic acid. To do this we use hot potassium permanganate in a basic solution followed by an acidic workup (see Section 14.13C). For (2), we must convert a carboxylic acid to an acid chloride. For this transformation we use thionyl chloride or phosphorus pentachloride (see Section 14.7). For (3), we must reduce an acid chloride to an aldehyde. For this we use lithium tri-*tert*-butoxyaluminum hydride (see above).

Aldehydes from Esters and Nitriles: $RCO_2R' \rightarrow RCHO$ and $RC{\equiv}N \rightarrow RCHO$

- Both esters and nitriles can be reduced to aldehydes by DIBAL-H.

Carefully controlled amounts of DIBAL-H must be used to avoid overreduction, and the ester reduction must be carried out at low temperatures. Both reductions result in the formation of a relatively stable intermediate by the addition of a hydride ion to the carbonyl carbon of the ester or to the carbon of the —C≡N group of the nitrile. Hydrolysis of the intermediate liberates the aldehyde. Schematically, the reactions can be viewed in the following way:

A MECHANISM FOR THE REACTION — Reduction of an Ester to an Aldehyde



The aluminum atom accepts an electron pair from the carbonyl oxygen atom in a Lewis acid-base reaction.

Transfer of a hydride ion to the carbonyl carbon brings about its reduction.

Addition of water at the end of the reaction hydrolyzes the aluminum complex and produces the aldehyde.

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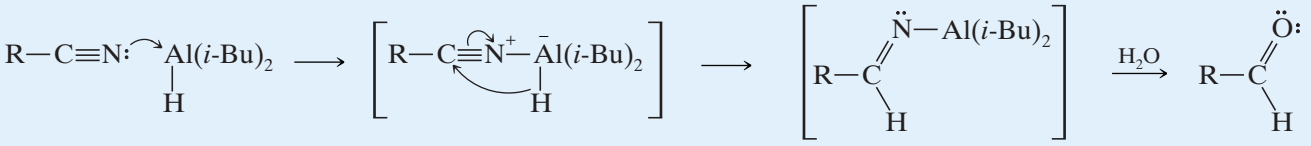
A MECHANISM FOR THE REACTION — Reduction of a Nitrile to an Aldehyde

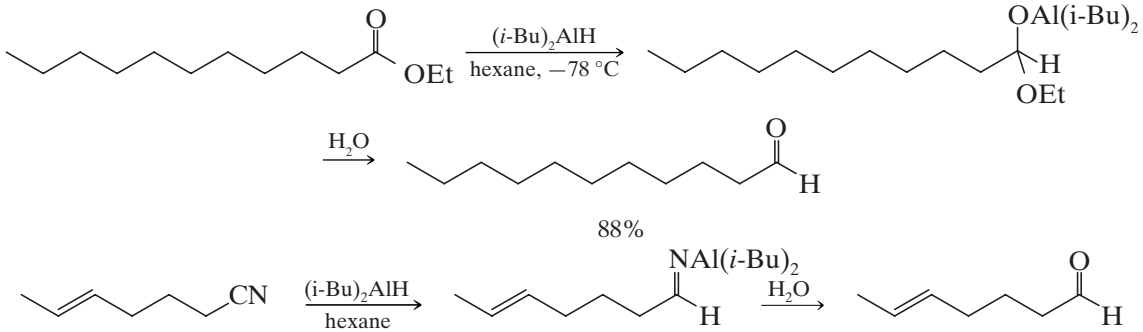


The aluminum atom accepts an electron pair from the nitrile in a Lewis acid–base reaction.

Transfer of a hydride ion to the nitrile carbon brings about its reduction.

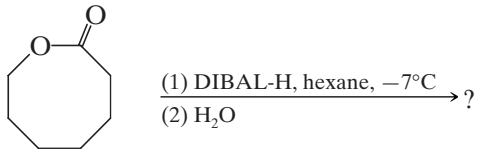
Addition of water at the end of the reaction hydrolyzes the aluminum complex and produces the aldehyde.

The following specific examples illustrate these syntheses:



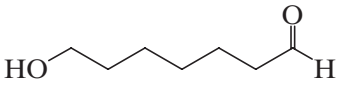
Solved Problem 15.3

What is the product of the following reaction?



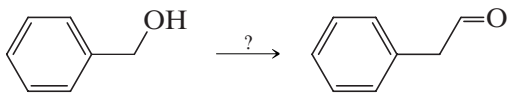
Answer

The starting compound is a cyclic ester, so the product would be an aldehyde that also contains an alcohol hydroxyl group.



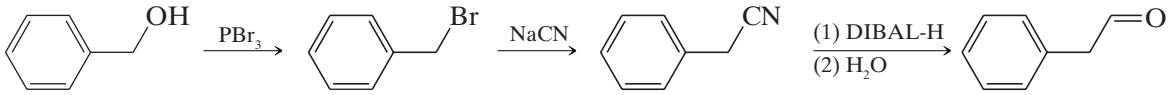
Solved Problem 15.4

Starting with benzyl alcohol, outline a synthesis of phenylethanal.



Answer

Convert the benzyl alcohol to benzyl bromide with PBr_3, then replace the bromine by cyanide in an S_N2 reaction. Lastly, reduce the nitrile to phenylethanal.



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Practice Problem 15.3

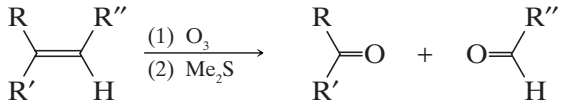
Show how you would synthesize propanal from each of the following: **(a)** 1-propanol and **(b)** propanoic acid ($CH_3CH_2CO_2H$).

15.5 | SYNTHESIS OF KETONES

15.5A Ketones from Alkenes, Arenes, and 2° Alcohols

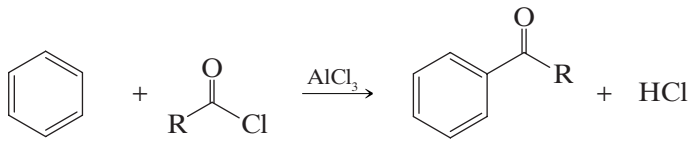
We have seen three laboratory methods for the preparation of ketones in earlier chapters:

1. Ketones (and aldehydes) by ozonolysis of alkenes (discussed in Section 8.17B).



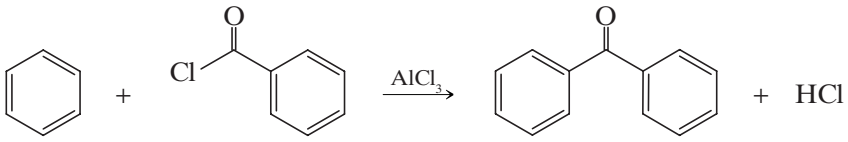
Ketone **Aldehyde**

2. Ketones from arenes by Friedel–Crafts acylations (discussed in Section 14.7). For example:



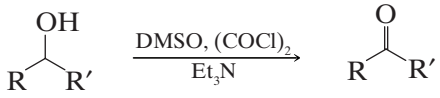
An alkyl aryl ketone

Alternatively,



A diaryl ketone

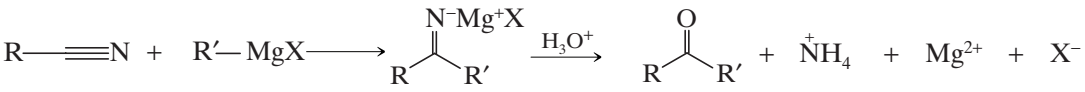
3. Ketones from secondary alcohols by Swern oxidation and other methods (discussed in Section 11.4):

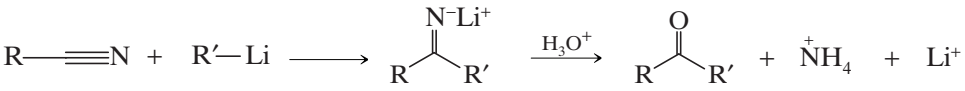


15.5B Ketones from Nitriles

Treating a nitrile (R—C≡N) with either a Grignard reagent or an organolithium reagent followed by hydrolysis yields a ketone.

General Reactions





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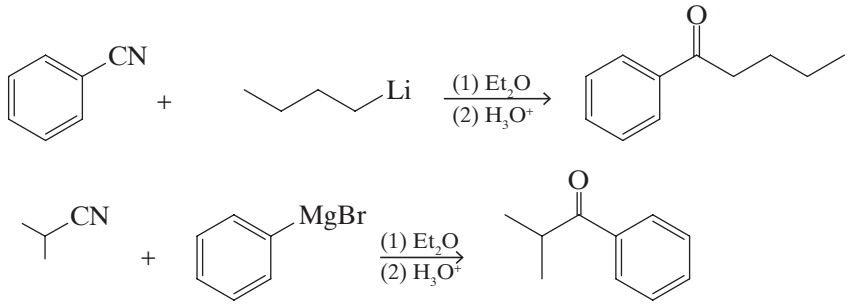
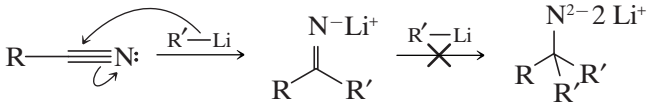
The mechanism for the acidic hydrolysis step is the reverse of one that we shall study for imine formation in Section 15.8A.

Specific Examples



2-Cyanopropane **2-Methyl-1-phenylpropanone (isopropyl phenyl ketone)**

Even though a nitrile has a triple bond, addition of the Grignard or lithium reagent takes place only once. The reason: if addition took place twice, this would place a double negative charge on the nitrogen.



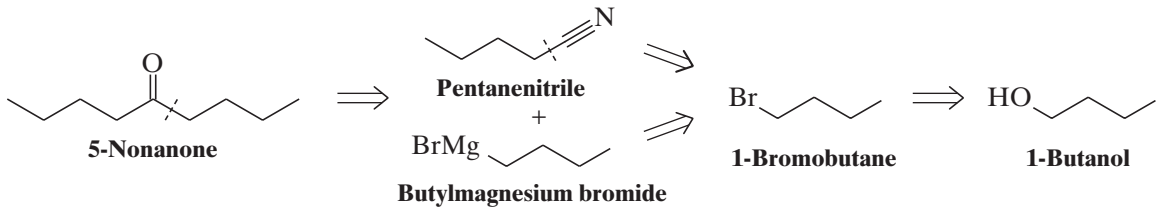
(The dianion does not form.)

Solved Problem 15.5

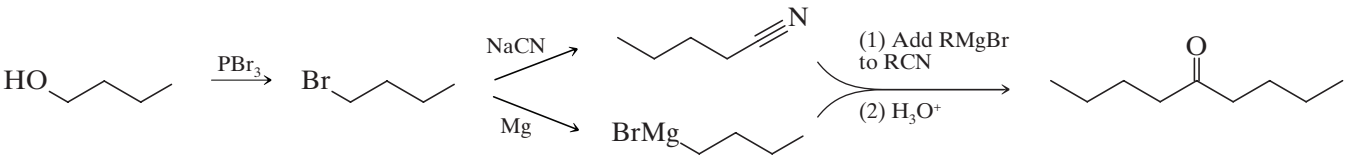
With 1-butanol as your only organic starting compound, devise a synthesis of 5-nonanone. Begin by writing a retrosynthetic analysis.

Answer

Retrosynthetic Analysis



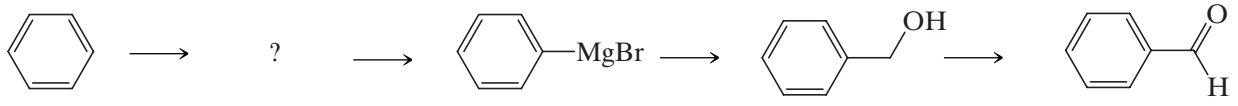
Synthesis



Practice Problem 15.4

Provide the reagents and indicated intermediates in each of the following syntheses.

(a)



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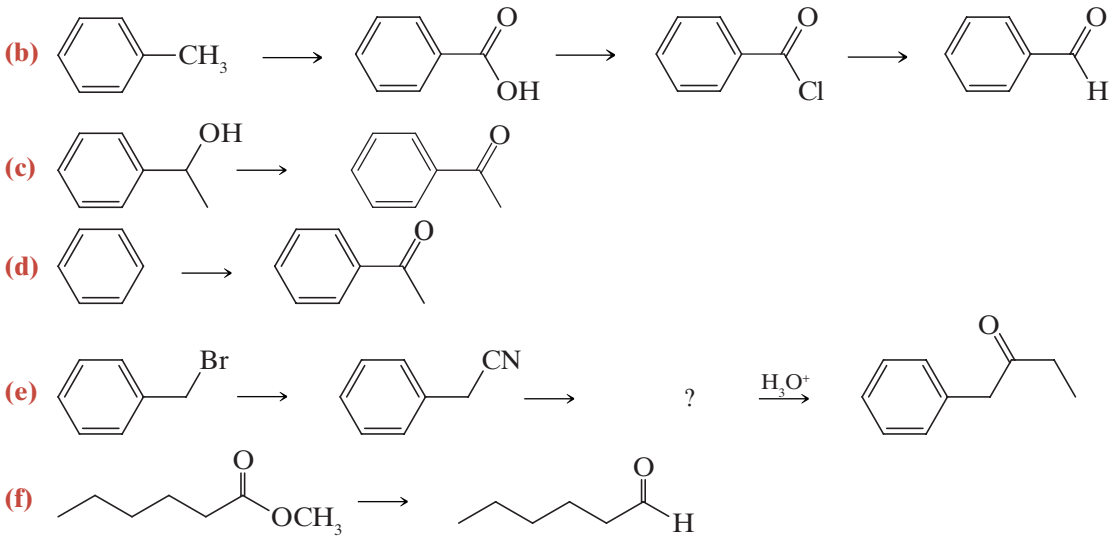
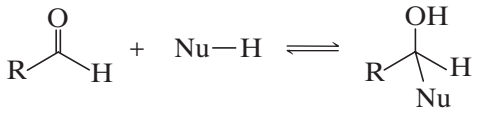


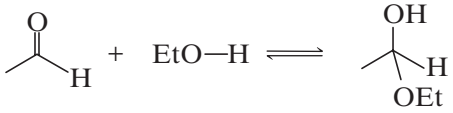
15.6 | NUCLEOPHILIC ADDITION TO THE CARBON–OXYGEN DOUBLE BOND

- The most characteristic reaction of aldehydes and ketones is *nucleophilic addition* to the carbon–oxygen double bond.

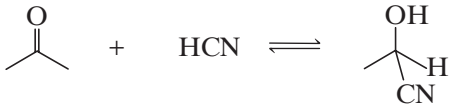
General Reaction



Specific Examples

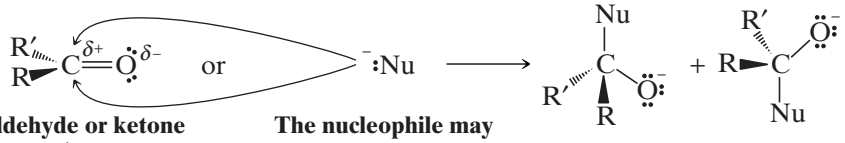


A hemiacetal (see Section 15.7)



A cyanohydrin (see Section 15.9)

Aldehydes and ketones are especially susceptible to nucleophilic addition because of the structural features that we discussed in Section 11.1 and that are shown below.



Aldehyde or ketone (R or R′ may be H) **The nucleophile may attack from above or below.**

- The trigonal planar arrangement of groups around the carbonyl carbon atom means that the carbonyl carbon atom is relatively open to attack from above or below the plane of the carbonyl group (see above).
- The positive charge on the carbonyl carbon atom means that it is especially susceptible to attack by a nucleophile.
- The negative charge on the carbonyl oxygen atom means that nucleophilic addition is susceptible to acid catalysis.

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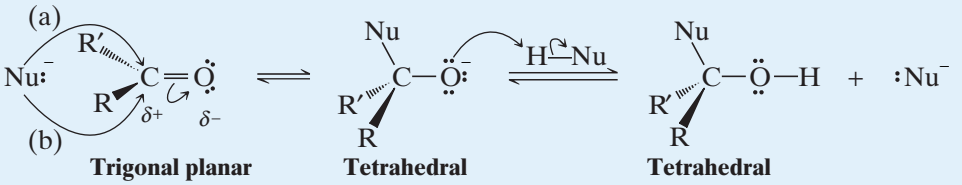
Nucleophilic addition to the carbon–oxygen double bond occurs, therefore, in either of two general ways.

1. **When the reagent is a strong nucleophile (Nu:⁻)**, addition usually takes place in the following way (see the mechanism box on the following page), converting the trigonal planar aldehyde or ketone into a tetrahedral product.

   In this type of addition the nucleophile uses its electron pair to form a bond to the carbonyl carbon atom. As this happens the electron pair of the carbon–oxygen π bond shifts out to the electronegative carbonyl oxygen atom and the hybridization state of both the carbon and the oxygen changes from sp^2 to sp^3. ***The important aspect of this step is the ability of the carbonyl oxygen atom to accommodate the electron-pair of the carbon–oxygen double bond.***

A MECHANISM FOR THE REACTION — Addition of a Strong Nucleophile to an Aldehyde or Ketone



In this step the nucleophile forms a bond to the carbon by donating an electron pair to the top or bottom face of the carbonyl group [path (a) or (b)]. An electron pair shifts out to the oxygen.

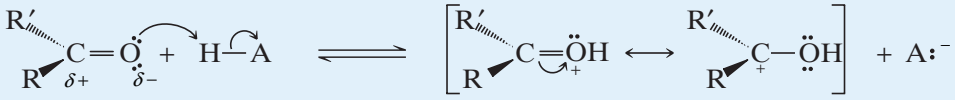
In the second step the alkoxide oxygen, because it is strongly basic, removes a proton from H—Nu or some other acid.

In the second step the oxygen atom accepts a proton. This happens because the oxygen atom is now much more basic; it carries a full negative charge as an alkoxide anion.

2. **When an acid catalyst is present and the nucleophile is weak**, reaction of the carbonyl oxygen with the acid enhances electrophilicity of the carbonyl group.

A MECHANISM FOR THE REACTION — Acid-Catalyzed Nucleophilic Addition to an Aldehyde or Ketone

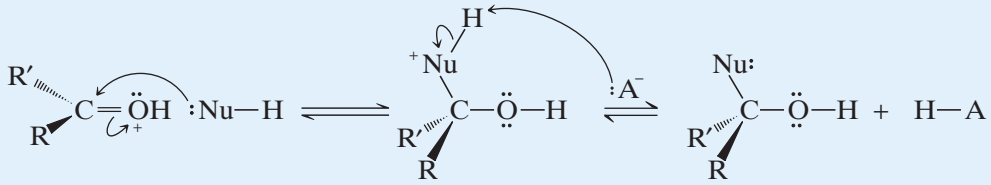
Step 1



(or a Lewis acid)

In this step an electron pair of the carbonyl oxygen accepts a proton from the acid (or associates with a Lewis acid), producing an oxonium cation. The carbon of the oxonium cation is more susceptible to nucleophilic attack than the carbonyl of the starting ketone.

Step 2



In the first of these two steps, the oxonium cation accepts the electron pair of the nucleophile. In the second step, a base removes a proton from the positively charged atom, regenerating the acid.

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This mechanism operates when carbonyl compounds are treated with *strong acids* in the presence of *weak nucleophiles*. In the first step the acid donates a proton to an electron pair of the carbonyl oxygen atom. The resulting protonated carbonyl compound, an **oxonium cation**, is highly reactive toward nucleophilic attack at the carbonyl carbon atom because the carbonyl carbon atom carries more positive charge than it does in the unprotonated compound.

15.6A Reversibility of Nucleophilic Additions to the Carbon–Oxygen Double Bond

- Many nucleophilic additions to carbon–oxygen double bonds are reversible; the overall results of these reactions depend, therefore, on the position of an equilibrium.

This contrasts markedly with most electrophilic additions to carbon–carbon double bonds and with nucleophilic substitutions at saturated carbon atoms. The latter reactions are essentially irreversible, and overall results are a function of relative reaction rates.

15.6B Relative Reactivity: Aldehydes versus Ketones

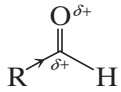
- In general, aldehydes are more reactive in nucleophilic additions than are ketones. Both steric and electronic factors favor aldehydes.

Steric Factors

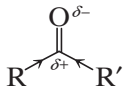
In aldehydes, where one group is a hydrogen atom, the central carbon of the tetrahedral product formed from the aldehyde is less crowded and the product is more stable. Formation of the product, therefore, is favored at equilibrium. With ketones, the two alkyl substituents at the carbonyl carbon cause greater steric crowding in the tetrahedral product and make it less stable. Therefore, a smaller concentration of the product is present at equilibrium.

Electronic Factors

Because alkyl groups are electron releasing, aldehydes are more reactive on electronic grounds as well. Aldehydes have only one electron-releasing group to partially neutralize, and thereby stabilize, the positive charge at their carbonyl carbon atom. Ketones have two electron-releasing groups and are stabilized more. Greater stabilization of the ketone (the reactant) relative to its product means that the equilibrium constant for the formation of the tetrahedral product from a ketone is smaller and the reaction is less favorable:



Aldehyde



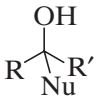
Ketone

The ketone carbonyl carbon is less positive because it has two electron-releasing alkyl groups.

On the other hand, electron-withdrawing substituents (e.g., —CF_3 or —CCl_3 groups) cause the carbonyl carbon to be more positive (and the starting compound to become less stable), causing the **addition reaction** to be more favorable.

15.6C Addition Products Can Undergo Further Reactions

Nucleophilic addition to a carbonyl group may lead to a product that is stable under the reaction conditions that we employ. If this is the case we are then able to isolate products with the following general structure:



In other reactions the product formed initially may be unstable and may spontaneously undergo subsequent reactions. One common subsequent reaction is an *elimination reaction*, especially *dehydration*. Even if the initial addition product is stable, we may deliberately bring about a subsequent reaction by our choice of reaction conditions.

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Practice Problem 15.5

The reaction of an aldehyde or ketone with a Grignard reagent (Section 11.8) is a nucleophilic addition to the carbon–oxygen double bond. **(a)** What is the nucleophile? **(b)** The magnesium portion of the Grignard reagent plays an important part in this reaction. What is its function? **(c)** What product is formed initially? **(d)** What product forms when water is added?

Practice Problem 15.6

The reactions of aldehydes and ketones with $LiAlH_4$ and $NaBH_4$ (Section 11.3) are nucleophilic additions to the carbonyl group. What is the nucleophile in these reactions?

15.7 | THE ADDITION OF ALCOHOLS: HEMIACETALS AND ACETALS

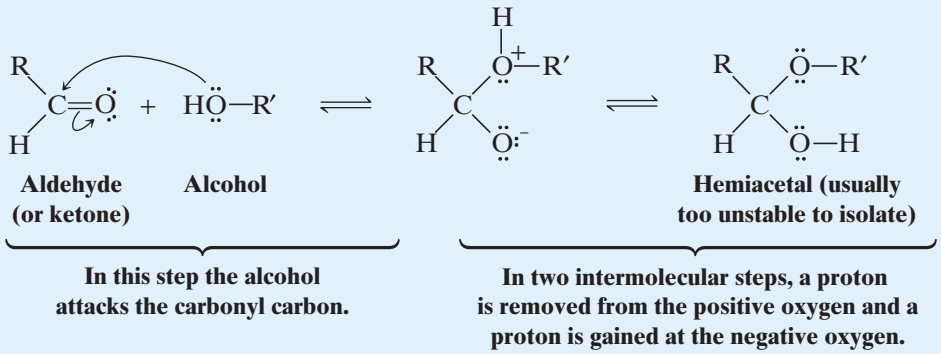
- Aldehydes and ketones react with alcohols to form **hemiacetals** and **acetals** by an equilibrium reaction.

15.7A Hemiacetals

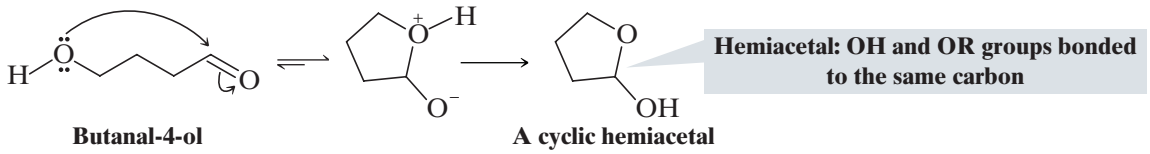
- The essential structural features of a **hemiacetal** are an —OH and an —OR group attached to the same carbon atom.

The hemiacetal results by nucleophilic addition of an alcohol oxygen to the carbonyl carbon of an aldehyde or ketone.

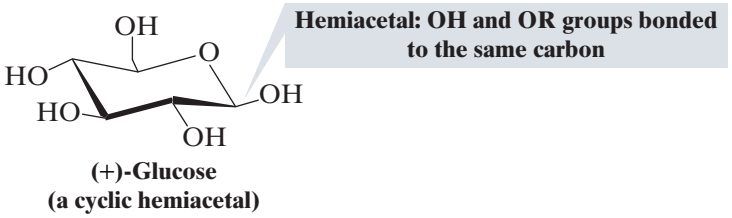
A MECHANISM FOR THE REACTION — Hemiacetal Formation



- Most open-chain hemiacetals are not sufficiently stable to allow their isolation. Cyclic hemiacetals with five- or six-membered rings, however, are usually much more stable.



Most simple sugars (Chapter 20) exist primarily in a cyclic hemiacetal form. Glucose is an example:



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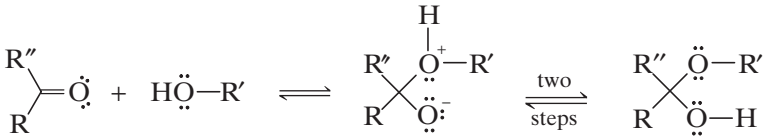
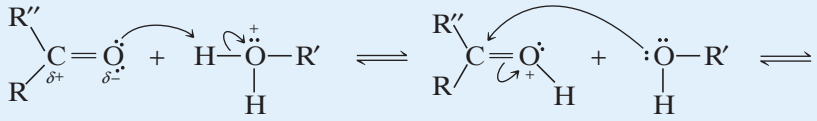
Whether the carbonyl reactant is an aldehyde or a ketone, the product with an —OH and an —OR group is called a **hemiacetal**.



Ketone **Hemiacetal**

- The formation of hemiacetals is catalyzed by acids and bases.

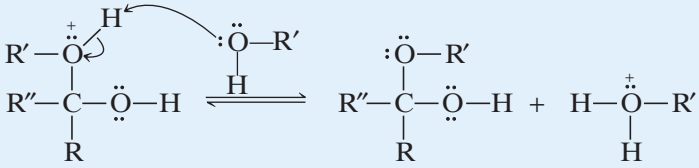
A MECHANISM FOR THE REACTION — Acid-Catalyzed Hemiacetal Formation



(R″ may be H)

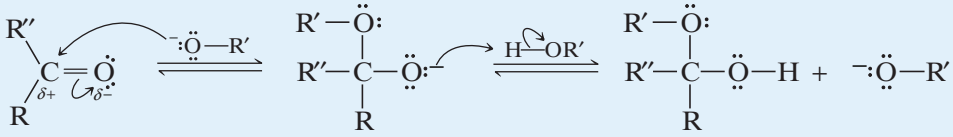
Protonation of the aldehyde or ketone oxygen atom makes the carbonyl carbon more susceptible to nucleophilic attack. [The protonated alcohol results from reaction of the alcohol (present in excess) with the acid catalyst, e.g., gaseous (anhydrous) HCl.]

An alcohol molecule adds to the carbon of the oxonium cation.



The transfer of a proton from the positive oxygen to another molecule of the alcohol leads to the hemiacetal.

A MECHANISM FOR THE REACTION — Base-Catalyzed Hemiacetal Formation



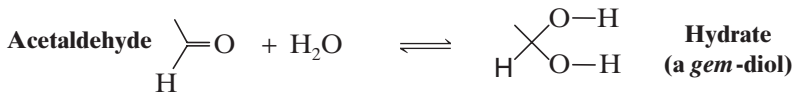
(R″ may be H)

An alkoxide anion acting as a nucleophile attacks the carbonyl carbon atom. An electron pair shifts onto the oxygen atom, producing a new alkoxide anion.

The alkoxide anion abstracts a proton from an alcohol molecule to produce the hemiacetal and regenerates an alkoxide anion.

Aldehyde Hydrates: gem-Diols

Dissolving an aldehyde such as acetaldehyde in water causes the establishment of an equilibrium between the aldehyde and its **hydrate**. This hydrate is in actuality a 1,1-diol, called a geminal diol (or simply a *gem*-diol).



Acetaldehyde **Hydrate (a *gem*-diol)**

The *gem*-diol results from a nucleophilic addition of water to the carbonyl group of the aldehyde.

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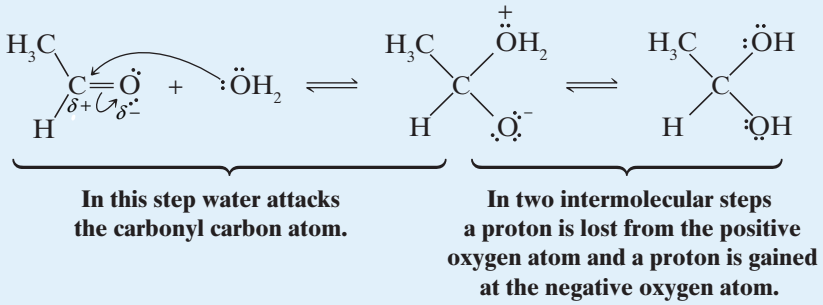
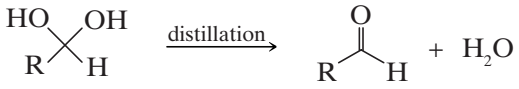
A MECHANISM FOR THE REACTION — Hydrate Formation

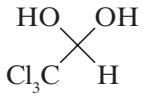


The equilibrium for the addition of water to most ketones is unfavorable, whereas some aldehydes (e.g., formaldehyde) exist primarily as the *gem*-diol in aqueous solution.

It is not possible to isolate most *gem*-diols from the aqueous solutions in which they are formed. Evaporation of the water, for example, simply displaces the overall equilibrium to the right and the *gem*-diol (or hydrate) reverts to the carbonyl compound:

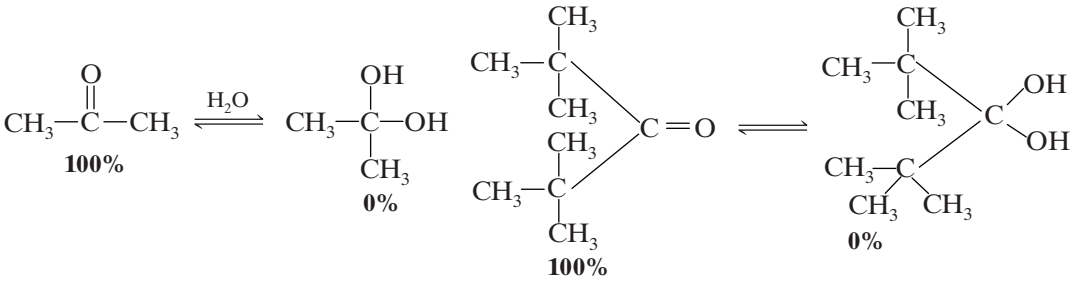


Compounds with strong electron-withdrawing groups attached to the carbonyl group can form stable *gem*-diols. An example is the compound called chloral hydrate:



Chloral hydrate

The hydrate of ketone is unstable as is shown below.



In the hydrate, the substituent groups are in close proximity (bond angle 109.5°) than in the starting carbonyl compound (bond angle 120°); thus, it would be expected that bulky R (alkyl) group would suppress product formation.

Greater the +I effect, more stable is the carbocation of carbonyl, and so there is less tendency to undergo attack by nucleophile H_2O. For example:

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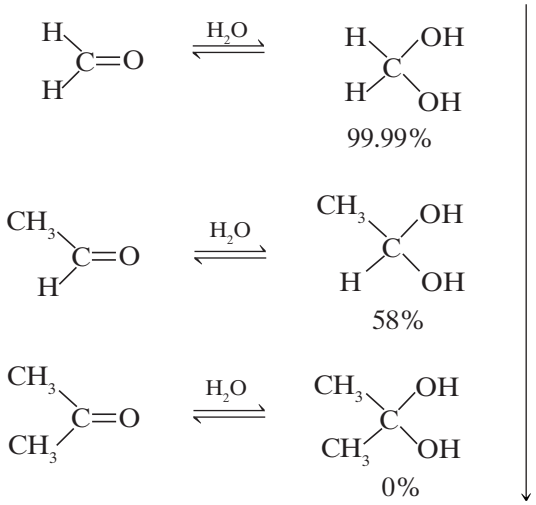
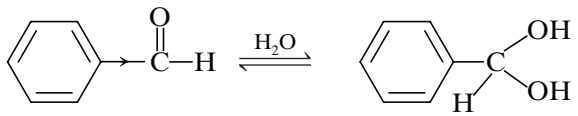
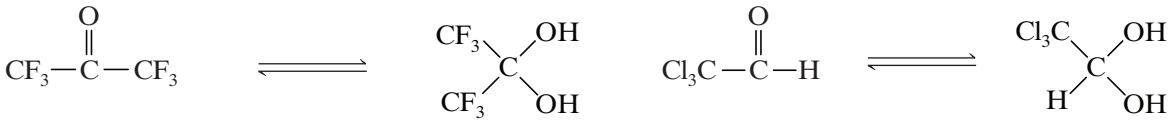


In case of benzaldehyde the hydrate formation is negligible (+M effect).



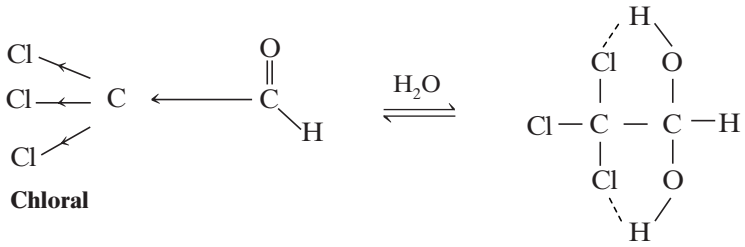
+M effect (100%) (0%)

Here, the carbonyl group is stabilized by electron delocalization, and so there is less tendency to undergo hydrate formation. Thus, electron donating groups tend to inhibit hydrate formation. Electron withdrawing groups, on the other hand, promote hydrate formation. The hydrate formation is proportional to I effect.



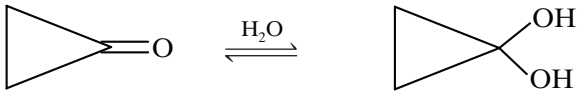
Hexafluoroacetone **100%** **Chloral** **100%**

It is assumed that powerful electron withdrawing chlorine atom in chloral destabilizes the original carbonyl compound, but not the hydrate formation thus promoting its formation.



Chloral

Hydrogen bonding is of additional advantage in the above example. In case of small ring ketones, the addition reaction results in the relief of a certain amount of ring strain.



0% **100%**

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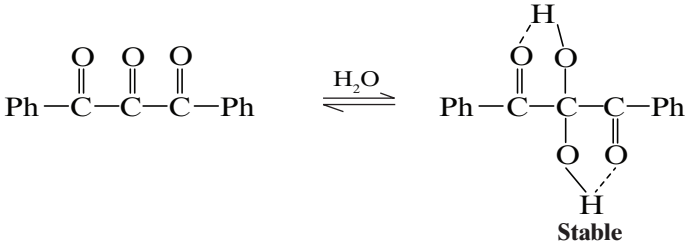
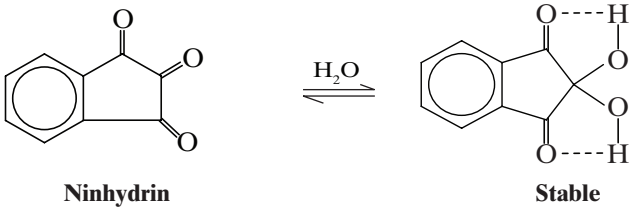
In the reactant, the angle strain at carbonyl carbon is given by 120°– 60°= 60°. In the product, the angle strain at the substituted carbon is given by 109°– 60°= 49°. Therefore, the driving force of the reaction is some relief in bond angle. The following compounds form a stable hydrate due to electronic effect and intramolecular hydrogen bond in hydrate.





Practice Problem 15.7

Dissolving formaldehyde in water leads to a solution containing primarily the *gem*-diol $CH_2(OH)_2$. Show the steps in its formation from formaldehyde.

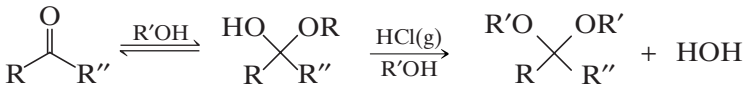
Practice Problem 15.8

When acetone is dissolved in water containing ^{18}O instead of ordinary ^{16}O (i.e., $H_2{}^{18}O$ instead of $H_2{}^{16}O$), the acetone soon begins to acquire ^{18}O and becomes $CH_3\overset{\overset{^{18}O}{\|}}{C}CH_3$. The formation of this oxygen-labeled acetone is catalyzed by traces of strong acids and by strong bases (e.g., HO^-). Show the steps that explain both the acid-catalyzed reaction and the base-catalyzed reaction.

15.7B Acetals

- An **acetal** has two —OR groups attached to the same carbon atom.

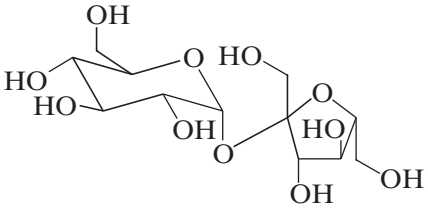
If we take an alcohol solution of an aldehyde (or ketone) and pass in to it a small amount of gaseous HCl, a hemiacetal forms, and then the hemiacetal reacts with a second molar equivalent of the alcohol to produce an **acetal**.



A hemiacetal (R″ may be H) **An acetal (R″ may be H)**

Practice Problem 15.9

Shown below is the structural formula for sucrose (table sugar). Sucrose has two acetal groupings. Identify these.



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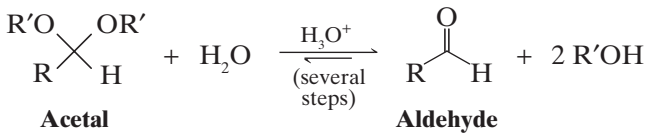
- The mechanism for acetal formation involves acid-catalyzed formation of the hemiacetal, then an acid-catalyzed elimination of water, followed by a second *addition* of the alcohol and loss of a proton.
- All steps in the formation of an acetal from an aldehyde are reversible.

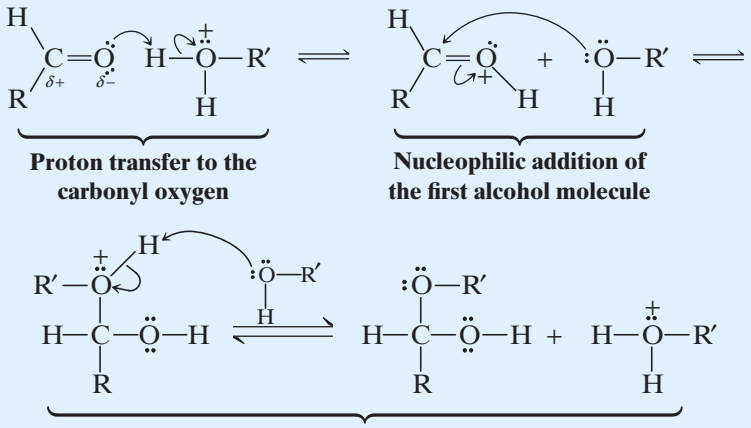
If we dissolve an aldehyde in a large excess of an anhydrous alcohol and add a small amount of an anhydrous acid (e.g., gaseous HCl or concentrated H_2SO_4), the equilibrium will strongly favor the formation of an acetal. After the equilibrium is established, we can isolate the acetal by neutralizing the acid and evaporating the excess alcohol.

If we then place the acetal in water and add a catalytic amount of acid, all of the steps reverse. Under these conditions (an excess of water), the equilibrium favors the formation of the aldehyde. The acetal undergoes ***hydrolysis***:



Acetal **Aldehyde**

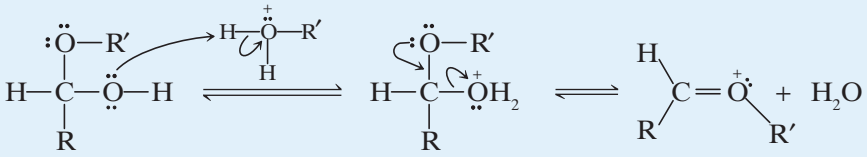
A MECHANISM FOR THE REACTION — Acid-Catalyzed Acetal Formation



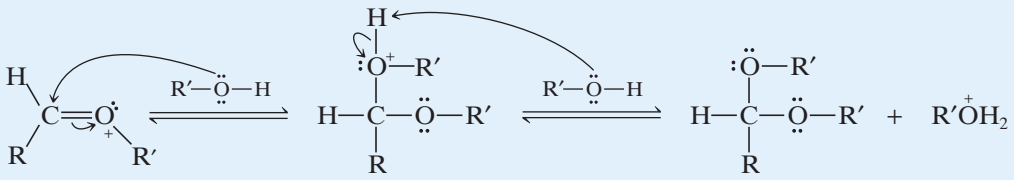
Proton transfer to the carbonyl oxygen

Nucleophilic addition of the first alcohol molecule

Proton removal from the positive oxygen results in formation of a hemiacetal.



Protonation of the hydroxyl group leads to elimination of water and formation of a highly reactive oxonium cation.



Attack on the carbon of the oxonium ion by a second molecule of the alcohol, followed by removal of a proton, leads to the acetal.

Practice Problem 15.10

Write a detailed mechanism for the formation of an acetal from benzaldehyde and methanol in the presence of an acid catalyst.

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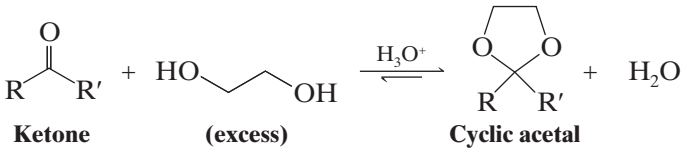
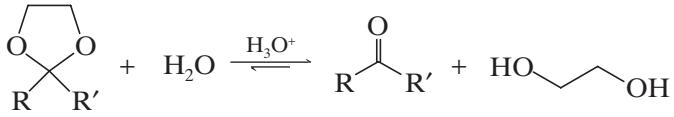
Cyclic Acetals

- Cyclic acetal formation is favored when a ketone or an aldehyde is treated with an excess of a 1,2-diol and a trace of acid:



Ketone **(excess)** **Cyclic acetal**

This reaction, too, can be reversed by treating the acetal with aqueous acid:



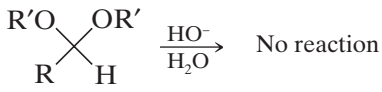
Acetal formation is not favored when ketones are treated with simple alcohols and gaseous HCl.

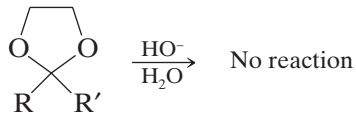
Practice Problem 15.11

Outline all steps in the mechanism for the formation of a cyclic acetal from acetone and ethylene glycol (1,2-ethanediol) in the presence of gaseous HCl.

15.7C Acetals Are Used as Protecting Groups

- Although acetals are hydrolyzed to aldehydes and ketones in aqueous acid, ***acetals are stable in basic solutions***:

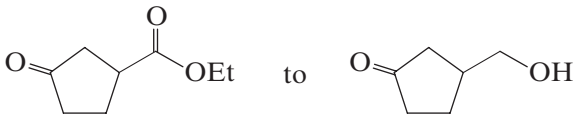




- Acetals are used to protect aldehydes and ketones from undesired reactions in basic solutions.

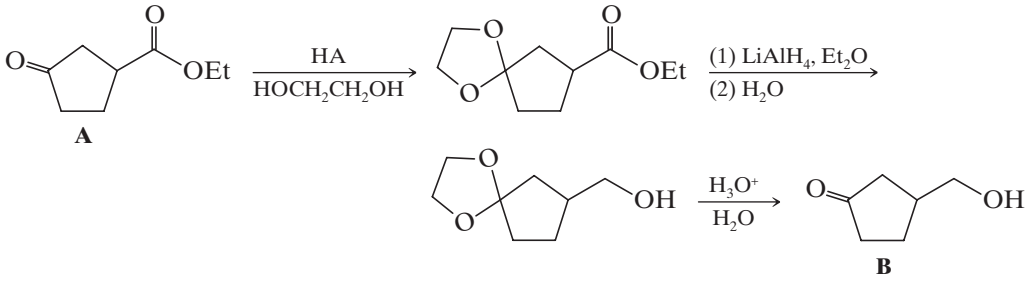
We can convert an aldehyde or ketone to an acetal, carry out a reaction on some other part of the molecule, and then hydrolyze the acetal with aqueous acid.

As an example, let us consider the problem of converting



A **B**

Keto groups are more easily reduced than ester groups. Any reducing agent (e.g., $LiAlH_4$ or H_2/Ni) that can reduce the ester group of **A** reduces the keto group as well. But if we "protect" the keto group by converting it to a cyclic acetal (the ester group does not react), we can reduce the ester group in basic solution without affecting the cyclic acetal. After we finish the ester reduction, we can hydrolyze the cyclic acetal and obtain our desired product, **B**:



A **B**

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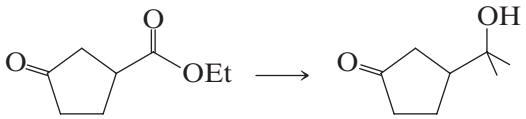
Practice Problem 15.12

What product would be obtained if **A** were treated with lithium aluminum hydride without first converting it to a cyclic acetal?

Practice Problem 15.13

(a) Show how you might use a cyclic acetal in carrying out the following transformation:

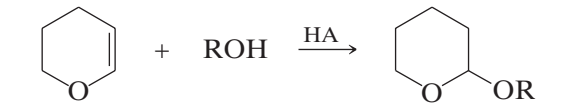


A **B**

(b) Why would a direct addition of methylmagnesium bromide to **A** fail to give **B**?

Practice Problem 15.14

Dihydropyran reacts readily with an alcohol in the presence of a trace of anhydrous HCl or H_2SO_4 to form a tetrahydropyranyl (THP) ether:

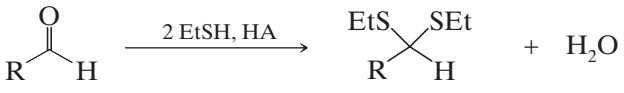


Dihydropyran **Tetrahydropyranyl ether**

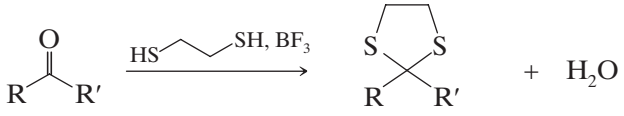
(a) Write a plausible mechanism for this reaction. **(b)** Tetrahydropyranyl ethers are stable in aqueous base but hydrolyze rapidly in aqueous acid to yield the original alcohol and another compound. Explain. (What is the other compound?) **(c)** The tetrahydropyranyl group can be used as a protecting group for alcohols and phenols. Show how you might use it in a synthesis of 5-methyl-1,5-hexanediol starting with 4-chloro-1-butanol.

15.7D Thioacetals

- Aldehydes and ketones react with thiols to form *thioacetals*:



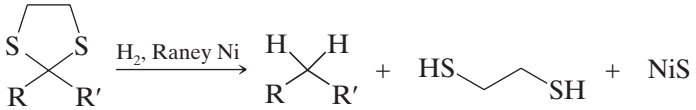
Thioacetal



Cyclic thioacetal

Thioacetals are important in organic synthesis because they react with hydrogen and Raney nickel to yield hydrocarbons. Raney nickel is a special nickel catalyst that contains adsorbed hydrogen.

- Thioacetal formation with subsequent "desulfurization" with hydrogen and Raney nickel gives us an additional method for converting carbonyl groups of aldehydes and ketones to —CH_2— groups:



The other methods we have studied are the **Clemmensen reduction** (Section 14.9A) and the **Wolff–Kishner reduction** (Section 14.9B). In Section 15.8C we will discuss the mechanism of the Wolff–Kishner reduction.

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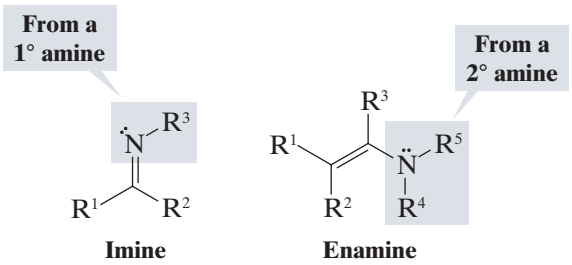
Practice Problem 15.15

Show how you might use thioacetal formation and Raney nickel desulfurization to convert: **(a)** cyclohexanone to cyclohexane and **(b)** benzaldehyde to toluene.

15.8 | THE ADDITION OF PRIMARY AND SECONDARY AMINES

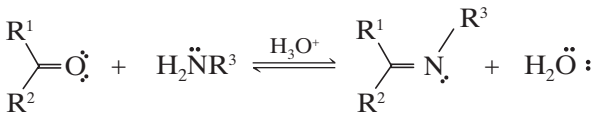
- Aldehydes and ketones react with primary amines to form **imines** and with secondary amines to form **enamines**.

Imines have a carbon–nitrogen double bond. Enamines have an amino group joined to a carbon–carbon double bond (they are alk*eneamines*).



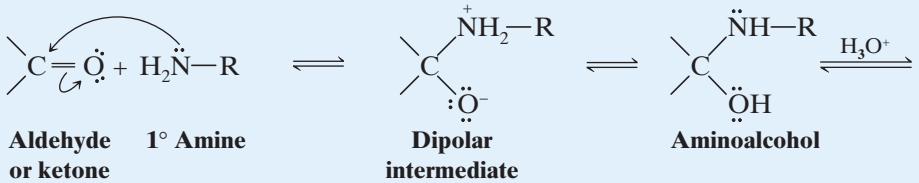
15.8A Imines

A general equation for the formation of an imine from a primary amine and an aldehyde or ketone is shown here. Imine formation is acid catalyzed, and the product can form as a mixture of (*E*) and (*Z*) isomers:



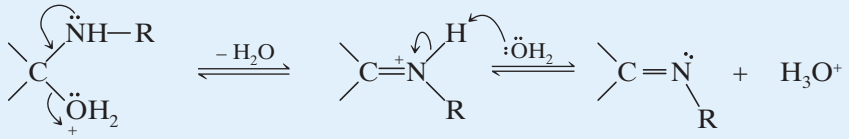
Imine formation generally takes place fastest between pH 4 and 5 and is slow at very low or very high pH. We can understand why an acid catalyst is necessary if we consider the mechanism that has been proposed for imine formation. The important step is the step in which the protonated aminoalcohol loses a molecule of water to become an iminium ion. By protonating the alcohol group, the acid converts a poor leaving group (an —OH group) into a good one (an —$^{+}OH_2$ group).

A MECHANISM FOR THE REACTION — Imine Formation



The amine adds to the carbonyl group to form a dipolar tetrahedral intermediate.

Intermolecular proton transfer from nitrogen to oxygen produces an aminoalcohol.



Protonation of the oxygen produces a good leaving group. Loss of a molecule of water yields an iminium ion.

Transfer of a proton to water produces the imine and regenerates the catalytic hydronium ion.

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The reaction proceeds more slowly if the hydronium ion concentration is too high, because protonation of the amine itself takes place to a considerable extent; this has the effect of decreasing the concentration of the nucleophile needed in the first step. If the concentration of the hydronium ion is too low, the reaction becomes slower because the concentration of the protonated aminoalcohol becomes lower. A pH between 4 and 5 is an effective compromise.

15.8B Oximes and Hydrazones

- Compounds such as hydroxylamine (NH_2OH), hydrazine (NH_2NH_2), and substituted hydrazines such as phenylhydrazine ($C_6H_5NHNH_2$) and 2,4-dinitrophenylhydrazine form C═N derivatives of aldehydes and ketones.

These derivatives are called oximes, hydrazones, phenylhydrazones, and 2,4-dinitrophenylhydrazones, respectively. The mechanisms by which these C═N derivatives form are similar to the mechanism for imine formation from a primary amine. As with imines, the formation of (*E*) and (*Z*) isomers is possible.

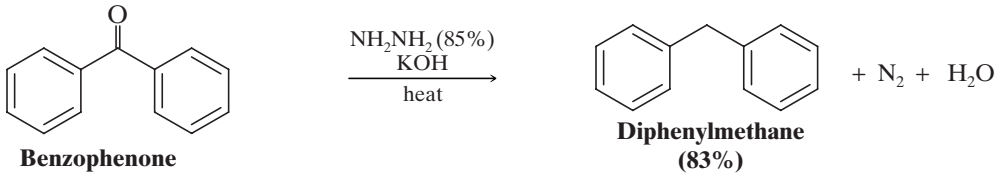
Oximes and the various **hydrazone** derivatives of aldehydes and ketones are sometimes used to identify unknown aldehydes and ketones. These derivatives are usually relatively insoluble solids that have sharp, characteristic melting points. The melting point of the derivative of an unknown compound can be compared with the melting point for the same derivative of a known compound or with data found in a reference table, and on this basis one can propose an identity for the unknown compound. Most laboratory textbooks for organic chemistry include extensive tables of derivative melting points. The method of comparing melting points is only useful, however, for compounds that have derivative melting points previously reported in the literature.

15.8C The Wolff–Kishner Reduction

A ketone can be reduced to a methylene group using the Wolff–Kishner reduction, which involves heating the ketone with hydrazine and base. The mechanism for the Wolff–Kishner reduction involves initial formation of a hydrazone followed by a tautomerization and elimination of nitrogen. The Wolff–Kishner reduction is complementary to the Clemmensen reduction (Section 14.9A), which involves acid, and to the reduction of dithioacetals (Section 15.7D), which involves catalytic hydrogenation.

Benzophenone can be reduced to diphenylmethane by the Wolff–Kishner reduction, for example.

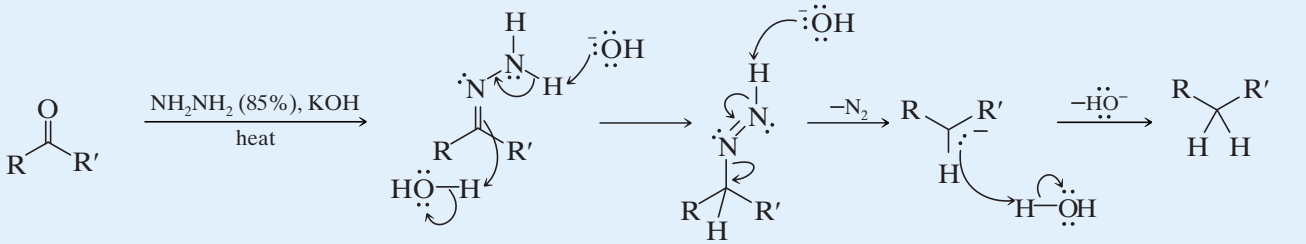
A Wolff–Kishner reduction



Benzophenone → **Diphenylmethane (83%)**

The mechanism for the Wolff–Kishner reaction is as follows:

A MECHANISM FOR THE REACTION — The Wolff–Kishner Reduction



Hydrazine hydrate reacts with the carbonyl compound to form a hydrazone.

Base promoted tautomerization transfers a proton from nitrogen to carbon.

Elimination of N_2 leads to a carbanion, which is then protonated.

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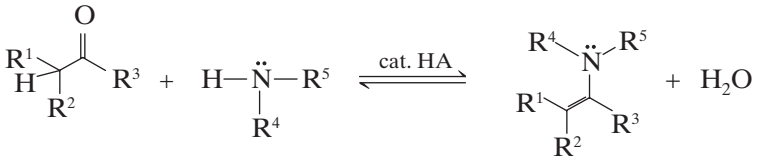
15.8D Enamines

Aldehydes and ketones react with secondary amines to form enamines. The following is a general equation for enamine formation:



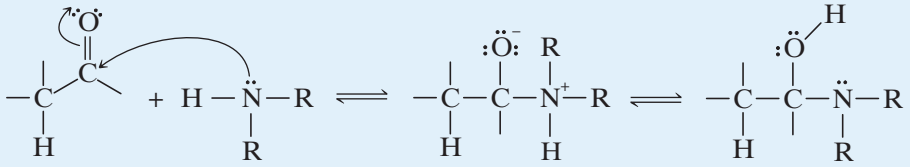
Secondary amine **Enamine**

A mechanism for the reaction is given in the following box. Note the difference between the previously described mechanism for imine formation and this mechanism for enamine formation. In enamine formation, which involves a secondary amine, there is no proton for removal from the nitrogen in the iminium cation intermediate. Hence, a neutral imine cannot be formed. A proton is removed from a carbon adjacent to the former carbonyl group instead, resulting in an enamine.

Tertiary amines do not form stable addition products with aldehydes and ketones because, on forming the tetrahedral intermediate, the resulting formal positive charge cannot be neutralized by loss of a proton.

A MECHANISM FOR THE REACTION — Enamine Formation

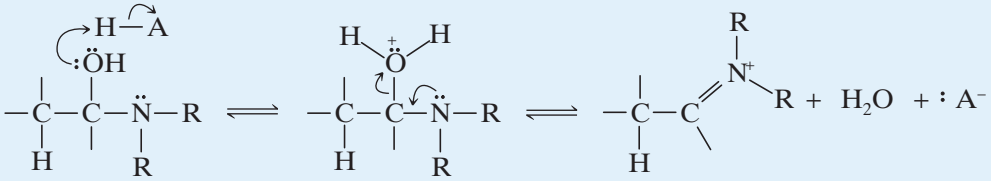
Step 1



Aldehyde or ketone **Secondary amine** **Aminoalcohol intermediate**

The amine adds to the ketone or aldehyde carbonyl to form a tetrahedral adduct. Intermolecular proton transfer leads to the aminoalcohol intermediate.

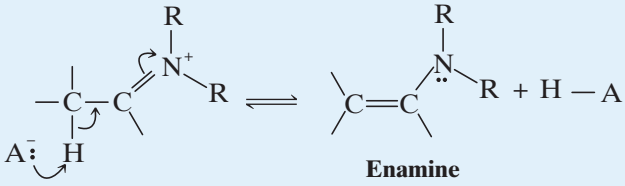
Step 2



Aminoalcohol intermediate **Iminium ion intermediate**

The aminoalcohol intermediate is protonated by the catalytic acid. Contribution of an unshared electron pair from the nitrogen atom and departure of a water molecule lead to an imin ium cation intermediate.

Step 3



Enamine

A proton is removed from the carbon adjacent to the iminium group. Proton removal occurs from the carbon because there is no pro ton to remove from the nitrogen of the iminium cation (as there would have been if a primary amine had been used). This step forms the enamine, neutralizes the formal charge, and regenerates the catalytic acid. (If there had been a proton to remove from the nitrogen of the iminium cation, the final product would have been an imine.)

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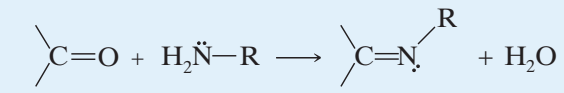
Table 15.2 summarizes the reactions of aldehydes and ketones with derivatives of ammonia.

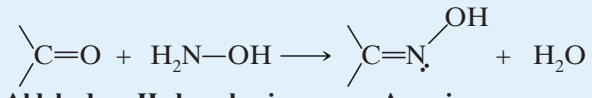
Table 15.2 Reactions of Aldehydes and Ketones with Derivatives of Ammonia

1. Imine formation—reaction with a primary amine



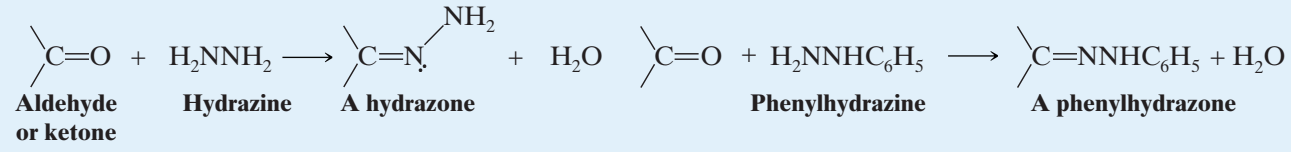
Aldehyde or ketone | A 1° amine | An imine [(*E*) and (*Z*) isomers]

2. Oxime formation—reaction with hydroxylamine

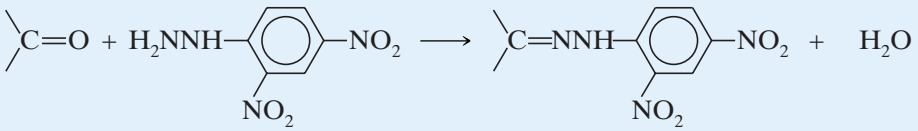


Aldehyde or ketone | Hydroxylamine | An oxime [(*E*) and (*Z*) isomers]

3. Hydrazone and substituted hydrazone formation—reactions with hydrazine, phenylhydrazine, and 2,4-dinitrophenylhydrazine [each derivative can form as an (*E*) or (*Z*) isomer]

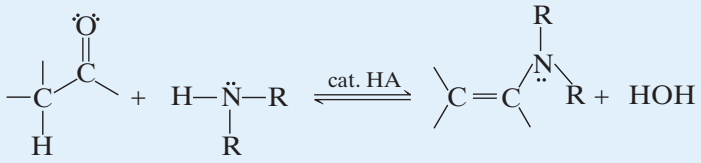


Aldehyde or ketone | Hydrazine | A hydrazone | Phenylhydrazine | A phenylhydrazone



2,4-Dinitrophenylhydrazine | A 2,4-dinitrophenylhydrazone

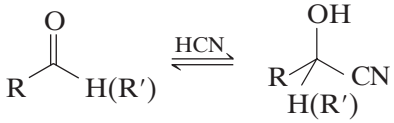
4. Enamine formation—reaction with a secondary amine



Secondary amine | Enamine

15.9 | THE ADDITION OF HYDROGEN CYANIDE: CYANOHYDRINS

- Hydrogen cyanide adds to the carbonyl groups of aldehydes and most ketones to form compounds called **cyanohydrins**. (Ketones in which the carbonyl group is highly hindered do not undergo this reaction.)



A cyanohydrin

Cyanohydrins form fastest under conditions where cyanide anions are present to act as the nucleophile. Use of potassium cyanide, or any base that can generate cyanide anions from HCN, increases the reaction rate as compared to the use of HCN alone. The addition of hydrogen cyanide itself to a carbonyl group is slow because the weak acidity of HCN (pK_a ~9) provides only a small concentration of the nucleophilic cyanide anion. The following is a mechanism for formation of a cyanohydrin.

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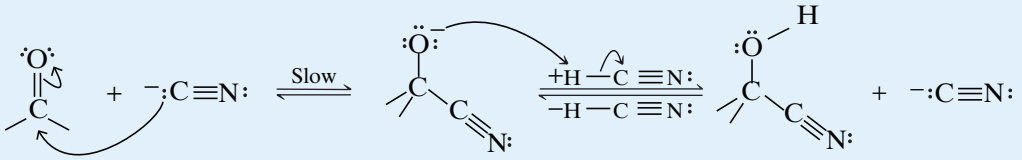
A MECHANISM FOR THE REACTION — Cyanohydrin Formation

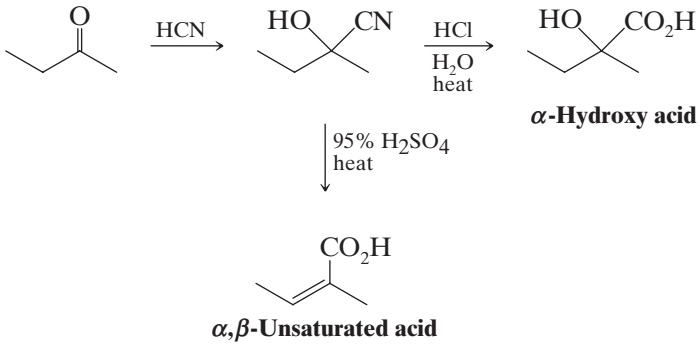


Great care must be taken when working with hydrogen cyanide due to its high toxicity and volatility. Reactions involving HCN must be conducted in an efficient fume hood.

Cyanohydrins are useful intermediates in organic synthesis because they can be converted to several other functional groups.

- Acidic hydrolysis converts cyanohydrins to α-hydroxy acids or to α,β-unsaturated acids.

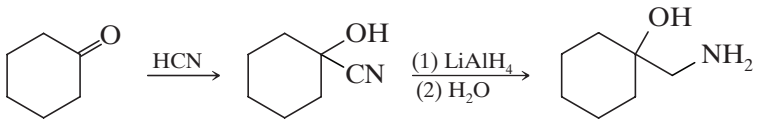
The mechanism for this hydrolysis is discussed in Section 17.8H. The preparation of α-hydroxy acids from cyanohydrins is part of the Kiliani–Fischer synthesis of simple sugars (Section 20.9A):



α-Hydroxy acid

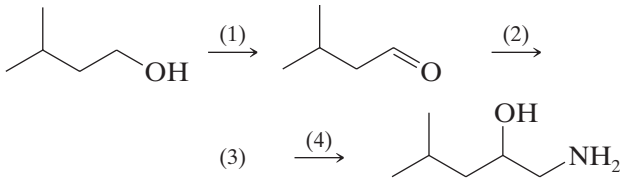
α,β-Unsaturated acid

- Reduction of a cyanohydrin with lithium aluminum hydride gives a β-aminoalcohol:



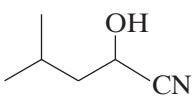
Solved Problem 15.6

Provide the missing reagents and intermediate in the following synthesis.



Answer

Step (1) requires oxidation of a primary alcohol to an aldehyde; use PCC (Section 11.4). To reach the final product from the aldehyde we need to add a carbon atom to the chain and introduce a primary amine. This combination suggests use of a nitrile, which we know can be reduced to a primary amine. Thus, adding HCN to the aldehyde in step (2) forms the cyanohydrin (3), shown below. This step also affords the alcohol group present in the final product. In step (4) we reduce the nitrile to a primary amine using $LiAlH_4$.



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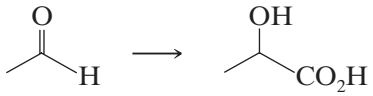
Practice Problem 15.16

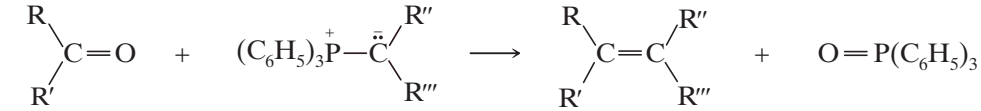
(a) Show how you might prepare lactic acid from acetaldehyde through a cyanohydrin intermediate. **(b)** What stereoisomeric form of lactic acid would you expect to obtain?



15.10 | THE ADDITION OF YLIDES: THE WITTIG REACTION

- Aldehydes and ketones react with phosphorus ylides to yield alkenes and triphenylphosphine oxide (a by-product). This reaction is known as the **Wittig reaction**.

The Wittig reaction has proved to be a valuable method for synthesizing alkenes. The **ylide** required for the reaction is a molecule with no net charge but which has a negative carbon atom adjacent to a positive heteroatom, which in the Wittig reaction is a phosphorus atom. Phosphorus ylides are also called phosphoranes.



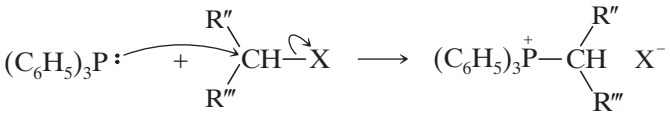
Aldehyde or ketone | **Phosphorus ylide (or phosphorane)** | **Alkene [(*E*) and (*Z*) isomers]** | **Triphenylphosphine oxide**

The Wittig reaction is applicable to a wide variety of compounds, and although a mixture of (*E*) and (*Z*) isomers may result, the Wittig reaction offers a great advantage over most other alkene syntheses in that *no ambiguity exists as to the location of the double bond in the product*. (This is in contrast to E1 eliminations, which may yield multiple alkene products by rearrangement to more stable carbocation intermediates, and both E1 and E2 elimination reactions, which may produce multiple products when different β hydrogens are available for removal.)

Phosphorus ylides are easily prepared from triphenylphosphine and primary or secondary alkyl halides. Their preparation involves two reactions:

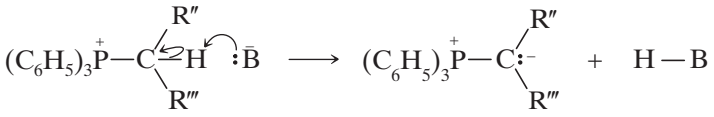
General Reaction

Reaction 1



Triphenylphosphine | **An alkyltriphenylphosphonium halide**

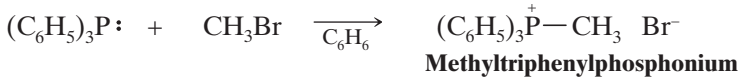
Reaction 2



A phosphorus ylide

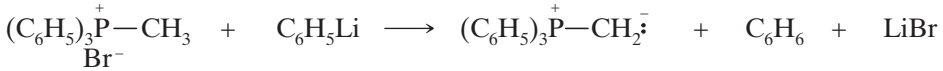
Specific Example

Reaction 1



Methyltriphenylphosphonium bromide (89%)

Reaction 2



The first reaction is a nucleophilic substitution reaction. Triphenylphosphine is an excellent nucleophile and a weak base. It reacts readily with 1° and 2° alkyl halides by an S_N2 mechanism to displace a halide ion from the alkyl halide to give an alkyltriphenylphosphonium salt. **The second reaction is an acid–base reaction.** A strong base (usually an alkyllithium or phenyllithium) removes a proton from the carbon that is attached to phosphorus to give the ylide.

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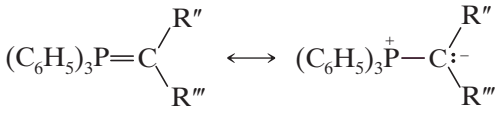
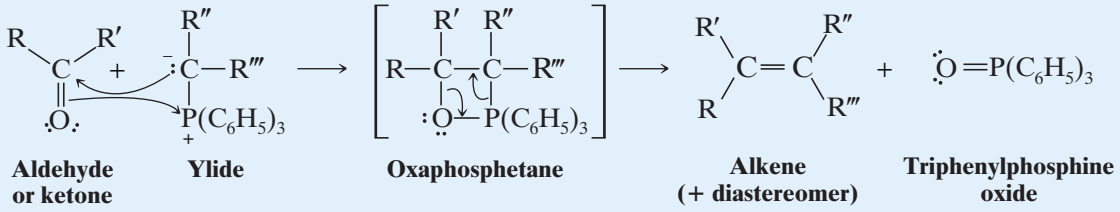
Phosphorus ylides can be represented as a hybrid of the two resonance structures shown here. Quantum mechanical calculations indicate that the contribution made by the first structure is relatively unimportant.

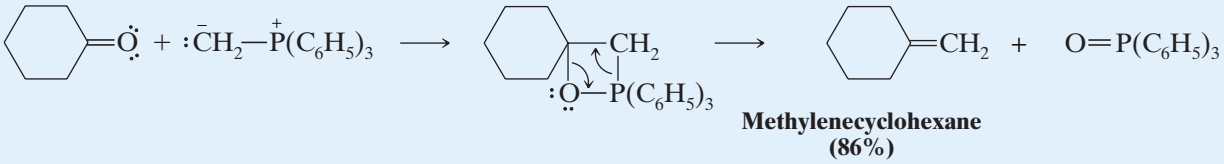


Studies by E. Vedejs (University of Michigan) indicate that the Wittig reaction takes place in two steps. In the first step (below), the aldehyde or ketone combines with the ylide in a cycloaddition reaction to form the four-membered ring of an oxaphosphetane. Then in a second step, the oxaphosphetane decomposes to form the alkene and triphenylphosphine oxide. The driving force for the reaction is the formation of the very strong ($DH° = 540$ kJ mol^{-1}) phosphorus–oxygen bond in triphenylphosphine oxide.

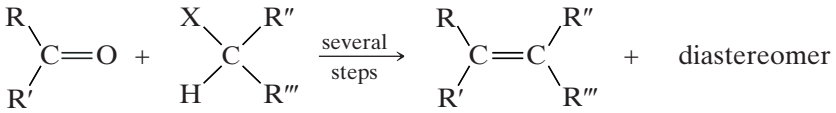
A MECHANISM FOR THE REACTION — The Wittig Reaction



Specific Example



While Wittig syntheses may appear to be complicated, in practice they are easy to carry out. Most of the steps can be carried out in the same reaction vessel, and the entire synthesis can be accomplished in a matter of hours. The overall result of a Wittig synthesis is:

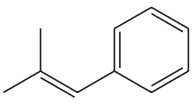


15.10A HOW TO Plan a Wittig Synthesis

Planning a Wittig synthesis begins with recognizing in the desired alkene what can be the aldehyde or ketone component and what can be the halide component. Any or all of the R groups may be hydrogen, although yields are generally better when at least one group is hydrogen. The halide component must be a primary, secondary, or methyl halide.

Solved Problem 15.7

Synthesize 2-methyl-1-phenylprop-1-ene using a Wittig reaction. Begin by writing a retrosynthetic analysis.



2–Methyl–1–phenylprop–1–ene

Answer

We examine the structure of the compound, paying attention to the groups on each side of the double bond:

We see that two retrosynthetic analyses are possible.

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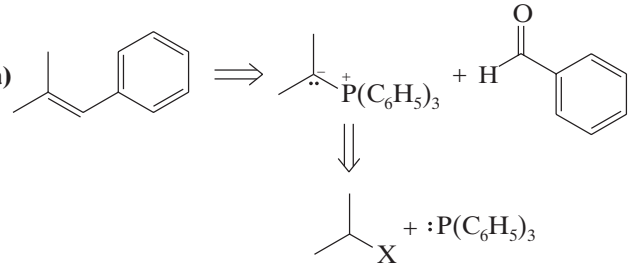
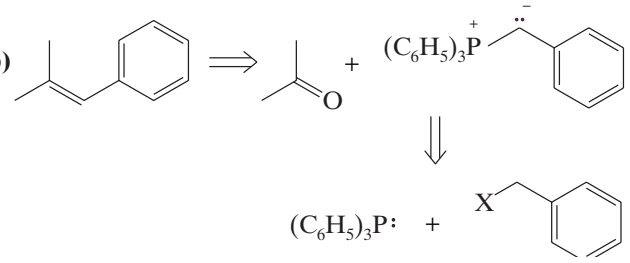
Retrosynthetic Analysis

(a)



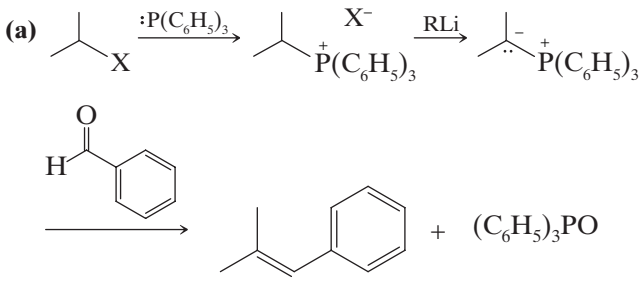
(b)



Synthesis

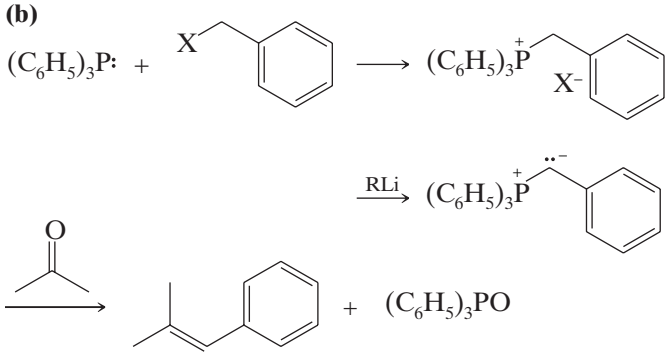
Following retrosynthetic analysis (a), we begin by making the ylide from a 2-halopropane and then allow the ylide to react with benzaldehyde:

(a)



Following retrosynthetic analysis (b), we make the ylide from a benzyl halide and allow it to react with acetone:

(b)



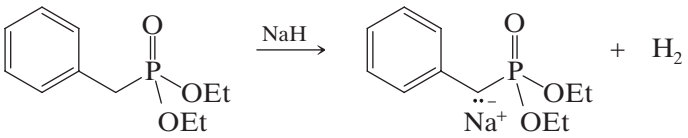
15.10B The Horner–Wadsworth–Emmons Reaction: A Modification of the Wittig Reaction

A widely used variation of the Wittig reaction is the **Horner–Wadsworth–Emmons** modification.

- The Horner–Wadsworth–Emmons reaction involves use of a phosphonate ester instead of a triphenylphosphonium salt. The major product is usually the (*E*)-alkene isomer.

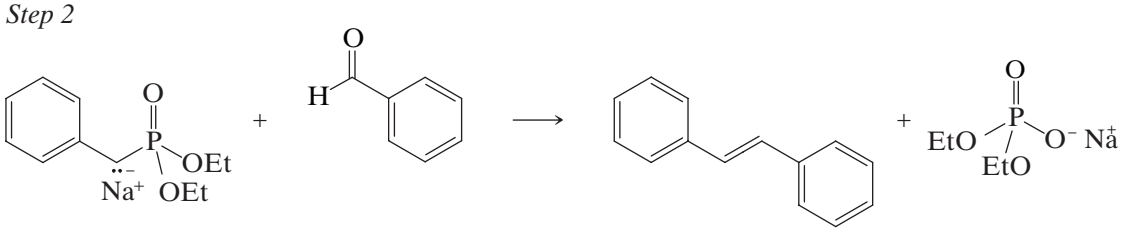
Some bases that are typically used to form the phosphonate ester carbanion include sodium hydride, potassium *tert*-butoxide, and butyllithium. The following reaction sequence is an example:

Step 1



A phosphonate ester

Step 2



84%

The phosphonate ester is prepared by reaction of a trialkyl phosphite [$(RO)_3P$] with an appropriate halide (a process called the Arbuzov reaction). The following is an example:

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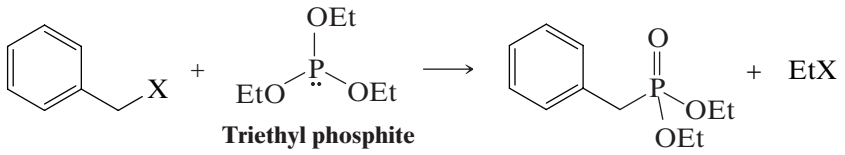
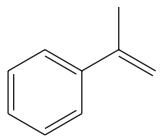


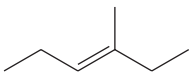
Triethyl phosphite

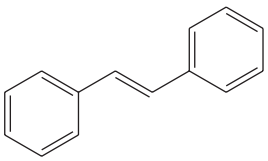
Practice Problem 15.17

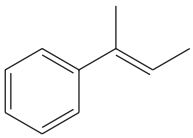
In addition to triphenylphosphine, assume that you have available as starting materials any necessary aldehydes, ketones, and organic halides. Show how you might synthesize each of the following alkenes using the Wittig reaction:

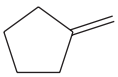
(a) 

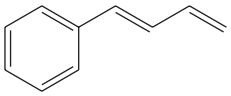
(c) 

(e) 

(g) 

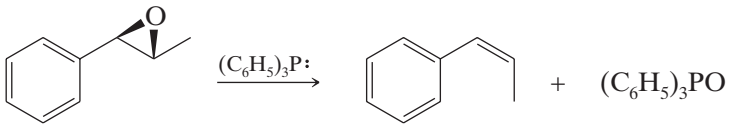
(b) 

(d) 

(f) 

Practice Problem 15.18

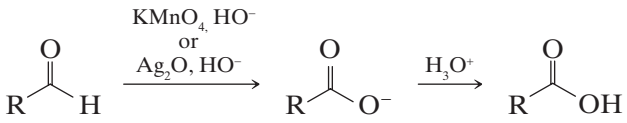
Triphenylphosphine can be used to convert epoxides to alkenes—for example,



Propose a likely mechanism for this reaction.

15.11 | OXIDATION OF ALDEHYDES

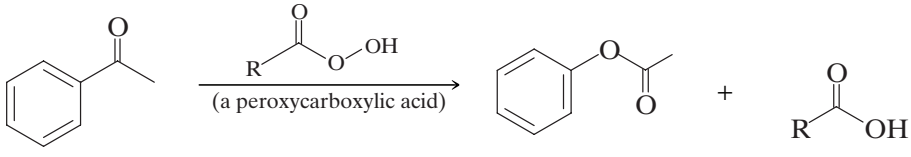
Aldehydes are much more easily oxidized than ketones. Aldehydes are readily oxidized by strong oxidizing agents such as potassium permanganate, and they are also oxidized by such mild oxidizing agents as silver oxide:



Notice that in these oxidations aldehydes lose the hydrogen that is attached to the carbonyl carbon atom. Because ketones lack this hydrogen, they are more resistant to oxidation. Aldehydes undergo slow oxidation by oxygen in the air, and thus stored samples of aldehydes often contain the corresponding carboxylic acid as an impurity.

15.12 | THE BAEYER–VILLIGER OXIDATION

The Baeyer–Villiger oxidation is a useful method for conversion of aldehydes or ketones to esters by the insertion of an oxygen atom from a peroxycarboxylic acid (RCO_3H). For example, treating acetophenone with a peroxycarboxylic acid converts it to the ester, phenyl acetate.



Acetophenone **Phenyl acetate**

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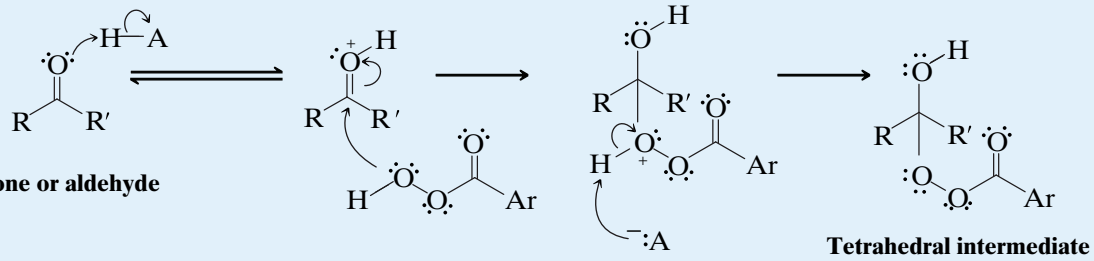
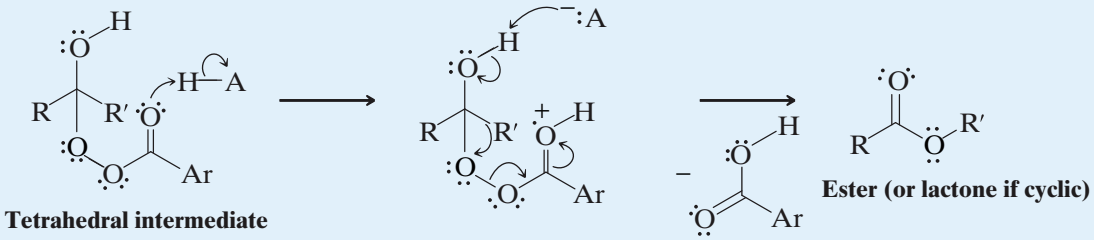
The Baeyer–Villiger oxidation is also widely used for synthesizing lactones (cyclic esters) from cyclic ketones. A common reagent used to carry out the Baeyer–Villiger oxidation is *meta*-chloroperoxybenzoic acid (*m*CPBA). Certain other peroxycarboxylic acids can be used as well. The following is a mechanism for Baeyer–Villiger oxidation.

A MECHANISM FOR THE REACTION — The Baeyer–Villiger Oxidation



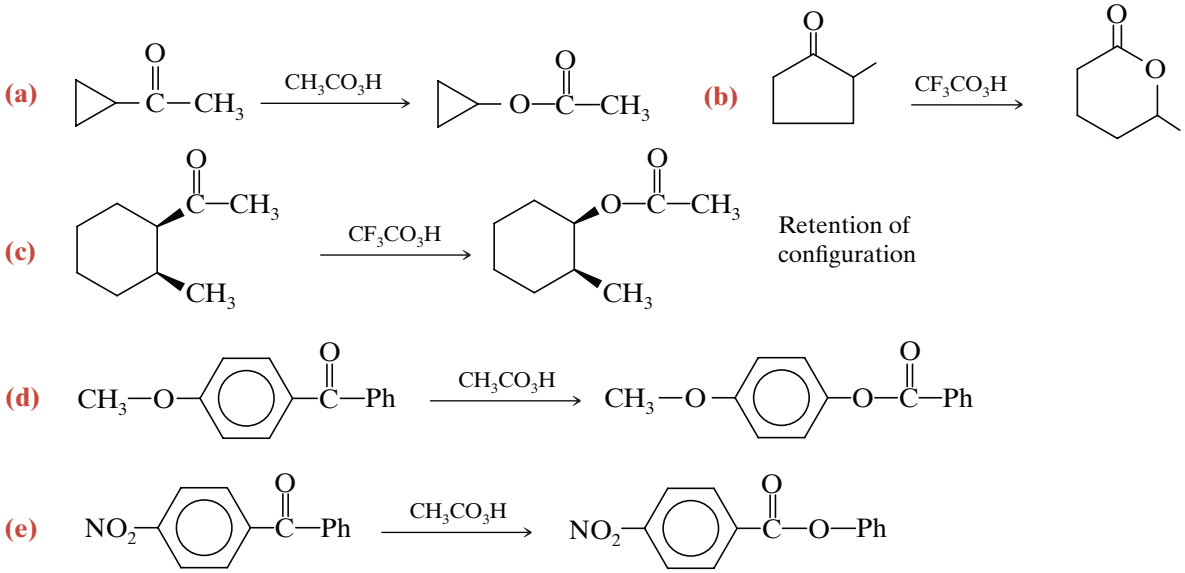
The peroxycarboxylic acid (e.g., *m*CPBA, where Ar is a 3-chlorophenyl group) attacks the carbonyl group of the protonated ketone or aldehyde, leading to a tetrahedral intermediate.



A group bonded to the initial ketone or aldehyde carbon migrates to oxygen, producing the ester (or lactone) as the peroxycarboxylic acid is released as a carboxylic acid.

The group that migrates from the original ketone or aldehyde carbon to the oxygen of the peroxycarboxylic acid is a function of "migratory aptitude." Studies have shown the migratory aptitude of groups is H > phenyl > 3° alkyl > 2° alkyl > 1° alkyl > methyl.

The major products obtained in some of the Baeyer–Villiger oxidation reactions are as follows:



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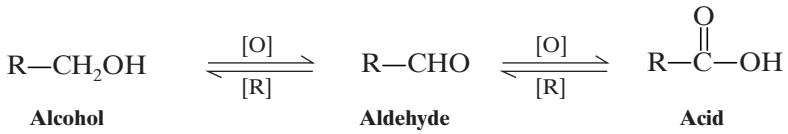
15.12A Cannizaro Reaction

Carbonyl group represents an intermediate state of oxidation between an alcohol and a carboxylic acid.

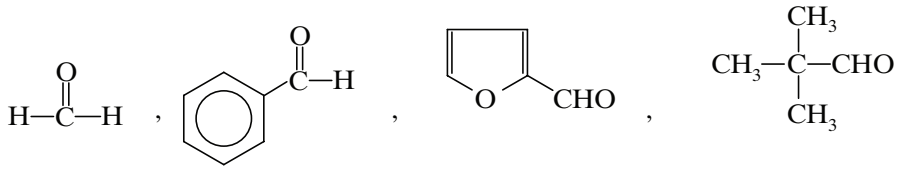


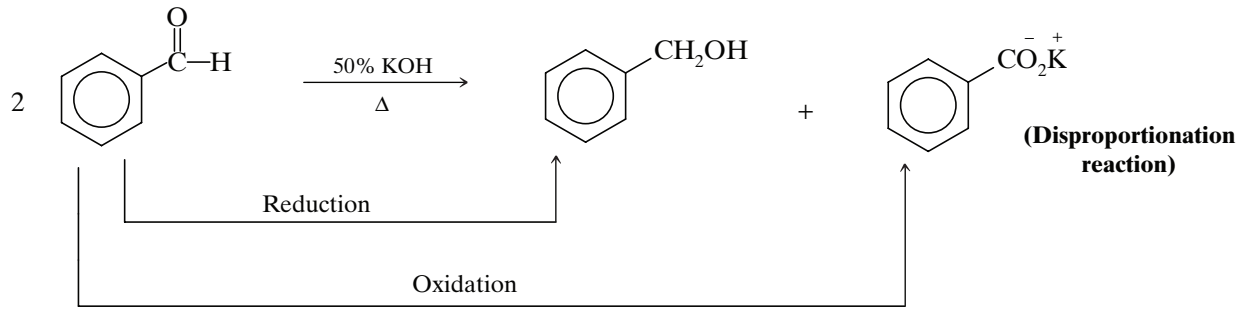
As such we can conceive a reaction in which two molecules of an aldehyde react to give one molecule of alcohol and one molecule of a carboxylic acid (disproportionation reaction).

The necessary conditions for Cannizaro reaction to occur are given below:

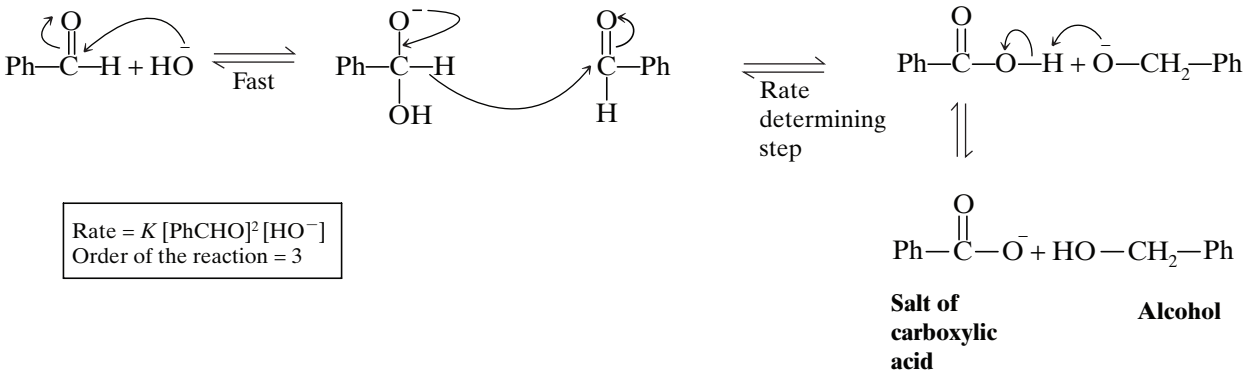
1. The reaction should take place in the presence of a concentrated base (50% KOH, 50% NaOH or 60% KOH).
2. The aldehyde involved should not have an α-hydrogen atom.

Some examples of aldehydes that can undergo Cannizaro reaction and a representative reaction are given below:





The reaction is believed to proceed as follows:



Rate = K [PhCHO]^2 [HO$^-$]
Order of the reaction = 3

Hydroxide ion is the initial nucleophile in this reaction, and addition to the aldehyde carbonyl group is a reversible process. Instead of reverting back to the original aldehyde due to loss of hydroxide, the adduct donates a hydride to a second molecule of aldehyde by a mechanistic sequence that also regenerates a carbonyl group. Although reversal of the initial step is energetically favorable, the second step (oxidation–reaction) is made effectively irreversible by rapid proton transfer between the products – the carboxylic acid and alkoxide.

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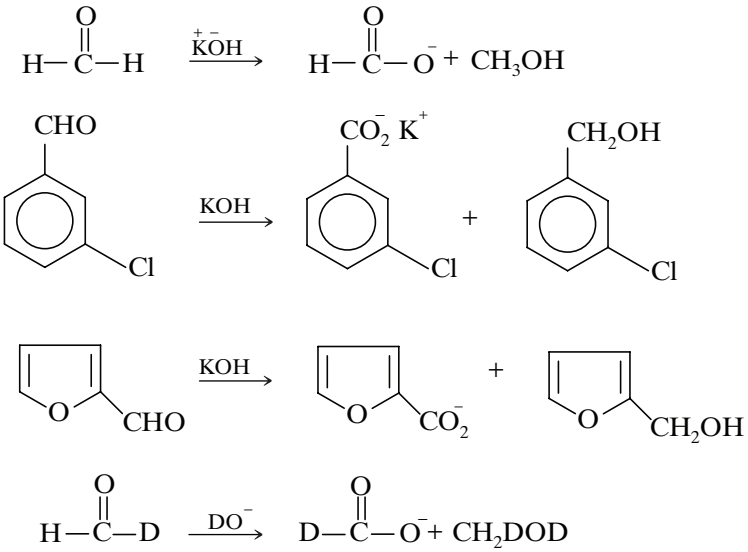
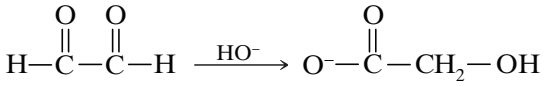
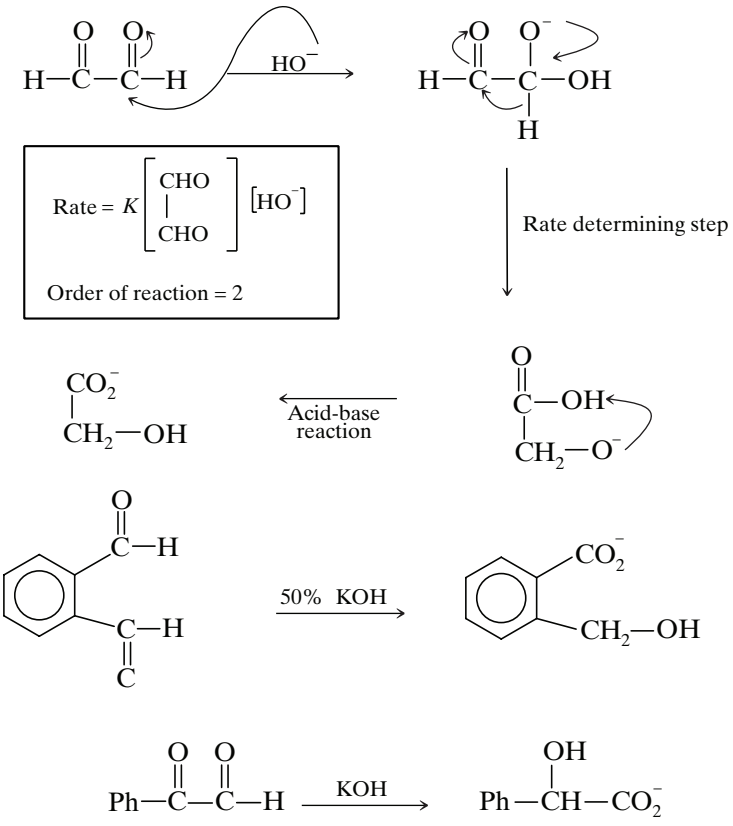
Some more examples of Cannizaro reaction are given below:



Intramolecular Cannizaro reaction: Dialdehyde can also undergo intramolecular hydride transfer in the Cannizaro reaction. For example, Cannizaro reaction of glyoxal.



The mechanism of the reaction is as follows:



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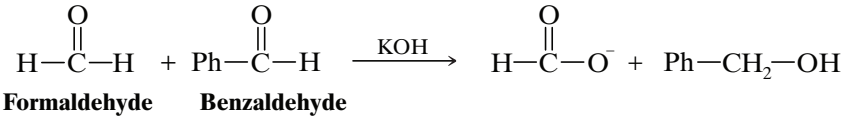
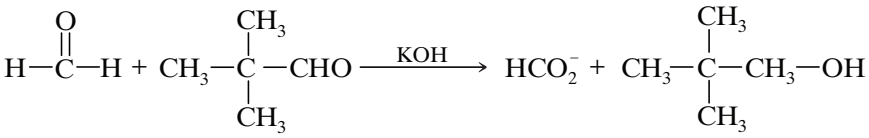
Crossed Cannizaro reaction: The reaction carried out by using equimolar quantities of two different aldehydes is named as crossed Cannizaro reaction.

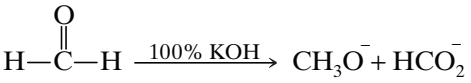


Formaldehyde **Benzaldehyde**

If one of the reactants in Cannizaro reaction is formaldehyde, then it will undergo oxidation and the other aldehyde will undergo reduction. For example



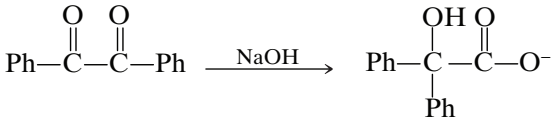
A special case of Cannizaro reaction is when formaldehyde is reacted with 100% KOH.



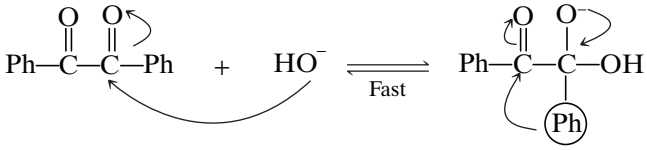
Rate = $K[HCHO]^2[HO^-]^2$
Order of reaction = 4

15.12B Benzilic Acid Rearrangement

Benzil on treatment with strong base forms benzilic acid (as salt). This reaction is known as Benzilic acid rearrangement.

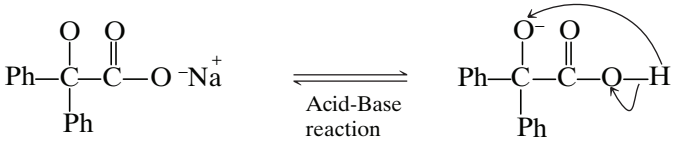


The mechanism of this reaction is as follows:



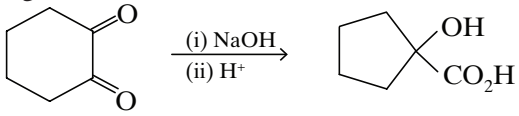
Rate = K [Ph—CO—CO—Ph] [HO^-]
Order of reaction = 2

Rate determining step



Sodium salt of benzilic acid

This rearrangement is analogous to intramolecular Cannizaro reaction of glyoxal. Some examples of Benzilic acid rearrangement are as follows:

1. 

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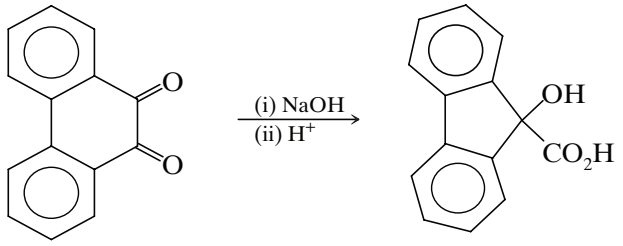
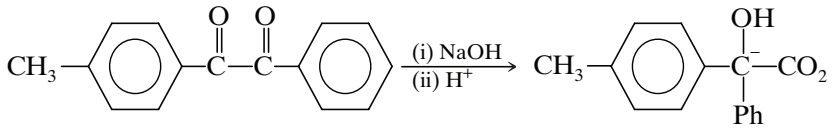
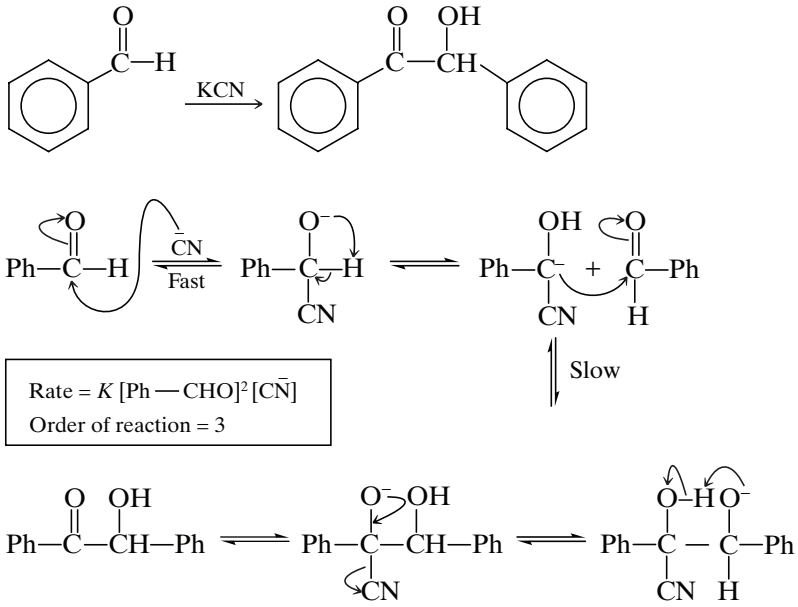
2. 

3. 

15.12C Benzoin Condensation

This reaction involves an aromatic aldehyde, Ph–CHO, and is similar to Cannizaro reaction; with the exception that, instead of hydride transfer, it is carbanion addition to the carbonyl carbon atom of the second molecule of Ph–CHO.



15.13 | CHEMICAL ANALYSES FOR ALDEHYDES AND KETONES

15.13A Derivatives of Aldehydes and Ketones

Aldehydes and ketones can be differentiated from noncarbonyl compounds through their reactions with derivatives of ammonia (Section 15.8B). 2,4-Dinitrophenylhydrazine and hydroxylamine react with aldehydes and ketones to form precipitates. Oximes are usually colorless, whereas 2,4-dinitrophenylhydrazones are usually orange. The melting points of these derivatives can also be used in identifying specific aldehydes and ketones.

15.13B Tollens' Test (Silver Mirror Test)

The ease with which aldehydes undergo oxidation differentiates them from most ketones. Mixing aqueous silver nitrate with aqueous ammonia produces a solution known as Tollens' reagent. The reagent contains the diaminosilver(I) ion, $Ag(NH_3)_2^+$. Although this ion is a very weak oxidizing agent, it oxidizes aldehydes to carboxylate anions. As it does this, silver is reduced from the +1 oxidation state [of $Ag(NH_3)_2^+$] to metallic silver. If the rate of reaction is slow and

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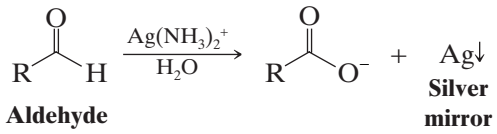
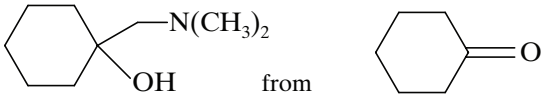
the walls of the vessel are clean, metallic silver deposits on the walls of the test tube as a mirror; if not, it deposits as a gray-to-black precipitate. Tollens' reagent gives a negative result with all ketones except α-hydroxy ketones:



Aldehyde

Solved Problem 15.8

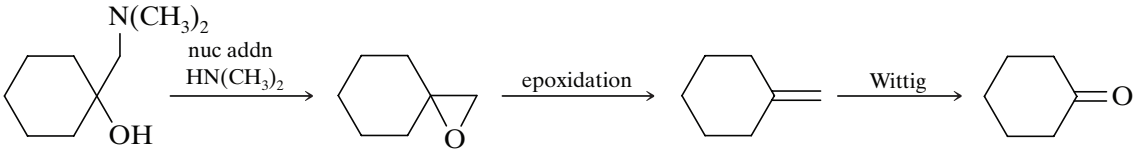
Suggest a sequence of reactions to carry out the following transformation, but one intermediate must be an alkene.



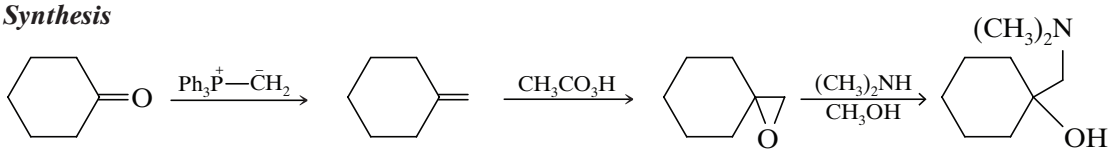
Answer

The starting compound ketone suggests that a Wittig route might be possible.

Retrosynthesis

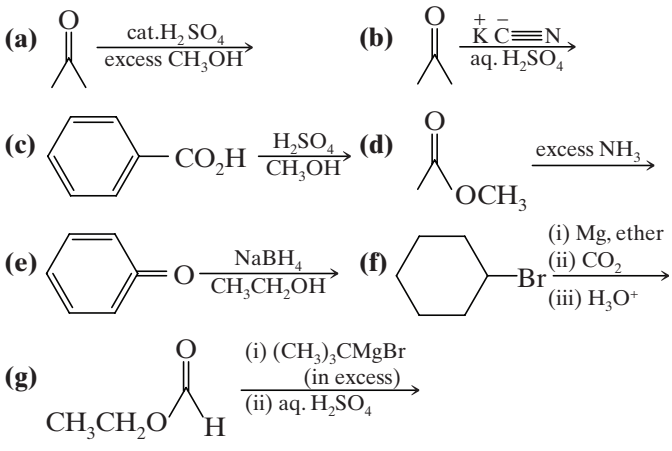


Synthesis

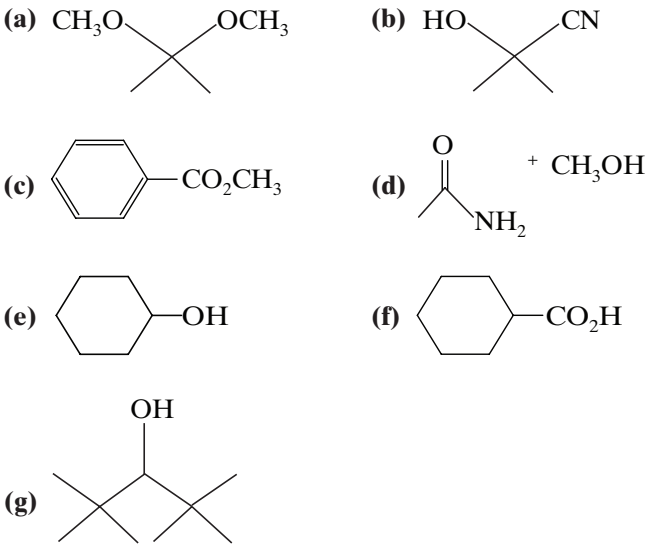


Solved Problem 15.9

Provide the organic product(s) for the following reactions. If more than one product is formed, indicate which product (if any) is the major one. If no reaction occurs, write "NR". (*Hint*: Almost any time you are asked to provide a reaction product, you should also be able to write the mechanism for the reaction as well. If you do not know the product, then trying to figure out the mechanism will guide you in the right direction.)



Answer



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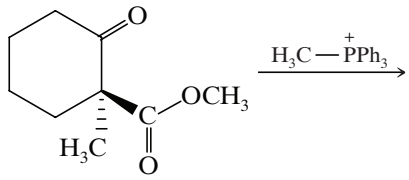
Solved Problem 15.10

(a) $CH_3(CH_2)_{10}Br \xrightarrow[(iii)\ CH_3(CH_2)_{10}CHO]{(i)\ Ph_3P,\ (ii)\ BuLi}$

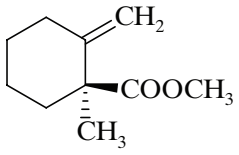
(b) 

Write a mechanism for part (a).

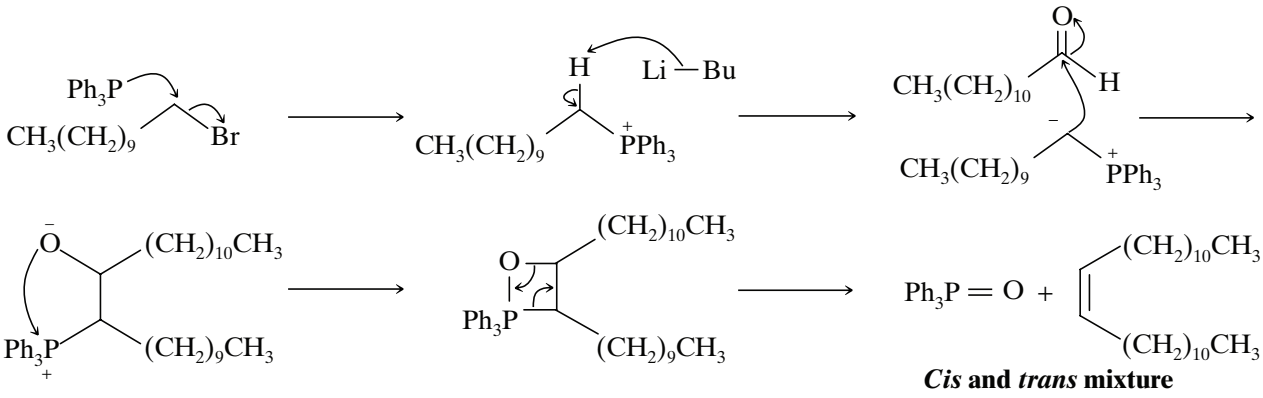
Answer

(a) $CH_3(CH_2)_{10}Br \xrightarrow[(iii)\ CH_3(CH_2)_{10}CHO]{(i)\ Ph_3P,\ (ii)\ BuLi} CH_3(CH_2)_9CH{=}CH(CH_2)_{10}CH_3$

Cis and *trans* mixture

(b) 

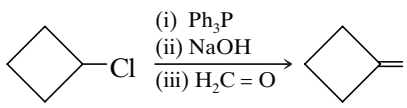
Mechanism for part (a):

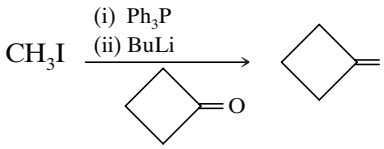


***Cis* and *trans* mixture**

Solved Problem 15.11

Consider the two Wittig reactions shown below. Select the most efficient route and provide three reasons for your choice.

Route A : 

Route B : 

Answer

Route B is the most efficient route. The reasons are as follows:

(a) Iodide (route B) is a better leaving group than chloride (route A), so the S_N2 reaction with Ph_3P in route A is expected to be less efficient. (Favors route B.)

(b) Hydroxide (route A) is not a strong enough base to deprotonate a simple phosphonium salt. BuLi (route B) is a much stronger base. (Favors Route B.)

(c) An aldehyde such as formaldehyde (route A) is a better electrophile than a ketone such as cyclobutanone (route B). (Favors route A).

(d) A methyl halide (route B) is less sterically hindered than a secondary halide (route A), so S_N2 reaction with Ph_3P of route B is more efficient than that of route A. (Favors route B.)

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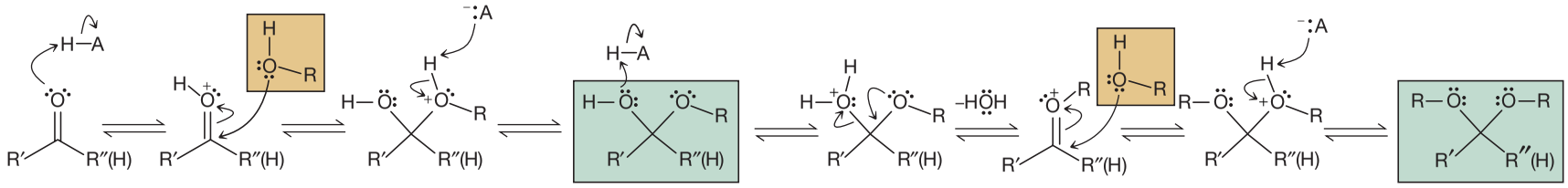
SUMMARY OF MECHANISMS

Acetals, Imines, and Enamines: Common Mechanistic Themes in Their Acid-catalyzed Formation from Aldehydes and Ketones

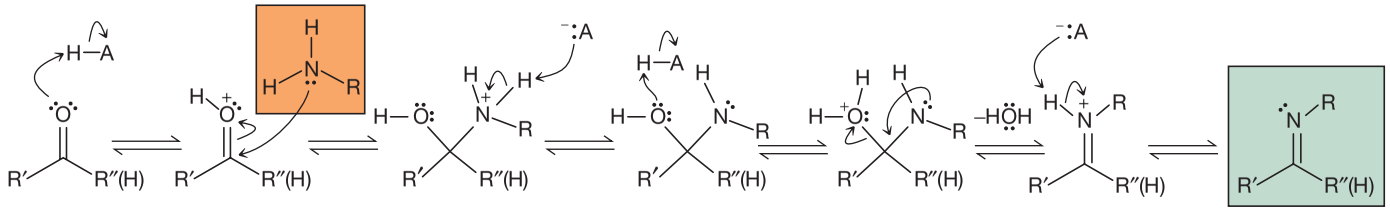
Many steps are nearly the same in acid-catalyzed reactions of aldehydes and ketones with alcohols and amines. Compare the mechanisms vertically to see the similarities and differences. Note differences in completion of the mechanism for each type of product.

I. Hemiacetal and acetal formation: reaction with alcohols



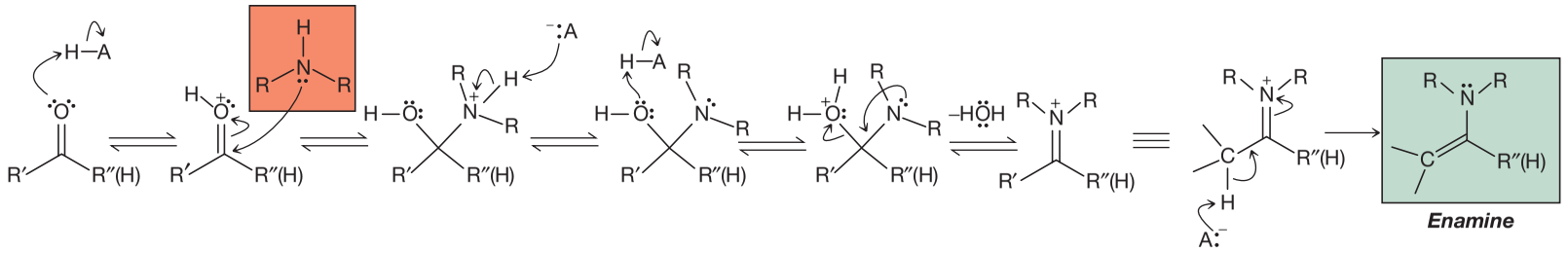
*In **acetal** formation, the oxonium ion is attacked by a second alcohol molecule.*

II. Imine formation: reaction with primary amines



*In **imine** formation, the proton on the initial iminium ion is removed, leading to the stable imine product.*

III. Enamine formation: reaction with secondary amines

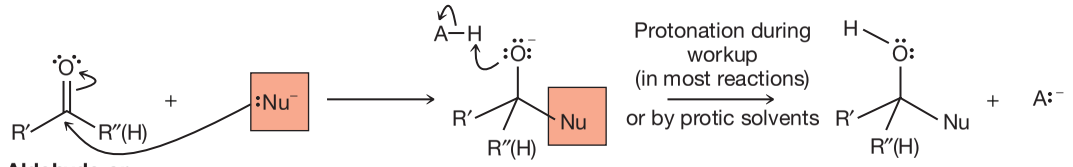


*In **enamine** formation, a proton is removed from a carbon adjacent to the iminium carbon (because no proton is available for removal from the nitrogen).*

SUMMARY OF MECHANISMS

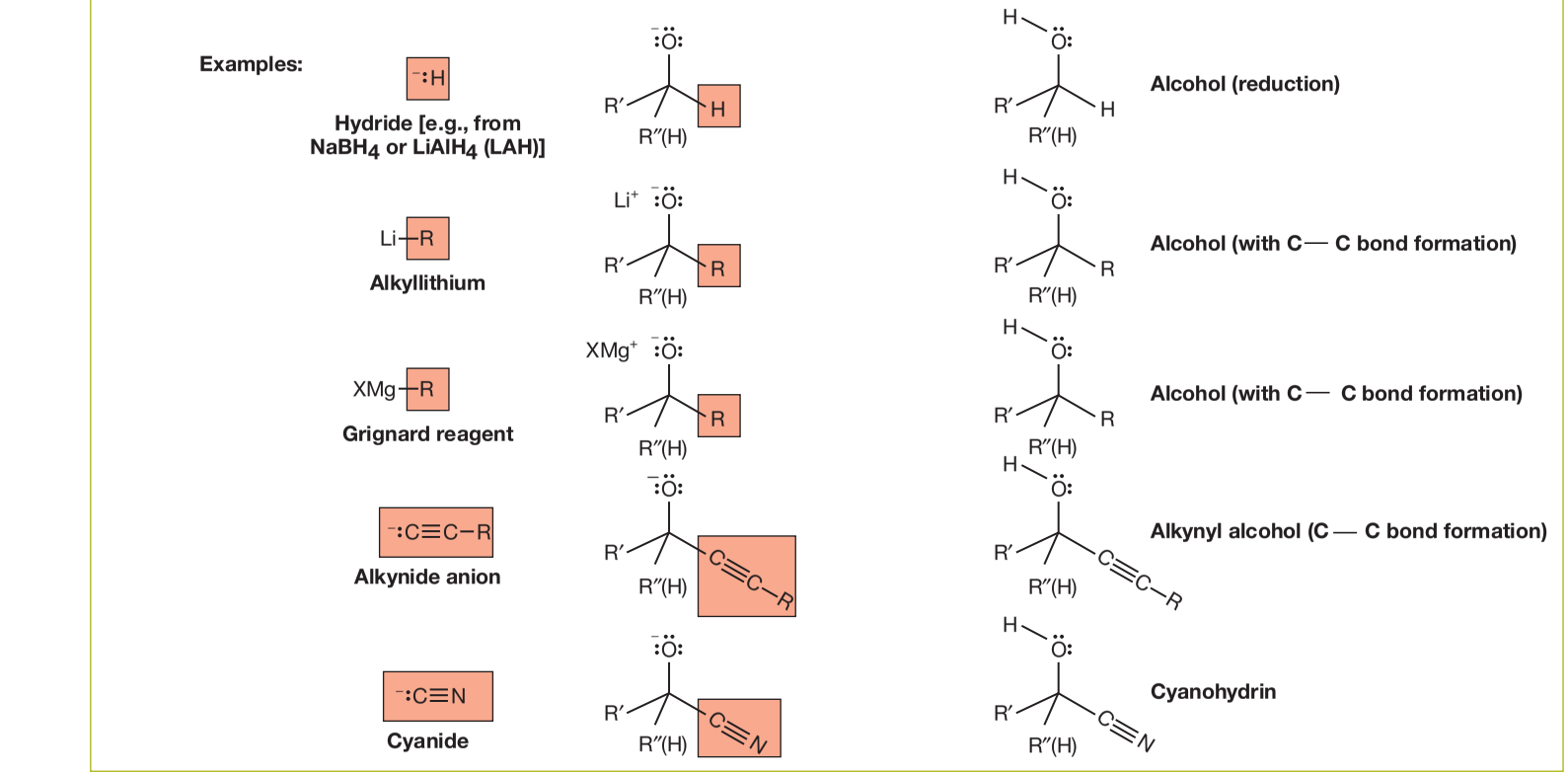
Nucleophilic Addition to Aldehydes and Ketones Under Basic Conditions

Generalized nucleophilic addition to an aldehyde or ketone:



Aldehyde or ketone | **Nucleophile** | **Tetrahedral intermediate** | **Product**

Examples:



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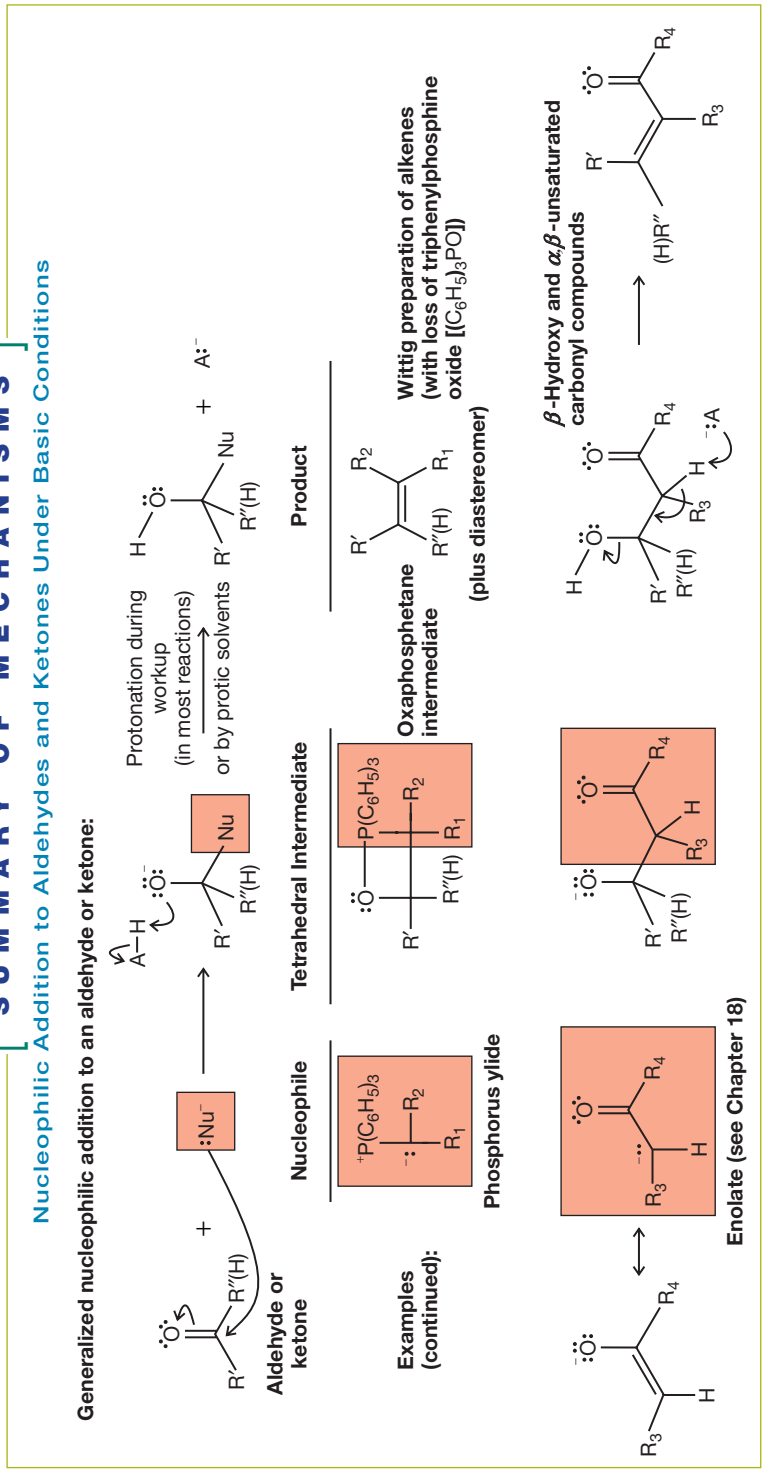


SYNTHETIC CONNECTIONS

Some Synthetic Connections of Aldehydes, Ketones, and Other Functional Groups

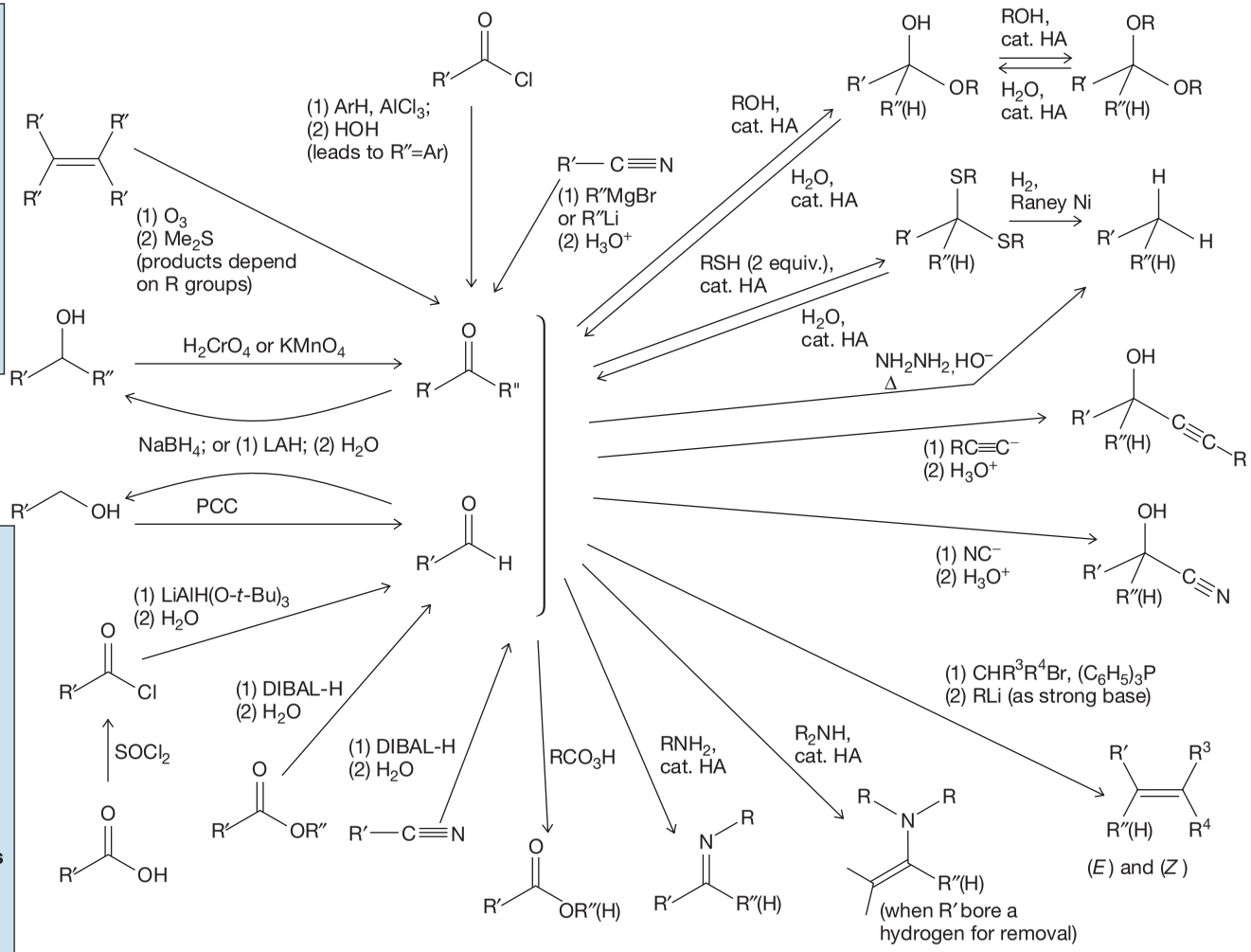
Clockwise from center, bottom:

I. Preparation of aldehydes and ketones:

- Nitrile, ester, acyl halide reduction
- Alcohol oxidation
- Ozonolysis
- Friedel–Crafts acylation
- Grignard with nitrile
- Acetal and hemiacetal hydrolysis

II. Reactions of aldehydes and ketones:

- Hemiacetal and acetal formation
- Thioacetal formation and reduction
- Wolff– Kishner reduction
- Alkynide anion addition
- Nitrile addition (cyanohydrin formation)
- Wittig synthesis of alkenes
- Enamine synthesis
- Baeyer–Villiger oxidation
- Imine synthesis
- Reduction to alcohols (left, center)



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REVIEW PROBLEMS

Reactions and Nomenclature

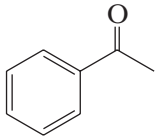
15.19 Give a structural formula and another acceptable name for each of the following compounds:

(a) Formaldehyde
(b) Acetaldehyde
(c) Phenylacetaldehyde
(d) Acetone
(e) Ethyl methyl ketone
(f) Acetophenone
(g) Benzophenone
(h) Salicylaldehyde
(i) Vanillin
(j) Diethyl ketone
(k) Ethyl isopropyl ketone
(l) Diisopropyl ketone
(m) Dibutyl ketone
(n) Dipropyl ketone
(o) Cinnamaldehyde

15.20 Write structural formulas for the products formed when propanal reacts with each of the following reagents:

(a) $NaBH_4$ in aqueous NaOH
(b) C_6H_5MgBr, then H_3O^+
(c) $LiAlH_4$, then H_2O
(d) Ag_2O, HO^-
(e) $(C_6H_5)_3\overset{+}{P}—\ddot{\underset{\cdot\cdot}{C}}H_2$
(f) H_2 and Pt
(g) HO—⟨⟩—OH and HA
(h) $CH_3C—\overset{+}{P}(\ddot{\underset{\cdot\cdot}{C}}_6H_5)_3$
(i) $Ag(NH_3)_2^+$
(j) Hydroxylamine
(k) Phenylhydrazine
(l) Cold dilute $KMnO_4$
(m) HS—⟨⟩—SH, HA
(n) HS—⟨⟩—SH, HA, then Raney nickel
(o) *m*CPBA

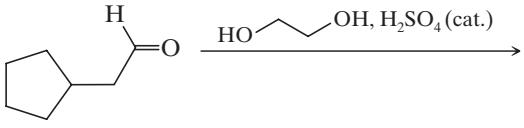
15.21 What products would be obtained when acetophenone reacts under each of the following conditions?

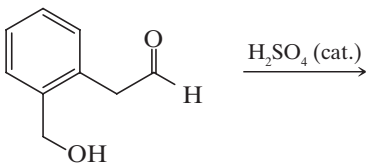


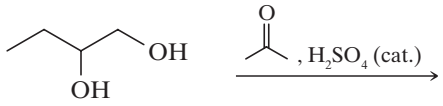
Acetophenone

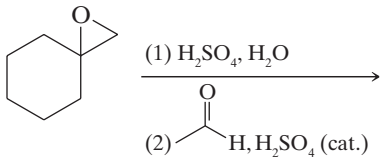
(a) $\xrightarrow[H_2SO_4]{HNO_3}$
(b) $\xrightarrow{C_6H_5NHNH_2,\ HA}$
(c) $\xrightarrow{H_2\ddot{\underset{\cdot\cdot}{C}}—\overset{+}{P}(C_6H_5)_3}$
(d) $\xrightarrow[CH_3OH]{NaBH_4}$
(e) $\xrightarrow[(2)\ NH_4Cl]{(1)\ C_6H_5MgBr}$
(f) $\xrightarrow[\Delta]{NH_2NH_2,HO^-}$
(g) $\xrightarrow{m\text{CPBA}}$

15.22 Predict the major organic product from each of the following reactions.

(a)


(b)


(c)


(d)


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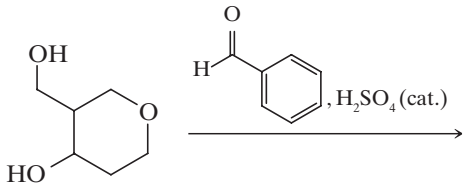
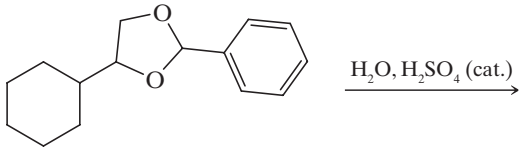
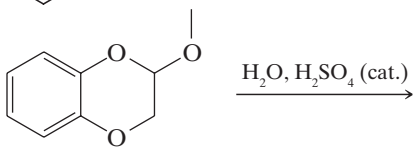
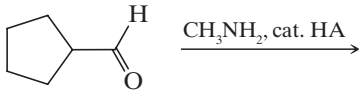


(f)


(g)


15.23 Predict the major product from each of the following reactions.

(a)


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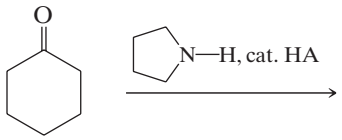

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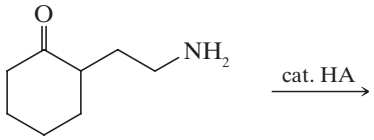

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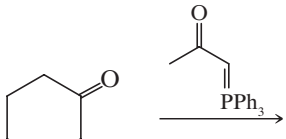

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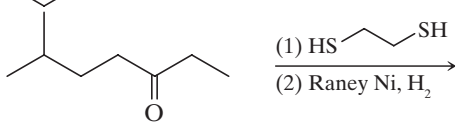

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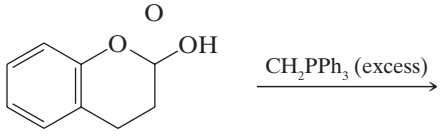

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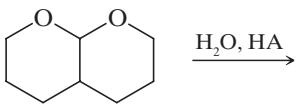
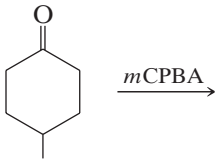
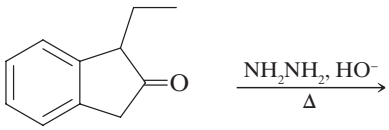
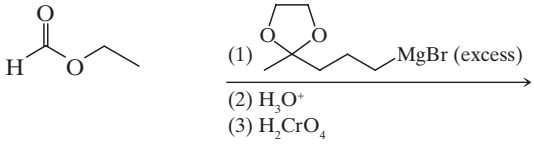
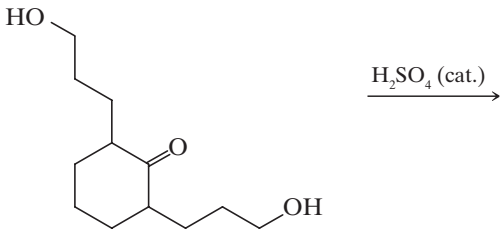
(g) 

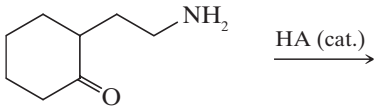
(h) 

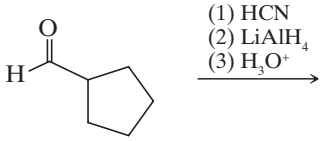
(i) 

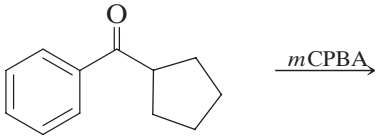
15.24 Predict the major product from each of the following reactions.

(a) 

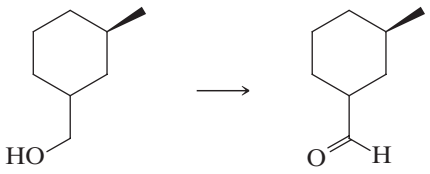
(b) 

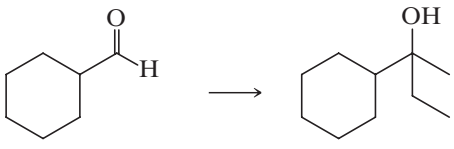
(c) 

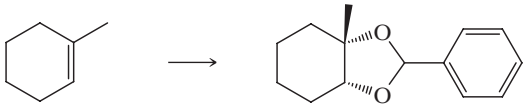
(d) 

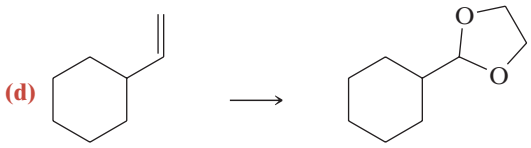
(e) 

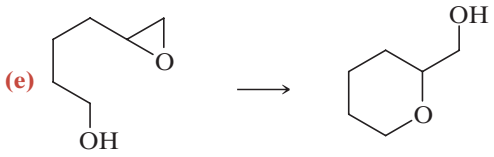
15.25 Provide the reagents needed to accomplish each of the following transformations.

(a) 

(b) 

(c) 

(d) 

(e) 

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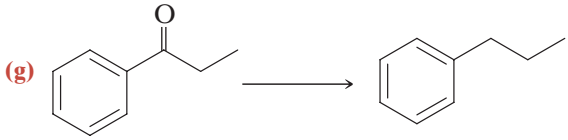
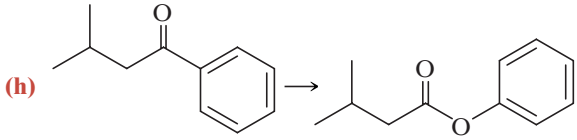
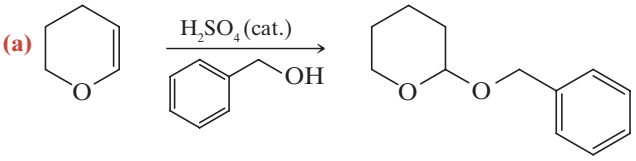
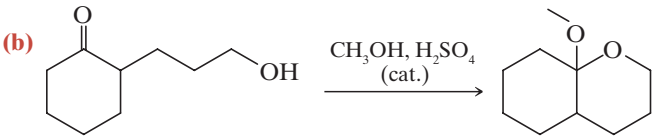
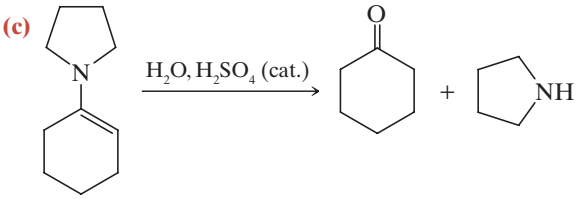
(g) 

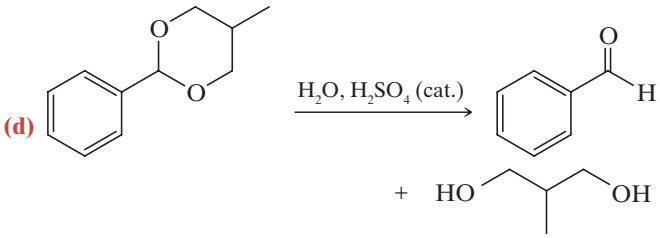
(h) 

15.26 Write detailed mechanisms for each of the following reactions.

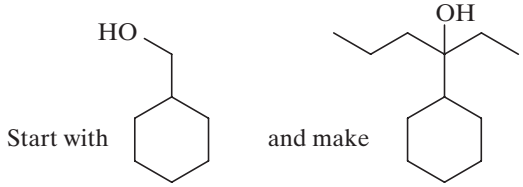
(a) 

(b) 

(c) 

(d) 

15.27 Provide the reagents necessary for the following synthesis.



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Synthesis

15.28 **(a)** Synthesize phenyl propyl ketone from benzene and any other needed reagents.
(b) Give two methods for transforming phenyl propyl ketone into butylbenzene.

15.29 Show how you would convert benzaldehyde into each of the following. You may use any other needed reagents, and more than one step may be required.
(a) Benzyl alcohol **(b)** Benzoic acid
(c) Benzoyl chloride **(d)** Benzophenone
(e) 1-Phenylethanol
(f) 3-Methyl-1-phenyl-1-butanol
(g) Benzyl bromide **(h)** Toluene
(i) $C_6H_5CH(OCH_3)_2$ **(j)** $C_6H_5CH^{18}O$
(k) C_6H_5CHDOH **(l)** $C_6H_5CH(OH)CN$
(m) $C_6H_5CH{=}NOH$ **(n)** $C_6H_5CH{=}NNHC_6H_5$
(o) $C_6H_5CH{=}CHCH{=}CH_2$

15.30 Show how ethyl phenyl ketone ($C_6H_5COCH_2CH_3$) could be synthesized from each of the following:
(a) Benzene **(b)** Benzonitrile, C_6H_5CN
(c) Benzaldehyde

15.31 Show how benzaldehyde could be synthesized from each of the following:
(a) Benzyl alcohol **(b)** Benzoic acid
(c) Phenylethyne **(d)** Phenylethene (styrene)
(e) $C_6H_5CO_2CH_3$ **(f)** $C_6H_5C{\equiv}N$

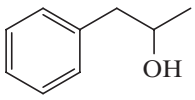
15.32 Give structures for compounds **A–E**.

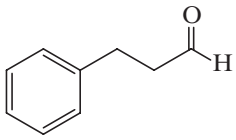
$$\text{Cyclohexanol} \xrightarrow[\text{acetone}]{H_2CrO_4} \mathbf{A}\ (C_6H_{10}O) \xrightarrow[(2)\ H_3O^+]{(1)\ CH_3MgI}$$

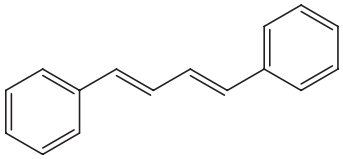
$$\mathbf{B}\ (C_7H_{14}O) \xrightarrow[\text{heat}]{HA} \mathbf{C}\ (C_7H_{12}) \xrightarrow[(2)\ Me_2S]{(1)\ O_3}$$

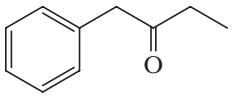
$$\mathbf{D}\ (C_7H_{12}O_2) \xrightarrow[(2)\ H_3O^+]{(1)\ Ag_2O,\ HO^-} \mathbf{E}\ (C_7H_{12}O_3)$$

15.33 Starting with benzyl bromide, show how you would synthesize each of the following:

(a) 

(b) 

(c) 

(d) 

15.34 Compounds **A** and **D** do not give positive Tollens' tests; however, compound **C** does. Give structures for **A–D**.

$$\text{4-Bromobutanal} \xrightarrow[HA]{HOCH_2CH_2OH,} \mathbf{A}\ (C_6H_{11}O_2Br) \xrightarrow{Mg,\ Et_2O}$$

$$[\mathbf{B}\ (C_6H_{11}MgO_2Br)] \xrightarrow[(2)\ H_3O^+,\ H_2O]{(1)\ CH_3CHO} \mathbf{C}\ (C_6H_{12}O_2)$$

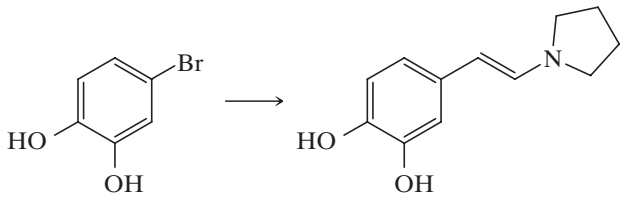
$$\xrightarrow[HA]{CH_3OH} \mathbf{D}\ (C_7H_{14}O_2)$$

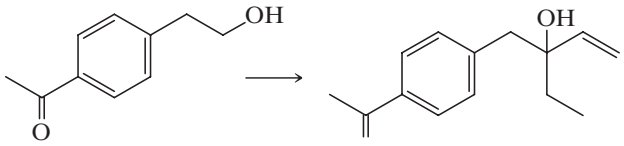
15.35 Outlined here is a synthesis of glyceraldehyde. What are the intermediates **A–C** and what stereoisomeric form of glyceraldehyde would you expect to obtain?

$$\text{OH} \xrightarrow[CH_2Cl_2]{PCC} \mathbf{A}\ (C_3H_4O) \xrightarrow{CH_3OH,HA} \mathbf{B}\ (C_5H_{10}O_2)$$

$$\xrightarrow[\text{cold, dilute}]{KMnO_4,\ HO^-} \mathbf{C}\ (C_5H_{12}O_4) \xrightarrow[H_2O]{H_3O^+} \text{glyceraldehyde}$$

15.36 Provide reagents that would accomplish each of the following syntheses. Begin by writing a retrosynthetic analysis.

(a) 

(b) 

ADDITIONAL OBJECTIVE QUESTIONS

Single Correct Choice Type

1. Hydrogenation of benzoyl chloride in the presence of Pd and $BaSO_4$ gives
(a) benzyl alcohol. **(b)** benzaldehyde.
(c) benzoic acid. **(d)** phenol.

2. *m*-chlorobenzaldehyde on reaction with conc. KOH at room temperature gives
(a) potassium *m*-chlorobenzoate and *m*-hydroxybenzaldehyde.
(b) *m*-hydroxybenzaldehyde and *m*-chlorobenzyl alcohol.
(c) *m*-chlorobenzyl and *m*-hydroxybenzyl alcohol.
(d) potassium *m*-chlorobenzoate and *m*-chlorobenzyl alcohol.

3. Choose all of those reaction sequences that would be successful syntheses of the following aldehyde.

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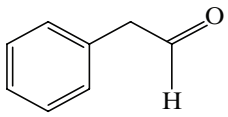
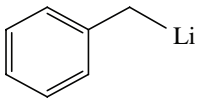
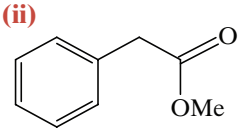
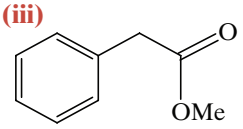


(i) 

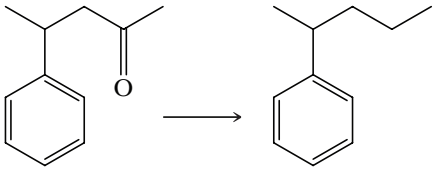
(ii) 

(iii) 

(a) Only (i) **(b)** Only (iii)
(c) Both (i) and (ii) **(d)** Both (ii) and (iii)

4. $LiAlH_4$ (LAH) cannot be used to convert carboxylic acids to the corresponding aldehydes because
(a) LAH is not sufficiently reactive.
(b) RCOOH is converted into RCOOLi.
(c) RCOOH is reduced to RCH_2OH.
(d) RCOOH is reduced to RCH_3.

5. What reagents would allow you to accomplish the conversion of C=O to CH_2?



(a) $NaBH_4/CH_3OH$
(b) Zn(Hg) / aq. HCl
(c) H_2NNH_2, KOH, heat
(d) Both (b) and (c) are correct

6. In the Cannizzaro reaction given below

$$2Ph{-}CHO \xrightarrow{OH^-} Ph{-}CH_2OH + PhCO_2^-$$

the slowest step is
(a) the attack of OH^- at the carbonyl group.
(b) the transfer of hydride to the carbonyl group.
(c) the abstraction of proton from the carboxylic acid.
(d) the deprotonation of $Ph{-}CH_2OH$.

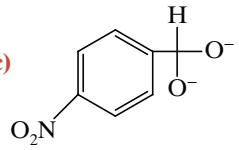
7. Arrange the given compounds in order of decreasing reactivity for nucleophilic addition reaction.

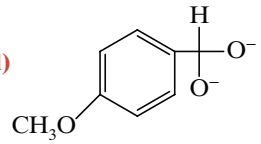
(i) $H_3C{-}\overset{\overset{O}{\|}}{C}{-}CH_2{-}Cl$
(ii) $Cl{-}CH_2{-}CHO$
(iii) CH_2O
(iv) $H_3C{-}\overset{\overset{O}{\|}}{C}{-}CH_3$

(a) (iv) > (iii) > (ii) > (i) **(b)** (iii) > (ii) > (i) > (iv)
(c) (ii) > (iv) > (iii) > (i) **(d)** (i) > (ii) > (iii) > (iv)

8. In a Cannizzaro reaction, the intermediate which is the best hydride donor is

(a) $C_6H_5{-}\overset{\overset{H}{|}}{\underset{\underset{OH}{|}}{C}}{-}O^-$ **(b)** $C_6H_5{-}\overset{\overset{H}{|}}{\underset{\underset{O^-}{|}}{C}}{-}O^-$

(c) 

(d) 

9. What carbonyl compound reacts with HCN to give the highest yield of cyanohydrin?
(a) Formaldehyde **(b)** Propanal
(c) 2-butanone **(d)** di-*t*-butyl ketone

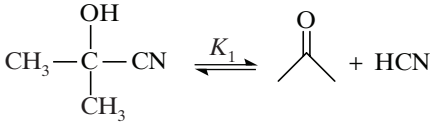
10. A mixture of benzaldehyde and formaldehyde on heating with aqueous NaOH solution gives
(a) benzyl alcohol and sodium formate.
(b) sodium benzoate and methyl alcohol.
(c) sodium benzoate and sodium formate.
(d) benzyl alcohol and methyl alcohol.

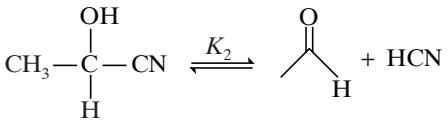
11. Which of the following carbonyl compounds reacts with HCN to give the lowest yield of cyanohydrin?
(a) Formaldehyde **(b)** Propanal
(c) 2-Butanone **(d)** di-*t*-butyl ketone

12. Compound A (molecular formula C_3H_8O) is treated with acidified potassium dichromate to form a product B (molecular formula C_3H_6O). B forms a shining silver mirror on warming with ammonical silver nitrate. B when treated with an aqueous solution of $H_2NCONHNH_2{\cdot}HCl$ and sodium acetate gives a product C. Identify the structure of C.

(a) $CH_3CH_2CH{=}NNHCONH_2$
(b) $CH_3{-}\underset{\underset{CH_3}{|}}{C}{=}NNHCONH_2$
(c) $CH_3{-}\underset{\underset{CH_3}{|}}{C}{=}NCONHNH_2$
(d) $CH_3CH_2CH{=}NCONHNH_2$

13.

(i) 

(ii) 

Relation between K_1 and K_2 is
(a) $K_1 = K_2$ **(b)** $K_1 > K_2$
(c) $K_2 > K_1$ **(d)** $K_1 = K_2 = 1$

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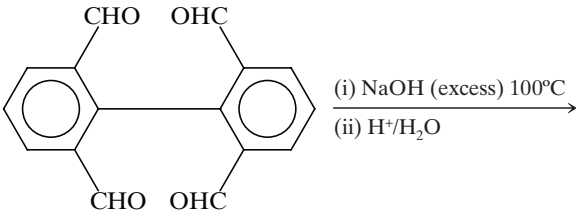
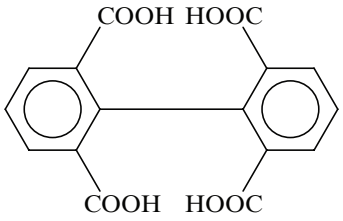
14. Any one of the products formed in the following reaction is



(a)


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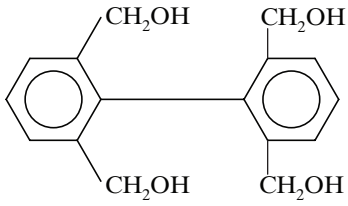

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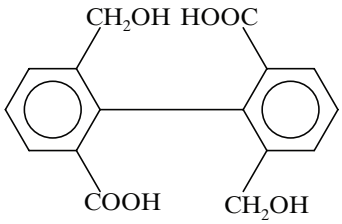

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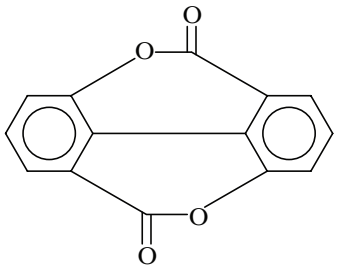
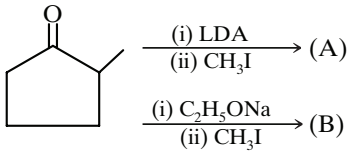


15. The reagent which does not react with both acetone and benzaldehyde is

(a) $NaHSO_3$ **(b)** phenyl hydrazine.
(c) Fehling solution. **(d)** Grignard reagent.

16. The formation of cyanohydrin from a ketone is an example of

(a) electrophilic addition.
(b) nucleophilic addition.
(c) nucleophilic substitution.
(d) electrophilic substitution.

17.


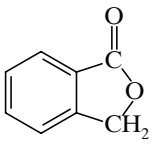
What is the relation between A and B?

(a) Tautomers **(b)** Chain isomers
(c) Position isomers **(d)** Geometrical isomers

18. An organic compound C_3H_6O does not give a precipitate with 2,4-dinitrophenyl hydrazine reagent and does not react with metallic sodium. It could be

(a) CH_3CH_2CHO **(b)** CH_3COCH_3
(c) $CH_2{=}CH{-}CH_2{-}OH$ **(d)** $CH_2{=}CH{-}O{-}CH_3$

19. Which of the following reactants on reaction with conc. NaOH followed by acidification gives the following lactone as the only product?



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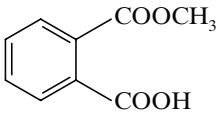

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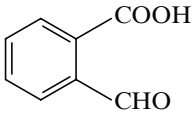

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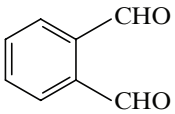
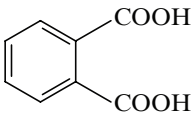


(d)


20. Among the given compounds, the most susceptible to nucleophilic attack at the carbonyl group is

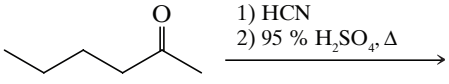
(a) MeCOCl **(b)** MeCHO
(c) MeCOOMe **(d)** MeCOOCOMe

21. $CH_3CHO + H_2NOH \longrightarrow CH_3{-}CH{=}N{-}OH$

The above reaction occurs at

(a) pH = 1 **(b)** pH = 4.5
(c) any value of pH **(d)** pH = 12

22. What is the product of the following reaction?



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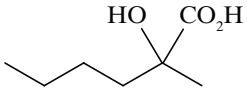

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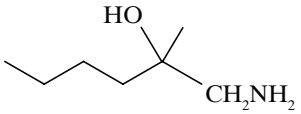

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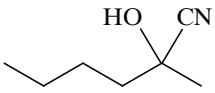

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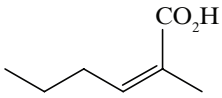
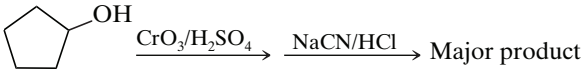
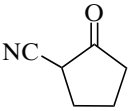


23. Give the major product of the following reaction:



(a)


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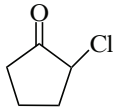

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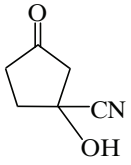

(d)


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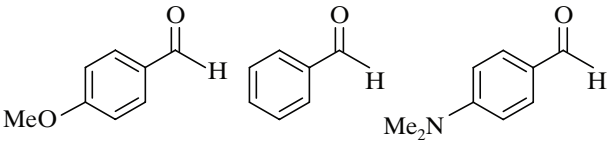
24. Which of the following is not a common reaction of aldehydes?

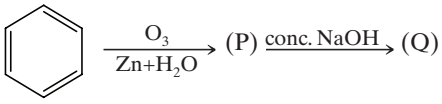
(a) Nucleophilic acyl addition
(b) Nucleophilic acyl substitution
(c) Alpha substitution
(d) Reduction to a ketone

25. The K_{eq} values in HCN addition to following aldehydes are in the order:

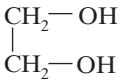
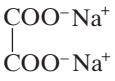


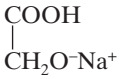
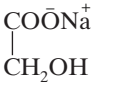
(I) (II) (III)

(a) I > II > III **(b)** II > III > I
(c) III > I > II **(d)** II > I > III

26. 

Product (Q) is

(a)  **(b)** 

(c)  **(d)** 

27. Which pair of the following carbonyl compounds can be differentiated by I_2/NaOH?

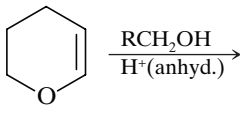
(a) $C_6H_5—CHO$ and $C_6H_5—\overset{\overset{O}{\|}}{C}—CH_2—CH_3$

(b) $C_6H_5—\overset{\overset{O}{\|}}{C}—CH_3$ and $CH_3—CH_2—\overset{\overset{O}{\|}}{C}—CH_3$

(c) $CH_3—CH_2—\overset{\overset{O}{\|}}{C}—CH_2—CH_3$ and $C_6H_5—\overset{\overset{O}{\|}}{C}—CH_2—CH_3$

(d) $C_6H_5—\overset{\overset{O}{\|}}{C}—\underset{\underset{CH_3}{|}}{CH}—CH_3$ and $C_6H_5—\overset{\overset{O}{\|}}{C}—CH_3$

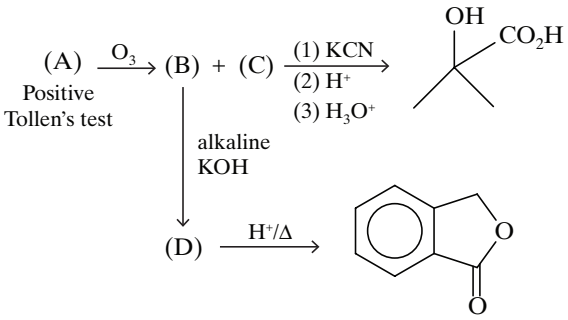
28. The major product of the following reaction is



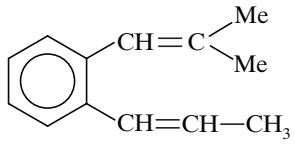
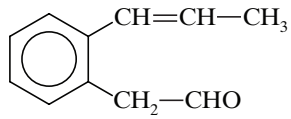
(a) hemiacetal. **(b)** acetal.
(c) ether. **(d)** ester.

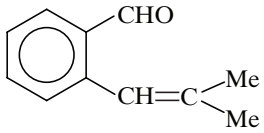
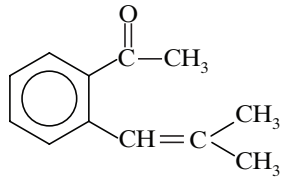
Linked Comprehension Type

Paragraph for Questions 1 to 3



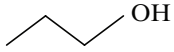
1. Structure of (A) is

(a)  **(b)** 

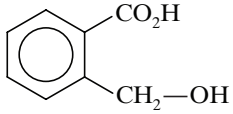
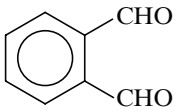
(c)  **(d)** 

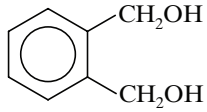
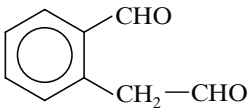
2. Structure of (C) is

(a)  **(b)** 

(c)  **(d)** 

3. Structure of (B) is

(a)  **(b)** 

(c)  **(d)** 

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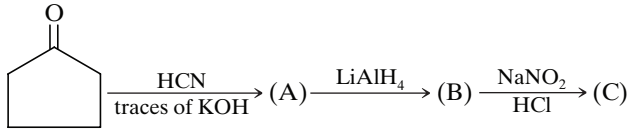
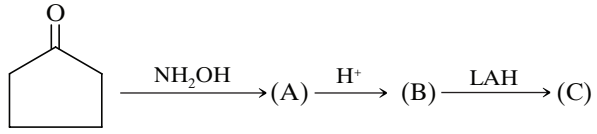
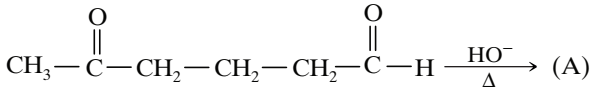
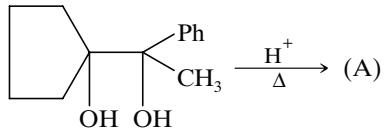
Matrix Match Type

1.

Column I	Column II
(a) 	**(p)** Formation of six member ring takes place
(b) 	**(q)** Final product is a ketone
(c) 	**(r)** Final product formed will give positive Tollens test
(d) 	**(s)** Final product formed will react with 2,4-DNP (2,4-dinitrophenyl hydrazine)

ANSWER KEY

Single Correct Choice Type

1. (b)	**2.** (d)	**3.** (c)	**4.** (c)	**5.** (d)
6. (b)	**7.** (b)	**8.** (d)	**9.** (a)	**10.** (a)
11. (d)	**12.** (a)	**13.** (b)	**14.** (c)	**15.** (c)
16. (b)	**17.** (c)	**18.** (d)	**19.** (c)	**20.** (a)
21. (b)	**22.** (d)	**23.** (d)	**24.** (d)	**25.** (d)
26. (d)	**27.** (d)	**28.** (b)		

Linked Comprehension Type

1. (c) **2.** (b) **3.** (b)

Matrix Match Type

1. a→(p, q, s); b→(p); c→(p, q, s); d→(p, q, s)

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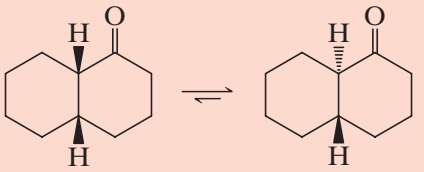
16

Aldehydes and Ketones II. Aldol Reactions



cis-Decalone *trans*-Decalone

Contents

16.1 | The Acidity of the α Hydrogens of Carbonyl Compounds: Enolate Anions
16.2 | Keto and Enol Tautomers
16.3 | Reactions via Enols and Enolates
16.4 | Aldol Reactions: Addition of Enolates and Enols to Aldehydes and Ketones
16.5 | Crossed Aldol Condensations
16.6 | Cyclizations via Aldol Condensation
16.7 | Lithium Enolates

16.1 | THE ACIDITY OF THE α HYDROGENS OF CARBONYL COMPOUNDS: ENOLATE ANIONS

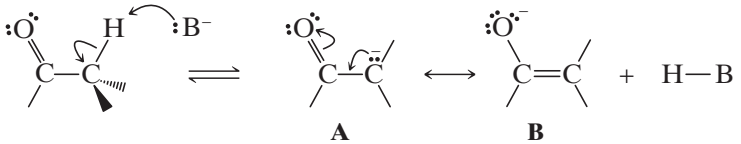
When we say that the α hydrogens of carbonyl compounds are acidic, *we mean that they are unusually acidic for hydrogen atoms attached to carbon*.

- The pK_a values for the α hydrogens of most simple aldehydes or ketones are of the order of 19–20.

This means that they are more acidic than hydrogen atoms of ethyne, pK_a = 25, and are far more acidic than the hydrogens of ethene (pK_a = 44) or of ethane (pK_a = 50).

The reasons for the unusual acidity of the α hydrogens of carbonyl compounds are straightforward.

- The carbonyl group is strongly electron withdrawing, and when a carbonyl compound loses an α proton, the anion that is produced, called an **enolate**, is stabilized by delocalization.



Resonance structures for the delocalized enolate

Two resonance structures, **A** and **B**, can be written for the enolate. In structure **A** the negative charge is on carbon, and in structure **B** the negative charge is on oxygen. Both structures contribute to the hybrid. Although structure **A** is favored by the strength of its carbon–oxygen π bond relative to the weaker

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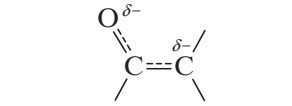
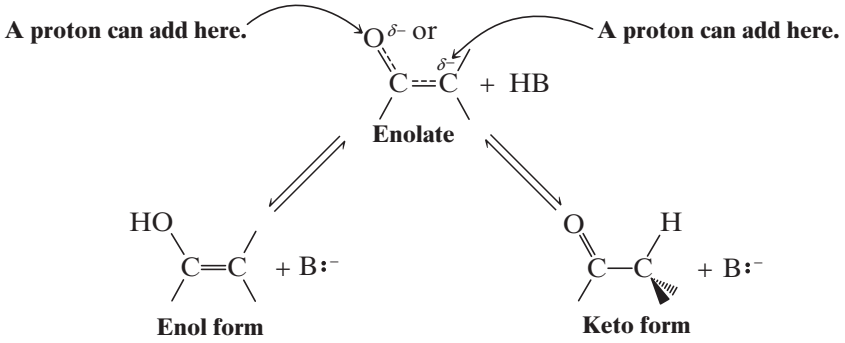
carbon–carbon π bond of **B**, structure **B** makes a greater contribution to the hybrid because oxygen, being highly electronegative, is better able to accommodate the negative charge. We can depict the enolate hybrid in the following way:



Hybrid resonance structure for an enolate

When this resonance-stabilized enolate accepts a proton, it can do so in either of two ways: It can accept the proton at carbon to form the original carbonyl compound in what is called the **keto form** or it may accept the proton at oxygen to form an **enol** (alkene alcohol).

- The enolate is the conjugate base of both the enol and keto forms.



- Both of these reactions are reversible.

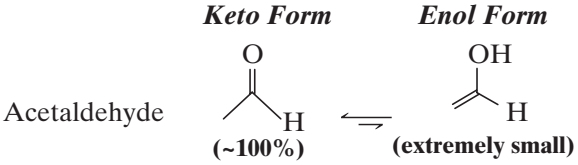
16.2 | KETO AND ENOL TAUTOMERS

The keto and enol forms of carbonyl compounds are constitutional isomers, but of a special type. Because they are easily interconverted by proton transfers in the presence of an acid or base, chemists use a special term to describe this type of constitutional isomerism.

- Interconvertible **keto and enol forms** are called **tautomers**, and their interconversion is called **tautomerization**.

Under most circumstances, we encounter keto–enol tautomers in a state of equilibrium. (The surfaces of ordinary laboratory glassware are able to catalyze the interconversion and establish the equilibrium.) For simple monocarbonyl compounds such as acetone and acetaldehyde, the amount of the enol form present at equilibrium is *very small*. In acetone it is much less than 1%; in acetaldehyde the enol concentration is too small to be detected. The greater stability of the following keto forms of monocarbonyl compounds can be related to the greater strength of the carbon–oxygen π bond compared to the carbon–carbon π bond (~364 versus ~250 kJ mol^{-1}):

Helpful Hint: Keto–enol tautomers are not resonance structures. They are constitutional isomers in equilibrium (generally favoring the keto form).



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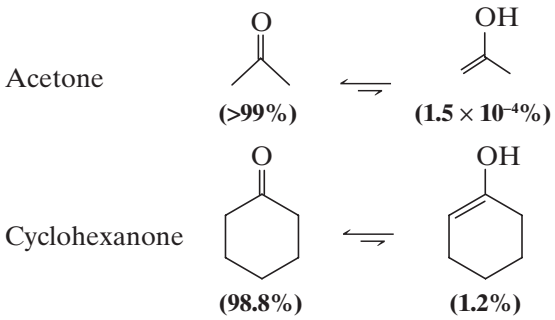
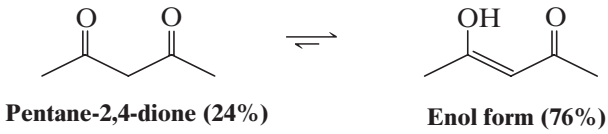
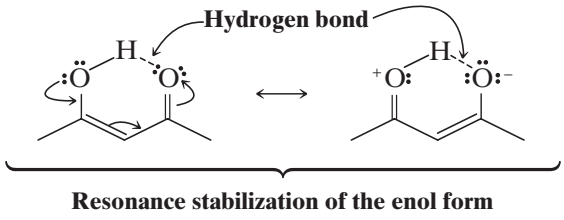


In compounds whose molecules have two carbonyl groups separated by one carbon atom (called β-dicarbonyl compounds), the amount of enol present at equilibrium is far higher. For example, pentane-2,4-dione exists in the enol form to an extent of 76%:



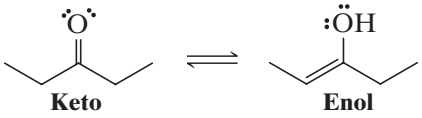
- The greater stability of the enol form of β-dicarbonyl compounds can be attributed to resonance stabilization of the conjugated double bonds and (in a cyclic form) through hydrogen bonding.



Solved Problem 16.1

Write bond-line structures for the keto and enol forms of 3-pentanone.

Answer



Practice Problem 16.1

For all practical purposes, the compound cyclohexa-2,4-dien-1-one exists totally in its enol form. Write the structure of cyclohexa-2,4-dien-1-one and of its enol form. What special factor accounts for the stability of the enol form?

16.3 | REACTIONS VIA ENOLS AND ENOLATES

16.3A Racemization

When a solution of (*R*)-(+)-2-methyl-1-phenylbutan-1-one (see the following reaction) in aqueous ethanol is treated with either acids or bases, the solution gradually loses its optical activity. After a time, isolation of the ketone shows that it has been completely racemized. The (+) form of the ketone has been converted to an equimolar mixture of its enantiomers through its enol form.

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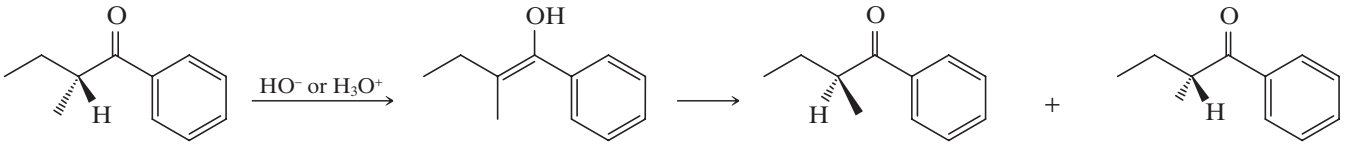
Racemization via an enol

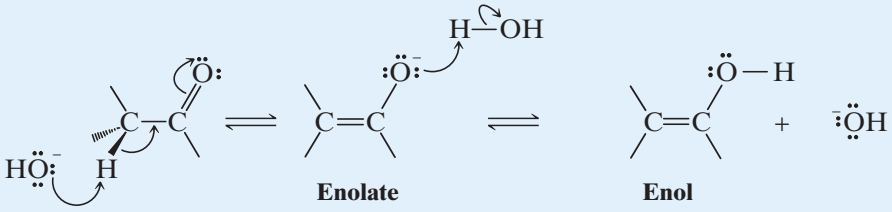


(*R*)-(+)-2-Methyl-1-phenylbutan-1-one | **Enol (achiral)** | **(±)-2-Methyl-1-phenylbutan-1-one (racemic form)**

- Racemization at an α carbon takes place in the presence of acids or bases because the keto form slowly but reversibly changes to its enol *and the enol is achiral*. When the **enol** reverts to the **keto form**, it can produce equal amounts of the two enantiomers.

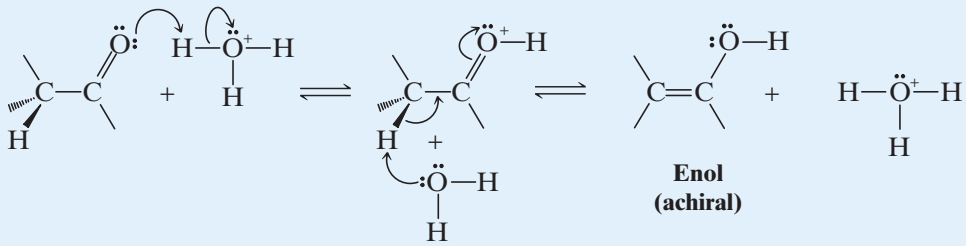
A base catalyzes the formation of an enol through the intermediate formation of an **enolate** anion.

A MECHANISM FOR THE REACTION — Base-Catalyzed Enolization



An acid can catalyze enolization in the following way.

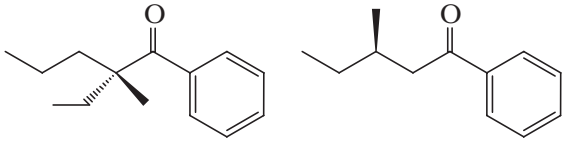
A MECHANISM FOR THE REACTION — Acid-Catalyzed Enolization



In acyclic ketones, the enol or enolate formed can be (*E*) or (*Z*). Protonation on one face of the (*E*) isomer and protonation on the same face of the (*Z*) isomer produces enantiomers.

Practice Problem 16.2

Would optically active ketones such as the following undergo acid- or base-catalyzed racemization? Explain your answer.



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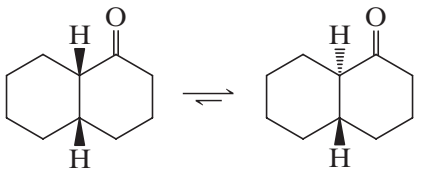
- Diastereomers that differ in configuration at only one of several chirality centers are sometimes called **epimers**.

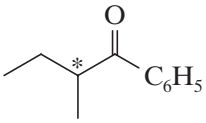
Keto–enol tautomerization can sometimes be used to convert a less stable epimer to a more stable one. This equilibration process is an example of **epimerization**. An example is the epimerization of *cis*-decalone to *trans*-decalone:



***cis*-Decalone** ***trans*-Decalone**

Solved Problem 16.2

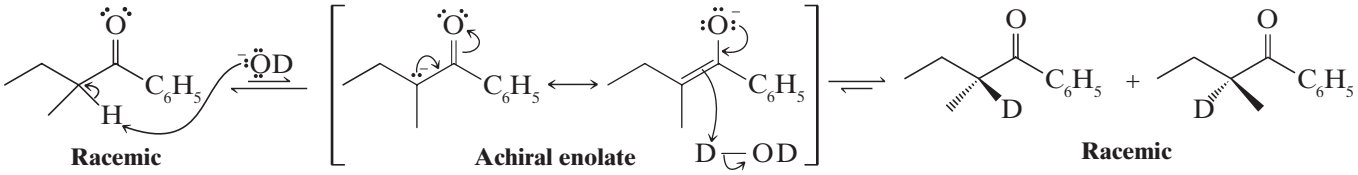
Treating racemic 2-methyl-1-phenylbutan-1-one with NaOD in the presence of D_2O produces a deuterium-labeled compound as a racemic form. Write a mechanism that explains this result.



Racemic

Answer

Either enantiomer of the ketone can transfer an α proton to the $^-$OD ion to form an achiral enolate that can accept a deuteron to form a racemic mixture of the deuterium-labeled product.



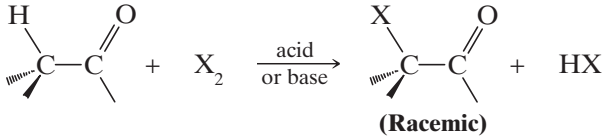
Racemic **Achiral enolate** **Racemic**

Practice Problem 16.3

Write a mechanism using sodium ethoxide in ethanol for the epimerization of *cis*-decalone to *trans*-decalone. Draw chair conformational structures that show why *trans*-decalone is more stable than *cis*-decalone. You may find it helpful to also examine handheld molecular models of *cis*- and *trans*-decalone.

16.3B Halogenation at the α Carbon

- Carbonyl compounds bearing an α hydrogen can undergo halogen substitution at the α carbon in the presence of acid or base.



(Racemic)

Base-Promoted Halogenation In the presence of bases, halogenation takes place through the slow formation of an enolate anion or an enol followed by a rapid reaction of the enolate or enol with halogen.

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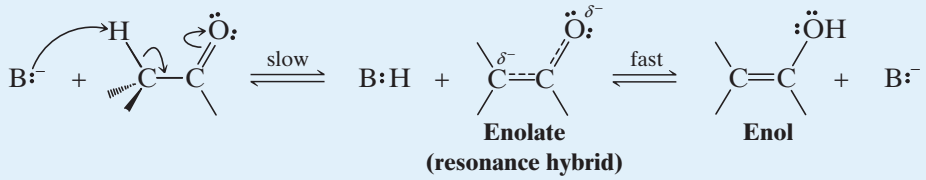
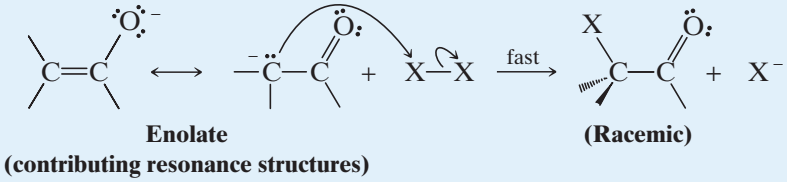
A MECHANISM FOR THE REACTION — Base-Promoted Halogenation of Aldehydes and Ketones

Step 1



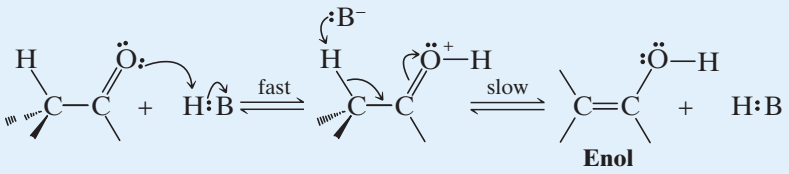
Step 2



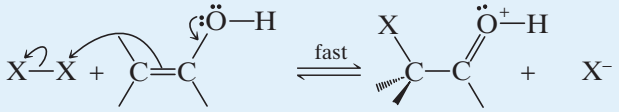
Acid-Catalyzed Halogenation In the presence of acids, halogenation takes place through the slow formation of an enol followed by rapid reaction of the enol with the halogen.

A MECHANISM FOR THE REACTION — Acid-Catalyzed Halogenation of Aldehydes and Ketones

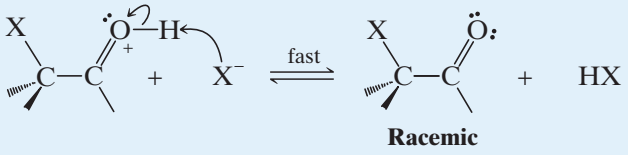
Step 1



Step 2



Step 3



Part of the evidence that supports these mechanisms comes from studies of reaction kinetics. Both base-promoted and acid-catalyzed halogenations of ketones *show initial rates that are independent of the halogen concentration*. The mechanisms that we have written are in accord with this observation: in both instances the slow step of the mechanism occurs before the intervention of the halogen. (The initial rates are also independent of the nature of the halogen; see Practice Problem 16.5.)

Practice Problem 16.4

Why do we say that the halogenation of ketones in a base is "base promoted" rather than "base catalyzed"?

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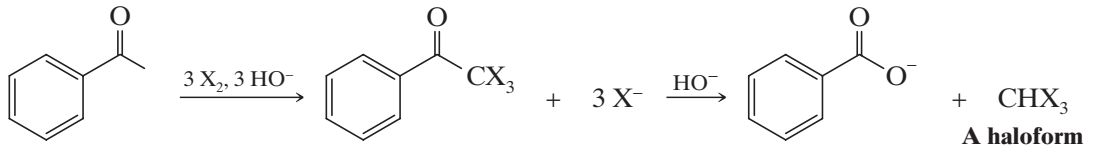
Practice Problem 16.5

Additional evidence for the halogenation mechanisms that we just presented comes from the following facts: **(a)** Optically active 2-methyl-1-phenylbutan-1-one undergoes acid-catalyzed racemization at a rate exactly equivalent to the rate at which it undergoes acid-catalyzed halogenation. **(b)** 2-Methyl-1-phenylbutan-1-one undergoes acid-catalyzed iodination at the same rate that it undergoes acid-catalyzed bromination. **(c)** 2-Methyl-1-phenylbutan-1-one undergoes base-catalyzed hydrogen–deuterium exchange at the same rate that it undergoes base-promoted halogenation. Explain how each of these observations supports the mechanisms that we have presented.

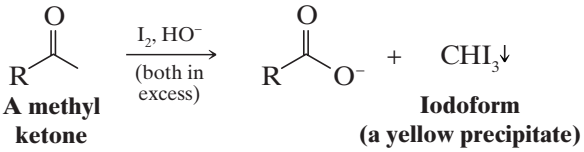
16.3C The Haloform Reaction

When methyl ketones react with halogens in the presence of excess base, multiple halogenations always occur at the carbon of the methyl group. Multiple halogenations occur because introduction of the first halogen (owing to its electronegativity) makes the remaining α hydrogens on the methyl carbon more acidic. The resulting CX_3 group bonded to the carbonyl can be a leaving group, however. Thus, when hydroxide is the base, an acyl substitution reaction follows, leading to a carboxylate salt and a haloform (CHX_3, e.g., chloroform, bromoform, or iodoform). The following is an example.



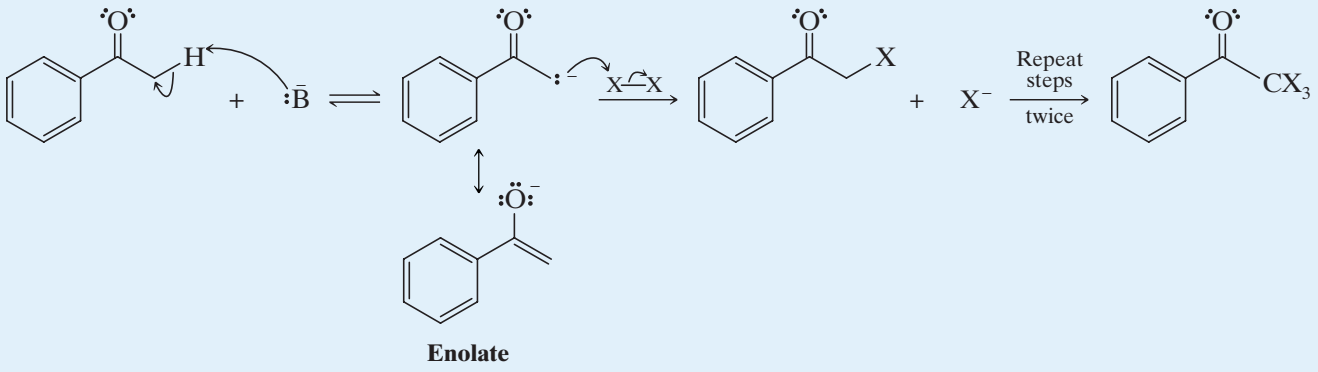
The haloform reaction is one of the rare instances in which a carbanion acts as a leaving group. This occurs because the trihalomethyl anion is unusually stable; its negative charge is dispersed by the three electronegative halogen atoms (when X = Cl, the conjugate acid, $CHCl_3$, has $pK_a = 13.6$). In the last step, a proton transfer takes place between the carboxylic acid and the trihalomethyl anion.

The **haloform reaction** is synthetically useful as a means of converting methyl ketones to carboxylic acids. When the haloform reaction is used in synthesis, chlorine and bromine are most commonly used as the halogen component. Chloroform ($CHCl_3$) and bromoform $CHBr_3$ are both liquids that are immiscible with water and are easily separated from the aqueous solution containing the carboxylate anion. When iodine is the halogen component, the bright yellow solid iodoform (CHI_3) results. This version is the basis of the iodoform classification test for methyl ketones and methyl secondary alcohols (which are oxidized to methyl ketones first under the reaction conditions):



A MECHANISM FOR THE REACTION — The Haloform Reaction

Halogenation Step



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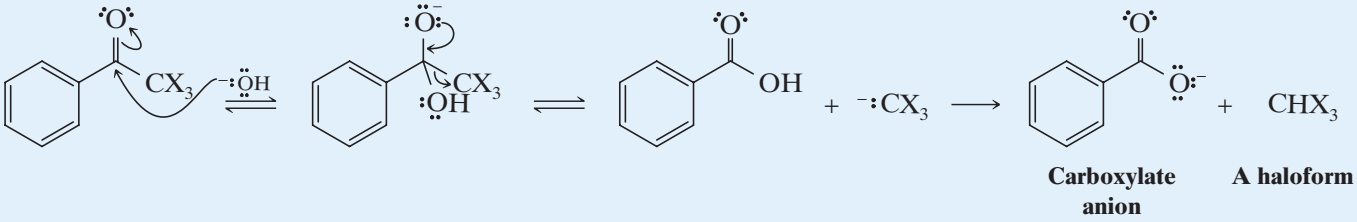
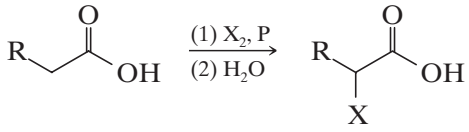
Acyl Substitution Step



16.3D α-Halo Carboxylic Acids: The Hell–Volhard–Zelinski Reaction

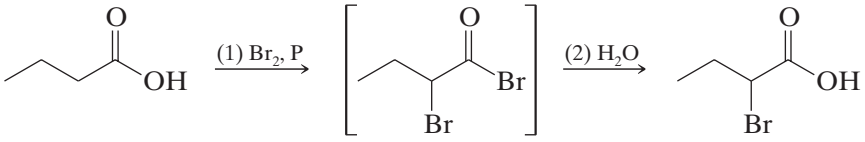
Carboxylic acids bearing α **hydrogen** atoms react with bromine or chlorine in the presence of phosphorus (or a phosphorus halide) to give α-halo carboxylic acids through a reaction known as the Hell–Volhard–Zelinski (or HVZ) reaction.

General Reaction



α-Halo acid

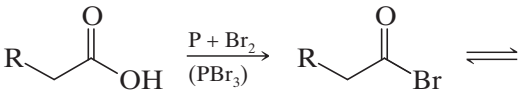
Specific Example



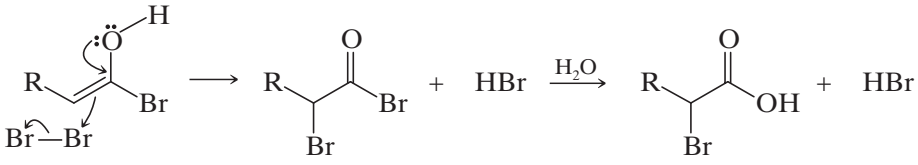
Butanoic acid **2-Bromobutanoic acid (77%)**

If more than one molar equivalent of bromine or chlorine is used in the reaction, the products obtained are α,α-dihalo acids or α,α,α-trihalo acids.

Important steps in the reaction are formation of an acyl halide and the enol derived from the acyl halide. The acyl halide is key because carboxylic acids do not form enols readily since the carboxylic acid proton is removed before the α hydrogen. Acyl halides lack the carboxylic acid hydrogen.



Acyl bromide



Enol form

An alternative method for α-halogenation has been developed by D. N. Harpp (McGill University). Acyl chlorides, formed *in situ* by the reaction of the carboxylic acid with $SOCl_2$, are treated with the appropriate *N*-halosuccinimide and a trace of HX to produce α-chloro and α-bromo acyl chlorides.

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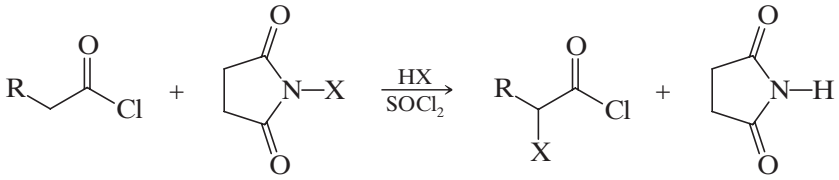
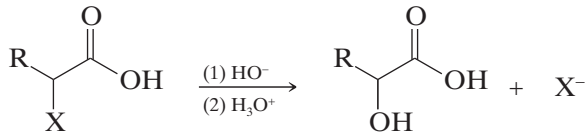


α-Iodo acyl chlorides can be obtained by using molecular iodine in a similar reaction.



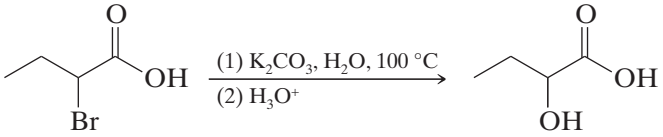
α-Halo acids are important synthetic intermediates because they are capable of reacting with a variety of nucleophiles:

Conversion to α-Hydroxy Acids



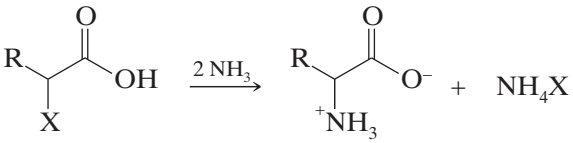
α-Halo acid **α-Hydroxy acid**

Specific Example



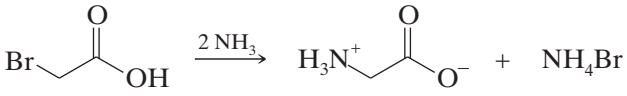
2-Hydroxybutanoic acid
(69%)

Conversion to α-Amino Acids



α-Halo acid **α-Amino acid**

Specific Example



Aminoacetic acid
(glycine)
(60–64%)

16.4 | ALDOL REACTIONS: ADDITION OF ENOLATES AND ENOLS TO ALDEHYDES AND KETONES

- Aldol additions and aldol condensations together represent an important class of carbon–carbon bond-forming reaction.

An **aldol reaction** begins with addition of an enolate or enol to the carbonyl group of an aldehyde or ketone, leading to a β-hydroxy aldehyde or ketone as the initial product. A simple example is shown below, whereby two molecules of acetaldehyde (ethanal) react to form 3-hydroxybutanal. 3-Hydroxybutanal is an "**aldol**" because it contains both an **ald**ehyde and an alcoh**ol** functional group. Reactions of this general type are known as **aldol additions**.

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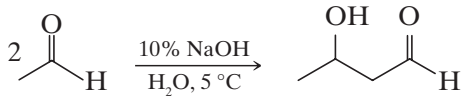


3-Hydroxybutanal (50%)

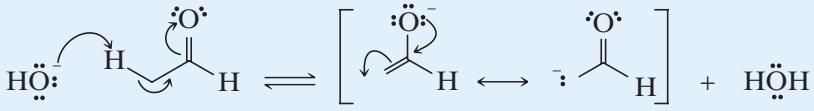
As we shall see, the initial aldol addition product often dehydrates to form an α,β–unsaturated aldehyde or ketone. When this is the result, the overall reaction is an **aldol condensation**. First let us consider the mechanism of an aldol addition.

16.4A Aldol Addition Reactions

An aldol addition is an equilibrium reaction when it is conducted in a protic solvent with a base such as hydroxide or an alkoxide. The mechanism for an aldol addition involving an aldehyde is shown here.

A MECHANISM FOR THE REACTION — The Aldol Addition

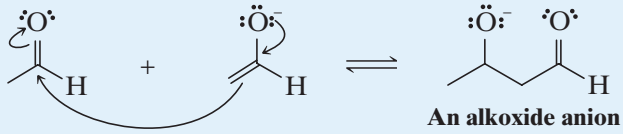
Step 1 *Enolate formation*



Enolate anion

In this step the base (a hydroxide ion) removes a proton from the α carbon of one molecule of acetaldehyde to give a resonance-stabilized enolate.

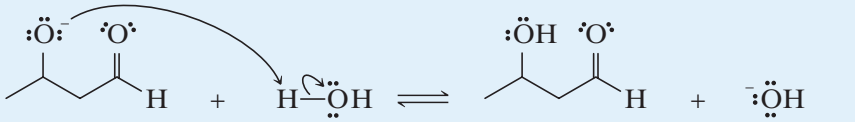
Step 2 *Addition of the enolate*



An alkoxide anion

The enolate then acts as a nucleophile and attacks the carbonyl carbon of a second molecule of acetaldehyde, producing an alkoxide anion.

Step 3 *Protonation of the alkoxide*



Stronger base **The aldol product** **Weaker base**

The alkoxide anion now removes a proton from a molecule of water to form the aldol product.

With ketones, the addition step leading to the aldol is unfavorable due to steric hindrance, and the equilibrium favors the aldol precursors rather than the addition product (Section 16.4B). However, as we shall see in Section 16.4C, dehydration of the aldol addition product can draw the equilibrium toward completion, whether the reactant is an aldehyde or a ketone. Enolate additions to both aldehydes and ketones are also feasible when a stronger base (such as LDA) is used in an aprotic solvent (Section 16.5B).

16.4B The Retro-Aldol Reaction

Because the steps in an aldol addition mechanism are readily reversible, a **retro-aldol reaction** can occur that converts a β-hydroxy aldehyde or ketone back to the precursors of an aldol addition. For example, when 4-hydroxy-4-methyl-2-pentanone is heated with hydroxide in water, the final equilibrium mixture consists primarily of acetone, the retro-aldol product.

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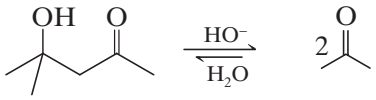


This result is not surprising, because we know that the equilibrium for an aldol addition (the reverse of the reaction above) is not favorable when the enolate adds to a ketone. But, as mentioned earlier, dehydration of an aldol addition product can draw the equilibrium forward. We shall discuss the dehydration of aldols next (Section 16.4C).

Solved Problem 16.3

The carbon–carbon bond cleavage step in a retro-aldol reaction involves, under basic conditions, a leaving group that is an enolate, or under acidic conditions, an enol. Write a mechanism for the retro-aldol reaction of 4-hydroxy-4-methyl-2-pentanone under basic conditions (shown above).

Answer

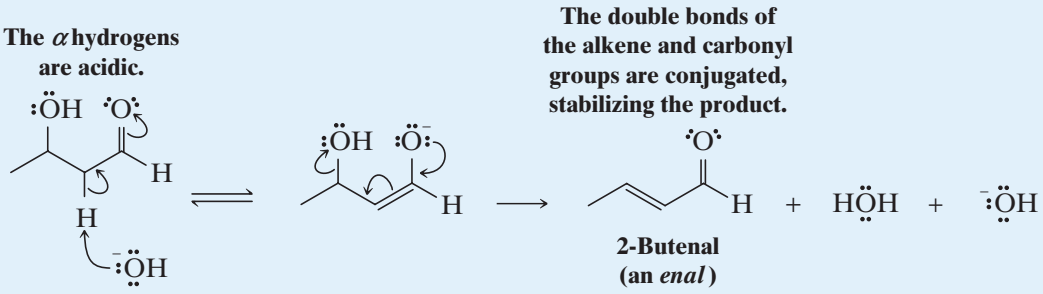
Base removes the proton from the β-hydroxyl group, setting the stage for reversal of the aldol addition. As the alkoxide reverts to the carbonyl group, a carbon–carbon bond breaks with expulsion of the enolate as a leaving group. This liberates one of the original carbonyl molecules. Protonation of the enolate forms the other.



16.4C Aldol Condensation Reactions: Dehydration of the Aldol Addition Product

Dehydration of an aldol addition product leads to a conjugated α,β-unsaturated carbonyl system. The overall process is called an **aldol condensation**, and the product can be called an enal (alk*ene* *al*dehyde) or enone (alk*ene* ket*one*), depending on the carbonyl group in the product. The stability of the conjugated enal or enone system means that the dehydration equilibrium is essentially irreversible. For example, the aldol addition reaction that leads to 3-hydroxybutanal, shown in Section 16.4, dehydrates on heating to form 2-butenal. A mechanism for the dehydration is shown here.

A MECHANISM FOR THE REACTION — Dehydration of the Aldol Addition Product



Even though hydroxide is a leaving group in this reaction, the fact that each dehydrated molecule forms irreversibly, due to the stability from conjugation, draws the reaction forward.

16.4D Acid-Catalyzed Aldol Condensations

Aldol reactions can occur under acid catalysis, in which case the reaction generally leads to the α,β-unsaturated product by direct dehydration of the β-hydroxy aldol intermediate. This is one way by which ketones can successfully

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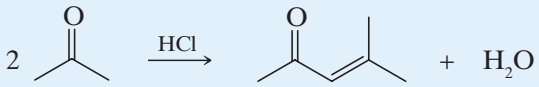
be utilized in an aldol reaction. The following is an example, in which acetone forms its aldol condensation product, 4-methylpent-3-en-2-one, on treatment with hydrogen chloride.

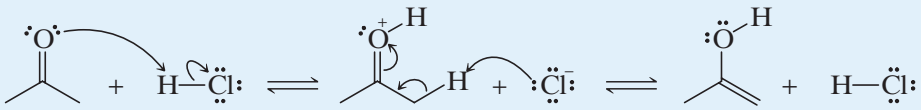
A MECHANISM FOR THE REACTION — The Acid-Catalyzed Aldol Reaction

Reaction

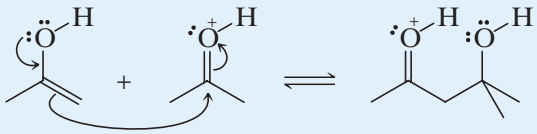


4-Methylpent-3-en-2-one

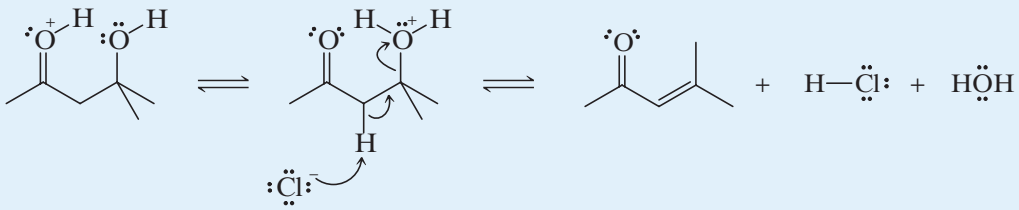
Mechanism



The mechanism begins with the acid-catalyzed formation of the enol.



Then the enol adds to the protonated carbonyl group of another molecule of acetone.



Finally, proton transfers and dehydration lead to the product.

Acid catalysis can promote further reactions after the aldol condensation. An example is given in Practice Problem 16.7. Generally, it is more common in synthesis for an aldol reaction to be conducted under basic rather than acidic conditions.

Practice Problem 16.6

The acid-catalyzed aldol condensation of acetone (just shown) also produces some 2,6-dimethylhepta-2,5-dien-4-one. Give a mechanism that explains the formation of this product.

Practice Problem 16.7

Heating acetone with sulfuric acid leads to the formation of mesitylene (1,3,5-trimethylbenzene). Propose a mechanism for this reaction.

16.4E Synthetic Applications of Aldol Reactions

As we are beginning to see, aldol additions and aldol condensations are important methods for carbon–carbon bond formation. They also result in β-hydroxy and α,β-unsaturated carbonyl compounds that are themselves useful for further synthetic transformations. Some representative reactions are shown below.

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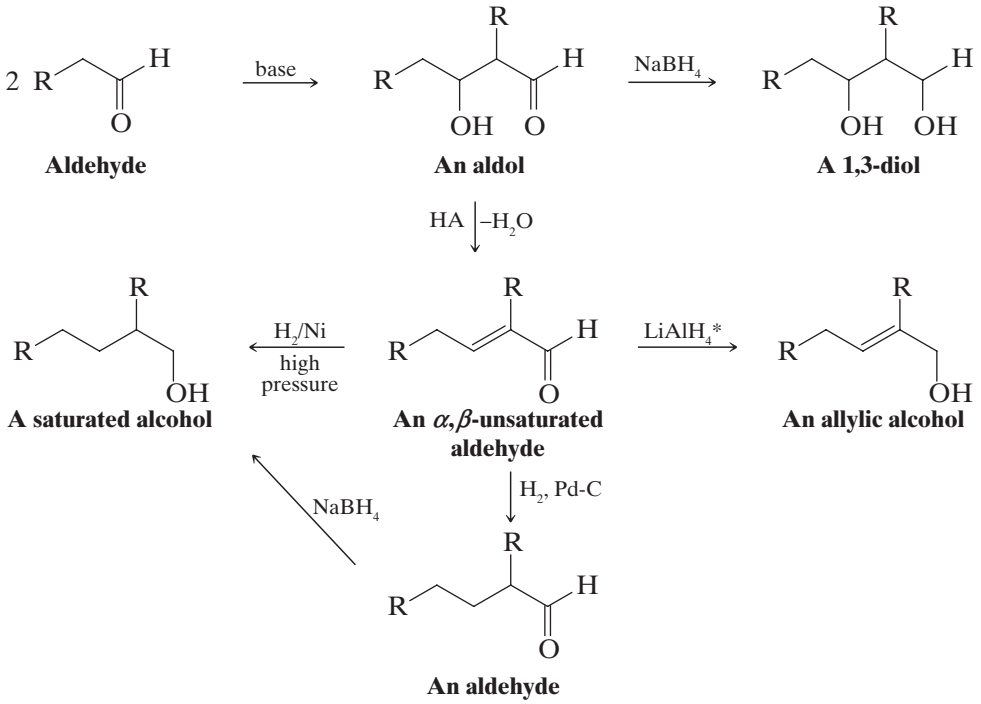
The Aldol Reaction in Synthesis

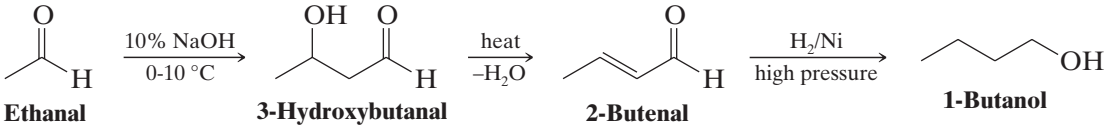


Solved Problem 16.4

One industrial process for the synthesis of 1-butanol begins with ethanal. Show how this synthesis might be carried out.

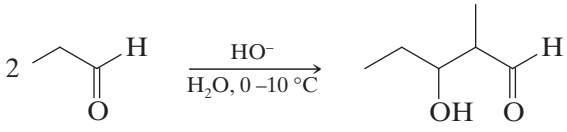
Answer

Ethanal can be converted to an aldol via an aldol addition. Then, dehydration would produce 2-butenal, which can be hydrogenated to furnish 1-butanol.



Practice Problem 16.8

(a) Provide a mechanism for the aldol addition of propanal shown here.



Propanal **3-Hydroxy-2-methylpentanal (55–60%)**

(b) How can you account for the fact that the product of the aldol addition is 3-hydroxy-2-methylpentanal and not 4-hydroxyhexanal?

(c) What products would be formed if the reaction mixture were heated?

*$LiAlH_4$ reduces the carbonyl group of α,β-unsaturated aldehydes and ketones cleanly. $NaBH_4$ often reduces the carbon–carbon double bond as well.

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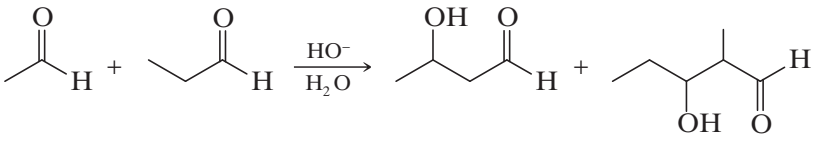
Practice Problem 16.9

Show how each of the following products could be synthesized from butanal:

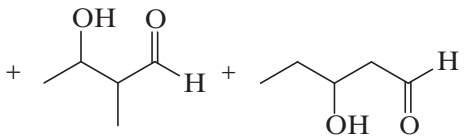
(a) 2-Ethyl-3-hydroxyhexanal
(b) 2-Ethylhex-2-en-1-ol
(c) 2-Ethylhexan-1-ol
(d) 2-Ethylhexane-1,3-diol

16.5 | CROSSED ALDOL CONDENSATIONS

An **aldol reaction** that starts with two different carbonyl compounds is called a **crossed aldol reaction**. Unless specific conditions are involved, a crossed aldol reaction can lead to a mixture of products from various pairings of the carbonyl reactants, as the following example illustrates with ethanal and propanal:



Ethanal **Propanal** **3-Hydroxybutanal (from two molecules of ethanal)** **3-Hydroxy-2-methylpentanal (from two molecules of propanal)**



3-Hydroxy-2-methylbutanal **3-Hydroxypentanal**
(from one molecule of ethanal and one molecule of propanal)

We shall therefore consider crossed aldol condensations by two general approaches that allow control over the distribution of products. The first approach hinges on structural factors of the carbonyl reactants and the role that favorable or unfavorable aldol addition equilibria play in determining the product distribution. In this approach relatively weak bases such as hydroxide or an alkoxide are used in a protic solvent such as water or an alcohol. The second approach, called a directed aldol reaction, involves use of a strong base such as LDA in an aprotic solvent. With a strong base, one reactant can be converted essentially completely to its enolate, which can then be allowed to react with the other carbonyl reactant.

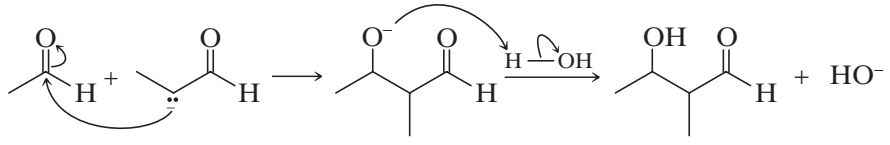
Solved Problem 16.5

Show how each of the four products shown at the beginning of this section is formed in the crossed aldol addition between ethanal and propanal.

Answer

In the basic aqueous solution, four organic entities will initially be present: molecules of ethanal, molecules of propanal, enolate anions derived from ethanal, and enolate anions derived from propanal.

3-Hydroxy-2-methylbutanal results when the enolate of propanal reacts with ethanal.



Ethanal **Enolate of propanal** **3-Hydroxy-2-methylbutanal**

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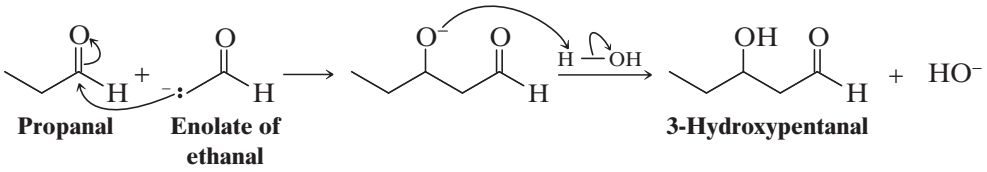
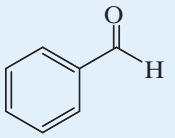
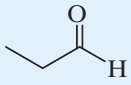
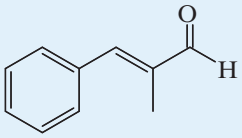
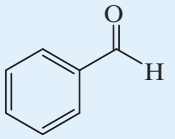
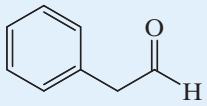
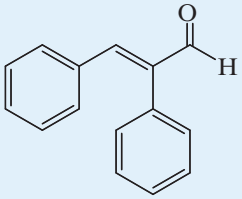
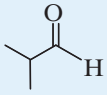
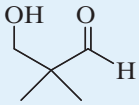
And finally, 3-hydroxypentanal results when the enolate of ethanal reacts with propanal.



16.5A Crossed Aldol Condensations Using Weak Bases

Crossed aldol reactions are possible with weak bases such as hydroxide or an alkoxide when one carbonyl reactant does not have an α hydrogen. A reactant without α hydrogens cannot self-condense because it cannot form an enolate. We avoid self-condensation of the other reactant, that which has an α hydrogen, by adding it slowly to a solution of the first reactant and the base. Under these conditions the concentration of the reactant with an α hydrogen is always low, and it is present mostly in its enolate form. The main reaction that takes place is between this enolate and the carbonyl compound that has no α hydrogens. The reactions shown in Table 16.1 illustrate results from this approach.

Table 16.1 Crossed Aldol Reactions

The reactant with no α hydrogen is placed in base	The reactant with an α hydrogen Is added slowly	Product
 **Benzaldehyde**	 **Propanal**	HO^-, 10 °C  **2-Methyl-3-phenyl-2-propenal (α-methylcinnamaldehyde) (68%)**
 **Benzaldehyde**	 **Phenylacetaldehyde**	HO^-, 20 °C  **2,3-Diphenyl-2-propenal**
 **Formaldehyde**	 **2-Methylpropanal**	dilute Na_2CO_3, 40 °C  **3-Hydroxy-2,2-dimethylpropanal (>64%)**

The crossed aldol examples shown in Table 16.1 involve aldehydes as both reactants. A ketone can be used as one reactant, however, because ketones do not self-condense appreciably due to steric hindrance in the aldol addition stage. The following are examples of crossed aldol condensations where one reactant is a ketone. Reactions such as these are sometimes called Claisen–Schmidt condensations. Schmidt discovered and Claisen developed this type of aldol reaction in the late 1800s.

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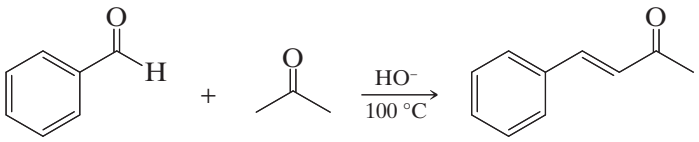
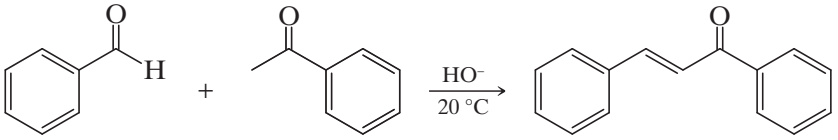


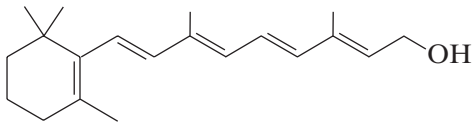
4-Phenylbut-3-en-2-one
(benzalacetone)
(70%)



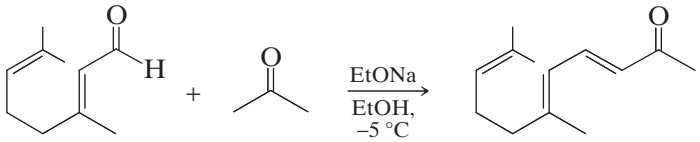
1,3-Diphenylprop-2-en-1-one
(benzalacetophenone)
(85%)

In these reactions, dehydration occurs readily because the double bond that forms is conjugated both with the carbonyl group and with the benzene ring. In general, dehydration of the aldol is especially favorable when it leads to extended conjugation.

As a further example, an important step in a commercial synthesis of vitamin A makes use of a crossed aldol condensation between geranial and acetone:



Vitamin A

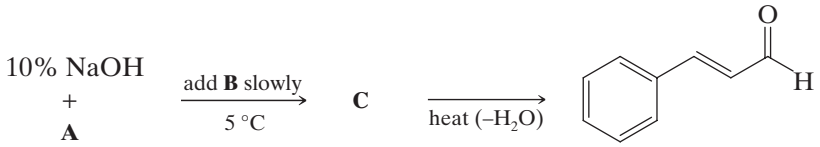


Geranial **Pseudoionone**
(49%)

Geranial is a naturally occurring aldehyde that can be obtained from lemongrass oil. Its α hydrogen is *vinylic* and, therefore, not appreciably acidic. Notice, in this reaction, too, dehydration occurs readily because dehydration extends the conjugated system.

Solved Problem 16.6

Outlined below is a practical crossed aldol reaction that can be used for the synthesis of cinnamaldehyde (the essence of cinnamon, used in cooking). Provide the missing ingredients for this recipe.



Cinnamaldehyde

Answer

Compound **A** is benzaldeohyde, **B** is ethanal (acetaldehyde), and the intermediate **C** is shown below as.

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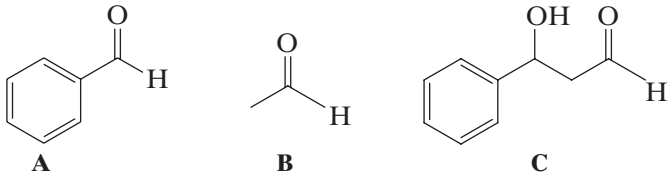


A **B** **C**

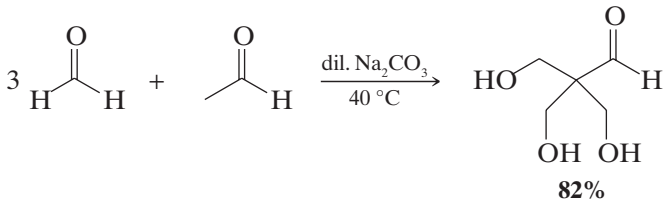
Practice Problem 16.10

Outlined below is a synthesis of a compound used in perfumes, called lily aldehyde. Provide all of the missing structures.

$$p\text{-tert-Butylbenzyl alcohol} \xrightarrow[CH_2Cl_2]{PCC} C_{11}H_{14}O \xrightarrow[HO^-]{\text{Propanal}} C_{14}H_{18}O \xrightarrow[CH_2Cl_2]{H_2,\ Pd\text{-}C} \text{lily aldehyde } (C_{14}H_{20}O)$$

Practice Problem 16.11

When excess formaldehyde in basic solution is treated with ethanal, the following reaction takes place:

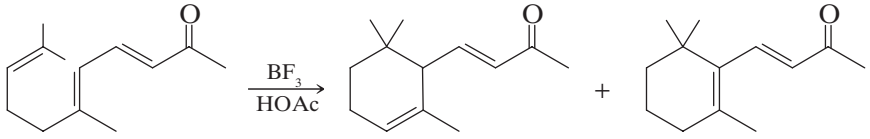


82%

Write a mechanism that accounts for the formation of the product.

Practice Problem 16.12

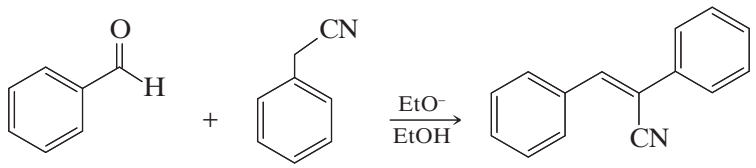
When pseudoionone is treated with BF_3 in acetic acid, ring closure takes place and α- and β-ionone are produced. This is the next step in the vitamin A synthesis.



Pseudoionone **α-Ionone** **β-Ionone**

(a) Write mechanisms that explain the formation of α- and β-ionone.
(b) β-Ionone is the major product. How can you explain this?

Nitriles with α hydrogens are also weakly acidic ($pK_a \cong 25$) and consequently these nitriles undergo condensations of the aldol type. An example is the condensation of benzaldehyde with phenylacetonitrile:



Practice Problem 16.13

(a) Write resonance structures for the anion of acetonitrile that account for its being much more acidic than ethane.
(b) Give a step-by-step mechanism for the condensation of benzaldehyde with acetonitrile.

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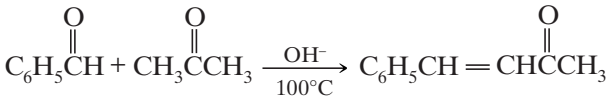
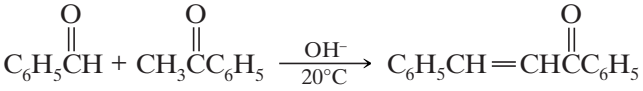
16.5B Claisen–Schmidt Reactions

When ketones are used as one component, the crossed aldol reactions are called **Claisen–Schmidt reactions,** after the German chemists J. G. Schmidt (who discovered the reaction in 1880) and Ludwig Claisen (who developed it between 1881 and 1889). These reactions are practical when bases such as sodium hydroxide are used because under these conditions ketones do not self-condense appreciably.

Two examples of Claisen–Schmidt reactions are the following:



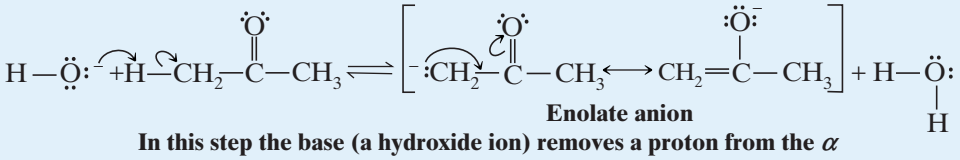
4-Phenylbut-3-en-2-one (benzalacetone) (70%)



1,3-Diphenylprop-2-en-1-one (benzalacetophenone) (85%)

A MECHANISM FOR THE REACTION — The Claisen–Schmidt Reaction

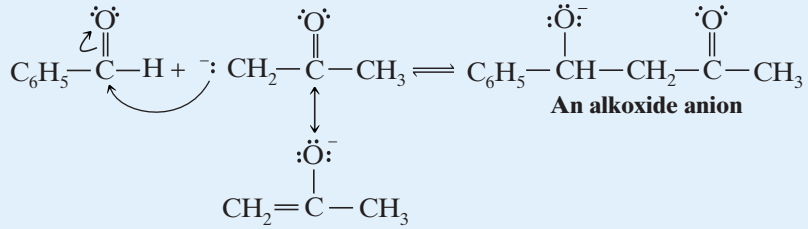
Step 1



Enolate anion

In this step the base (a hydroxide ion) removes a proton from the α carbon of one molecule of the ketone to give a resonance-stabilized enolate anion.

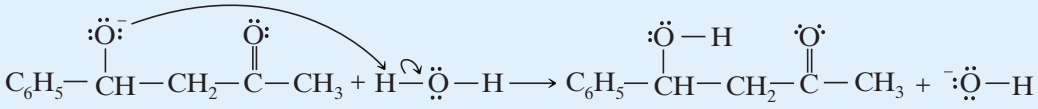
Step 2



An alkoxide anion

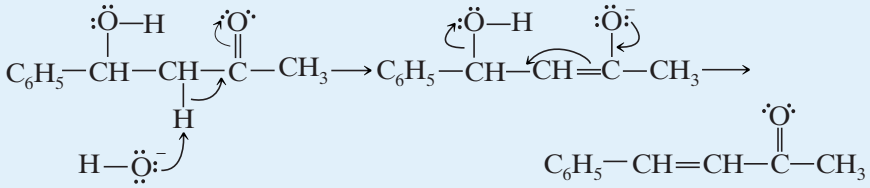
The enolate anion then acts as a nucleophile–as a carbanion–and attacks the carbonyl carbon of a molecule of aldehyde, producing an alkoxide anion.

Step 3



The alkoxide anion now removes a proton from a molecule of water.

Step 4



4-Phenylbut-3-en-2-one (benzalacetone)

Dehydration produces the conjugated product.

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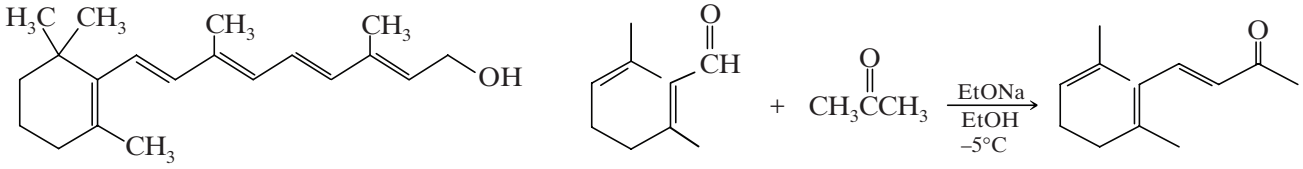
In the Claisen–Schmidt reactions given above dehydration occurs readily because the double bond that forms is conjugated both with the carbonyl group and with the benzene ring. The conjugated system is thereby extended. An important step in a commercial synthesis of vitamin A makes use of a Claisen–Schmidt reaction between geranial and acetone:

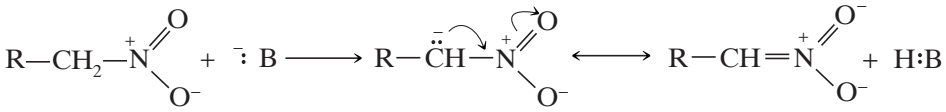


Vitamin A **Geranial** **Pseudoionone (49%)**

Geranial is a naturally occurring aldehyde that can be obtained from lemongrass oil. Its hydrogen is *vinylic* and, therefore, not appreciably acidic. Notice, in this reaction, too, dehydration occurs readily because dehydration extends the conjugated system.

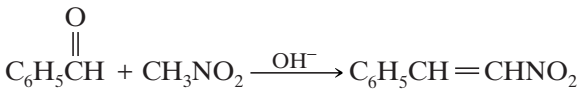
16.5C Condensations with Nitroalkanes

The α hydrogens of nitroalkanes are appreciably acidic ($pK_a = 10$), much more acidic than those of aldehydes and ketones. The acidity of these hydrogen atoms, like the α hydrogens of aldehydes and ketones, can be explained by the powerful electron-withdrawing effect of the nitro group and by resonance stabilization of the anion that is produced:

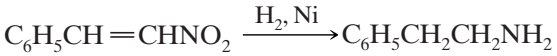


Resonance-stabilized anion

Nitroalkanes that have α hydrogens undergo base-catalyzed condensations with aldehydes and ketones that resemble aldol condensations. An example is the condensation of benzaldehyde with nitromethane:



This condensation is especially useful because the nitro group of the product can be easily reduced to an amino group. One technique that brings about this transformation uses hydrogen and a nickel catalyst. This combination not only reduces the nitro group but also reduces the double bond:



Practice Problem 16.14

Assuming that you have available the required aldehydes, ketones, and nitroalkanes, show how you would synthesize each of the following compounds and write a detailed mechanism for each reaction:

(a) $C_6H_5CH{=}C(CH_3)NO_2$ **(b)** $HOCH_2CH_2NO_2$

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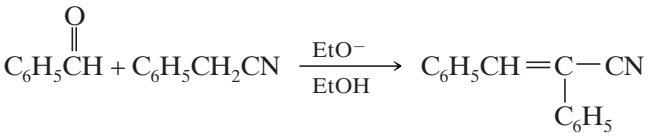
16.5D Condensations with Nitriles

The α hydrogens of nitriles are also appreciably acidic, but less so than those of aldehydes and ketones. The acidity constant for acetonitrile (CH_3CN) is about 10^{-25} ($pK_a \approx 25$). Other nitriles with α hydrogens show comparable acidities, and consequently these nitriles undergo condensations of the aldol type. An example is the condensation of benzaldehyde with phenylacetonitrile:

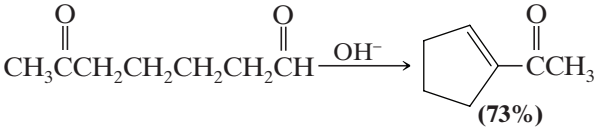


Practice Problem 16.15

(a) Write resonance structures for the anion of acetonitrile that account for its being much more acidic than ethane.
(b) Give a step-by-step mechanism for the condensation of benzaldehyde with acetonitrile.

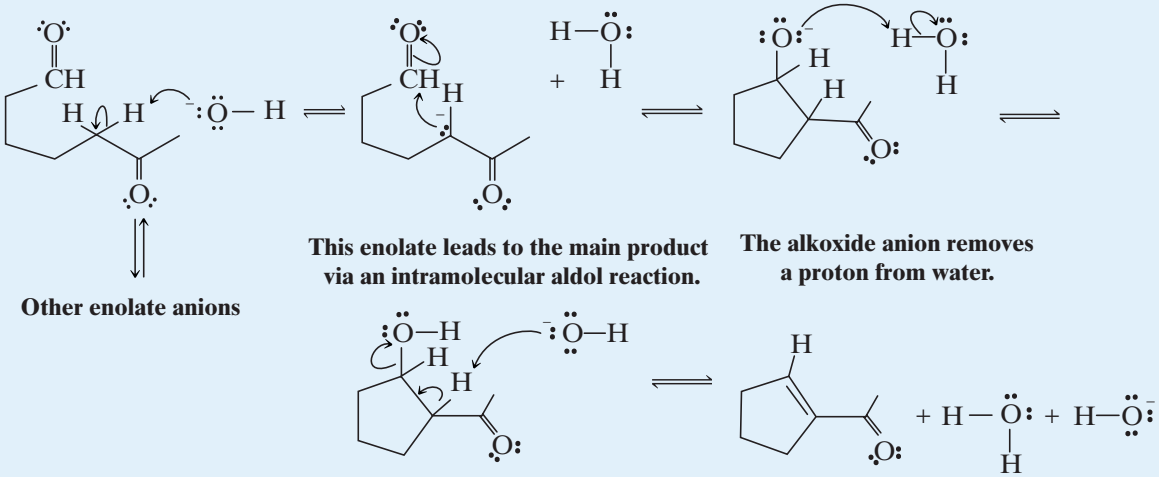
16.6 | CYCLIZATIONS VIA ALDOL CONDENSATION

The aldol condensation also offers a convenient way to synthesize molecules with five and six-membered rings (and sometimes even larger rings). This can be done by an intramolecular aldol condensation using a dialdehyde, a keto aldehyde, or a diketone as the substrate. For example, the following keto aldehyde cyclizes to yield 1-cyclopentenyl methyl ketone:



This reaction almost certainly involves the formation of at least three different enolates. However, it is the enolate from the ketone side of the molecule that adds to the aldehyde group leading to the product.

A MECHANISM FOR THE REACTION — The Aldol Cyclization



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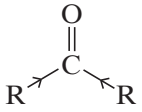
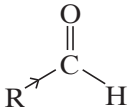
The reason the aldehyde group undergoes addition preferentially may arise from the greater reactivity of aldehydes toward nucleophilic addition generally. The carbonyl carbon atom of a ketone is less positive (and therefore less reactive toward a nucleophile) because it bears two electron-releasing alkyl groups; it is also more sterically hindered:



Ketones are less reactive toward nucleophiles.



Aldehydes are more reactive toward nucleophiles.

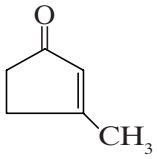
In reactions of this type, five-membered rings form far more readily than seven membered rings and six-membered rings are more favorable than four- or eight-membered rings when possible.

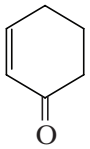
Practice Problem 16.16

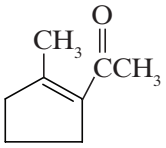
Assuming that dehydration occurs in all instances, write the structures of the two other products that might have resulted from the aldol cyclization just given. (One of these products will have a five-membered ring and the other will have a seven-membered ring.)

Practice Problem 16.17

What starting compound would you use in an aldol cyclization to prepare each of the following?

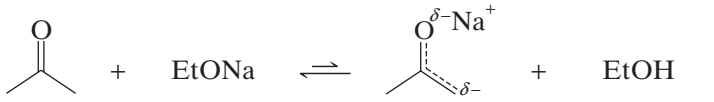
(a) 

(b) 

(c) 

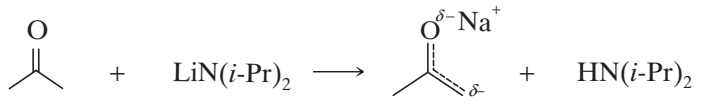
16.7 | LITHIUM ENOLATES

The position of the equilibrium by which an **enolate** forms depends on the strength of the base used. If the base employed is a weaker base than the enolate, then the equilibrium lies to the left. This is the case, for example, when a ketone is treated with sodium ethoxide in ethanol.



Weaker acid (pK_a = 19)	Weaker base	Stronger base	Stronger acid (pK_a = 16)

On the other hand, if a very strong base is employed, the equilibrium lies far to the right. One very useful strong base for converting carbonyl compounds to enolates is **lithium diisopropylamide (LDA)** or $LiN(i\text{-}Pr)_2$:



Ketone (stronger acid) (pK_a = 19)	LDA (stronger base)	Enolate (weaker base)	Diisopropylamine (weaker acid) (pK_a = 38)

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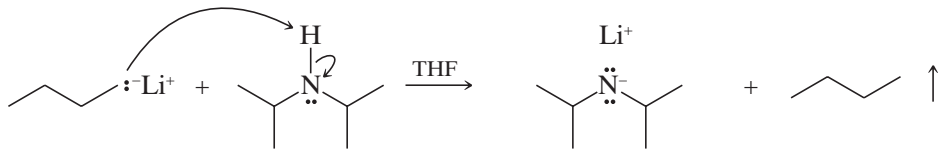
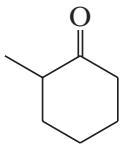
- Lithium diisopropylamide (LDA) can be prepared by dissolving diisopropylamine in a solvent such as diethyl ether or THF and treating it with an alkyllithium:



Butyllithium (BuLi) | **Diisopropylamine (pK_a = 38)** | **Lithium diisopropylamide [LDA or LiN(*i*-Pr)$_2$]** | **Butane (pK_a = 50)**

16.7A Regioselective Formation of Enolates

An unsymmetrical ketone such as 2-methylcyclohexanone can form two possible enolates, arising by removal of an α hydrogen from one side or the other of the carbonyl group. Which enolate predominates in the reaction depends on whether the enolate is formed under conditions that favor an acid–base equilibrium.

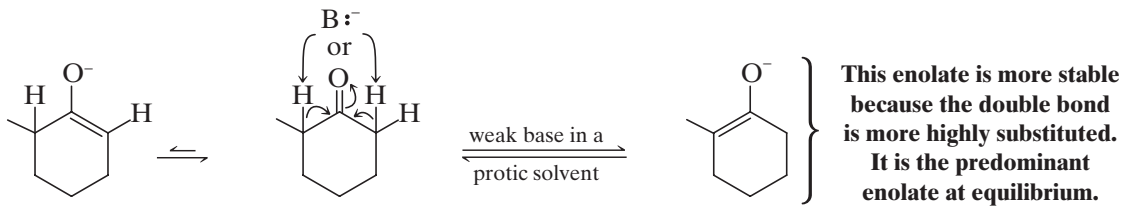


2-Methylcyclohexanone

- The **thermodynamic enolate** is that which is most stable among the possible enolates. Enolate stability is evaluated in the same way as for alkenes, meaning that the more highly substituted enolate is the more stable one.
- The **thermodynamic enolate** predominates under conditions of **thermodynamic control** where a deprotonation–protonation equilibrium allows interconversion among the possible enolates, such that eventually the more stable enolate exists in higher concentration. This is the case when the pK_a of the conjugate acid of the base is similar to the pK_a of the α hydrogen of the carbonyl compound. Use of hydroxide or an alkoxide in a protic solvent favors formation of the thermodynamic enolate.
- The **kinetic enolate** is that which is formed fastest. It is usually formed by removal of the least sterically hindered α hydrogen.
- The **kinetic enolate** predominates under conditions of **kinetic control** that do not favor equilibrium among the possible enolates. Use of a very strong and sterically hindered base in an aprotic solvent, such as LDA in tetrahydrofuran (THF) or dimethoxyethane (DME) favors formation of the kinetic enolate.

Conditions favoring formation of the thermodynamic and kinetic enolates from 2-methylcyclohexanone are illustrated below.

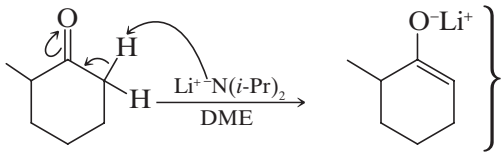
Formation of a Thermodynamic Enolate



Kinetic (less stable) enolate | **2-Methylcyclohexanone** | **Thermodynamic (more stable) enolate**

This enolate is more stable because the double bond is more highly substituted. It is the predominant enolate at equilibrium.

Formation of a Kinetic Enolate



Kinetic enolate

This enolate is formed faster because the hindered strong base removes the less hindered proton faster.

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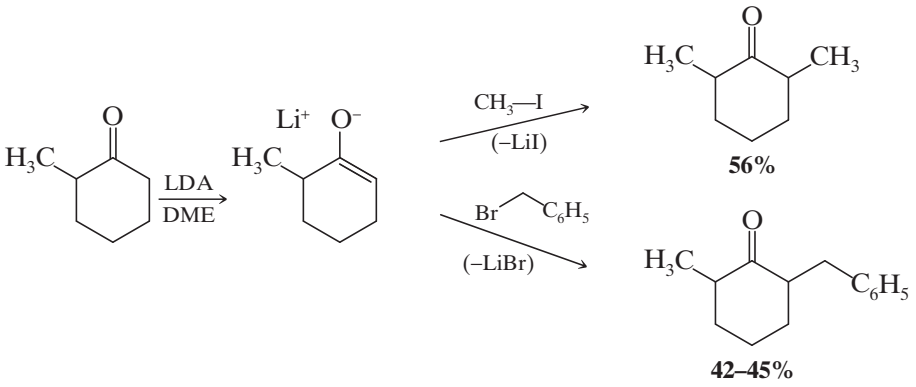
16.7B Direct Alkylation of Ketones via Lithium Enolates

The formation of lithium enolates using lithium diisopropylamide furnishes a useful way of alkylating ketones in a regioselective way. For example, the lithium enolate formed from 2-methylcyclohexanone can be methylated or benzylated at the less hindered α carbon by allowing it to react with LDA followed by methyl iodide or benzyl bromide, respectively:



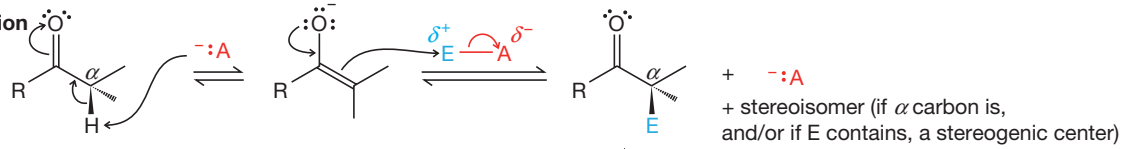
Alkylation reactions like these have an important limitation, however, because the reactions are S_N2 reactions, and also because enolates are strong bases.

- Successful alkylations occur only when primary alkyl, primary benzylic, and primary allylic halides are used. With secondary and tertiary halides, elimination becomes the main course of the reaction.

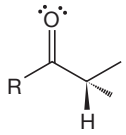
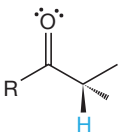
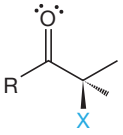
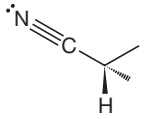
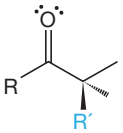
SUMMARY OF MECHANISMS

Enolates: α-Substitution

General Reaction



+ stereoisomer (if α carbon is, and/or if E contains, a stereogenic center)

Some groups that increase α-hydrogen acidity	Typical bases (⁻:A) and solvents for enolate formation	Possible electrophiles (E–A)	Product(s)
 Carbonyl	I. HO^- in H_2O or ROH; or RO^- in ROH; Useful for reactions involving thermodynamically favored enolates and equilibrium product control	H—A **Deprotonation–protonation** (may lead to racemization or epimerization)	
		:X—X: **Halogenation**	
 Nitrile (cyano group) (and in general, other groups that can stabilize an α-carbanion)	II. LDA (lithium diisopropylamide) in THF or DME; useful, in general, for forming enolates in aprotic solvents (especially kinetically favored enolates and direct alkylation)	R′—X: **Alkylation**	

Substitution of enolate α hydrogen by H, X, or R

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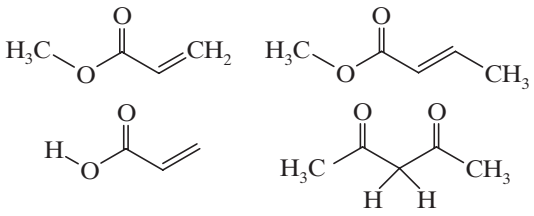
REVIEW PROBLEMS

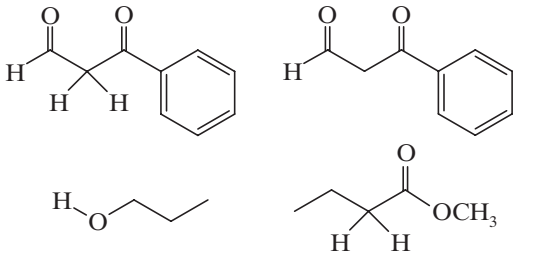
Enolates, Enols, and Carbonyl α-Carbon Reactivity

16.18 Rank the following in order of increasing acidity for the indicated hydrogen atoms (bold) (1 = least acidic; 4 = most acidic).

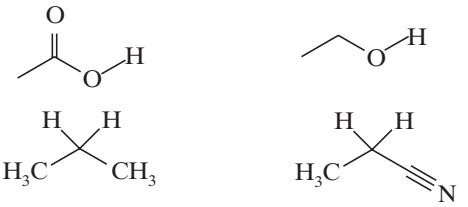
(a)



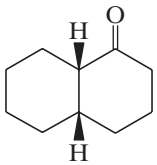
(b)



(c)



16.19 Treating a solution of *cis*-1-decalone with base causes an isomerization to take place. When the system reaches equilibrium, the solution is found to contain about 95% *trans*-1-decalone and about 5% *cis*-1-decalone. Explain this isomerization.



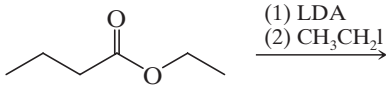
***cis*-1-Decalone**

16.20 Explain the variation in enol content that is observed for solutions of acetylacetone (pentane-2,4-dione) in the several solvents indicated:

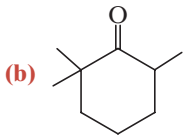
Solvent	% Enol
H_2O	15
CH_3CN	58
C_6H_{14}	92
Gas phase	92

16.21 Provide a structural formula for the product from each of the following reactions.

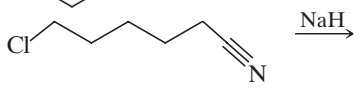
(a)



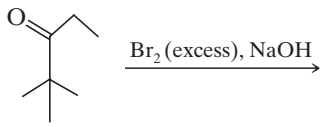
(b)



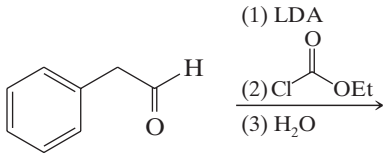
(c)



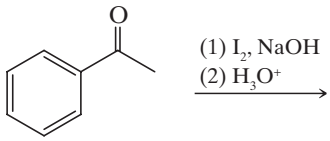
(d)



(e)

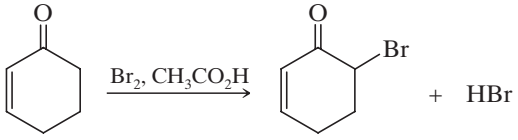


(f)

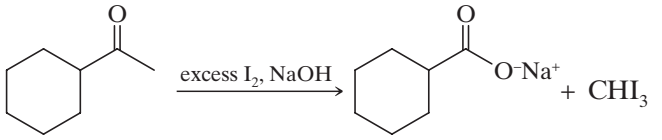


16.22 Write a stepwise mechanism for each of the following reactions.

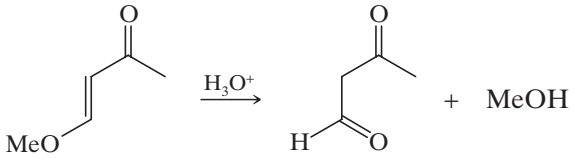
(a)



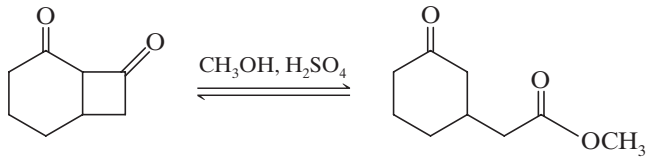
(b)



(c)

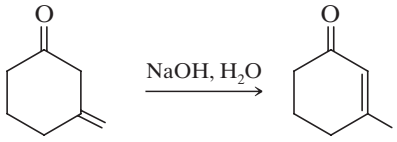


(d)



16.23 Write a stepwise mechanism for each of the following reactions.

(a)



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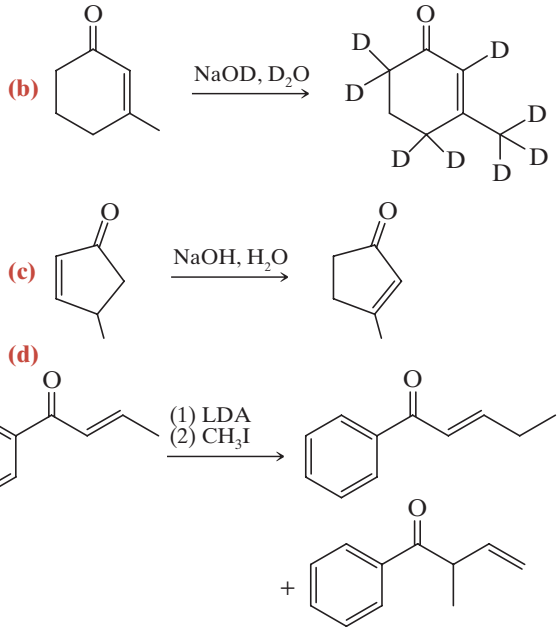
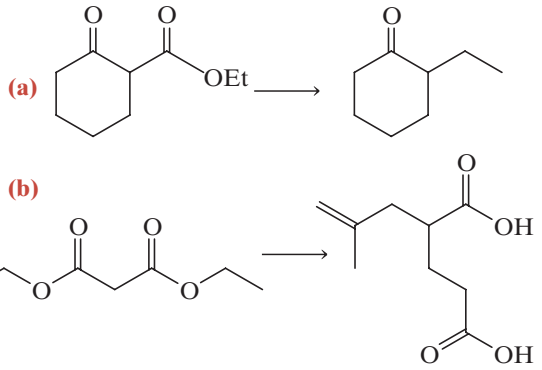
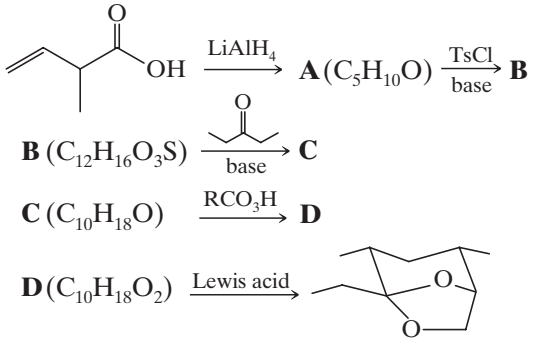


General Problems

16.24 Outline a reaction sequence for synthesis of each of the following compounds from the indicated starting material and any other organic or inorganic reagents needed.

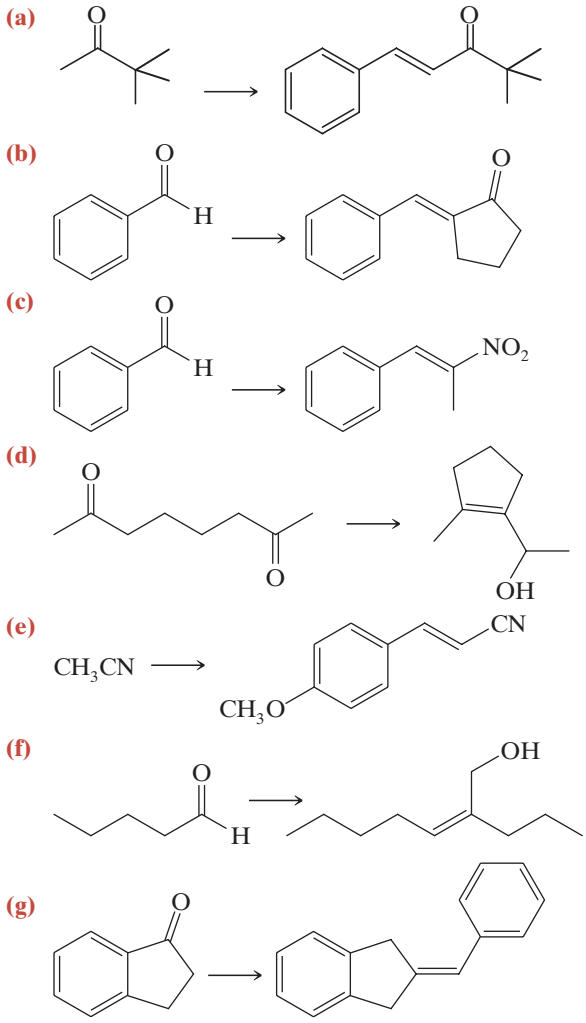


16.25 Shown below is a synthesis of the elm bark beetle pheromone, multistriatin). Give structures for compounds **A, B, C**, and **D**.

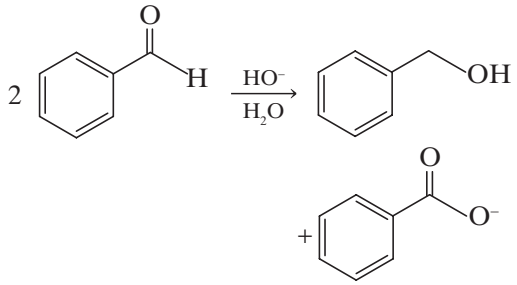


Multistriatin

16.26 Show how each of the following transformations could be accomplished. You may use any other required reagents.



16.27 Aldehydes that have no α hydrogen undergo an intermolecular oxidation–reduction called the **Cannizzaro reaction** when they are treated with concentrated base. An example is the following reaction of benzaldehyde:



(a) When the reaction is carried out in D_2O, the benzyl alcohol that is isolated contains no deuterium bound to carbon. It is $C_6H_5CH_2OD$. What does this suggest about the mechanism for the reaction?

(b) When $(CH_3)_2CHCHO$ and $Ba(OH)_2/H_2O$ are heated in a sealed tube, the reaction produces

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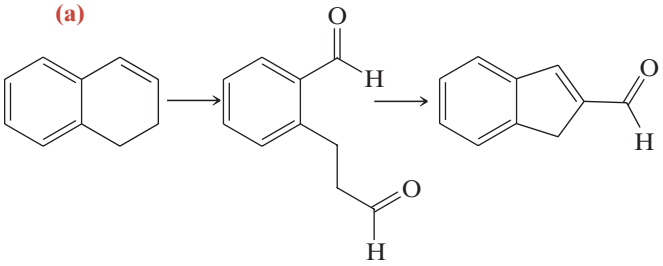
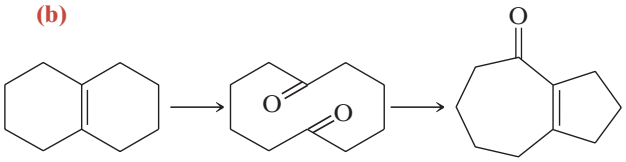
only $(CH_3)_2$—$CHCH_2OH$ and $[(CH_3)_2CHCO_2]_2Ba$. Provide an explanation for the formation of these products.

16.28 What reagents would you use to bring about each step of the following syntheses?

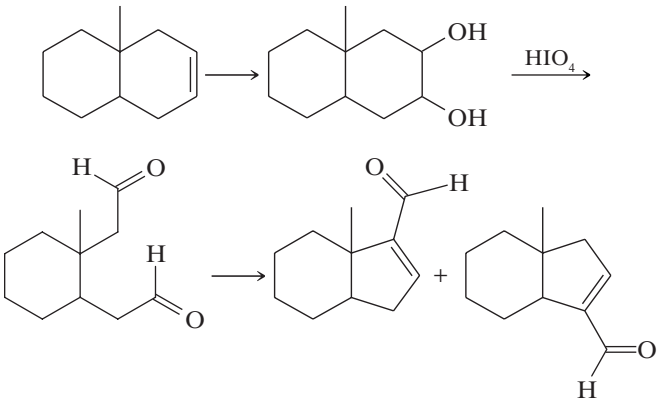
(a)



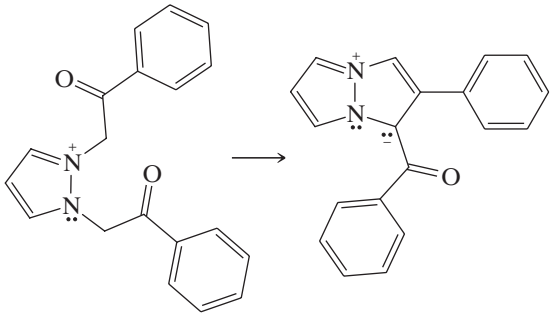
(b)



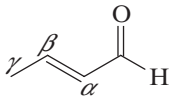
(c)



(d)

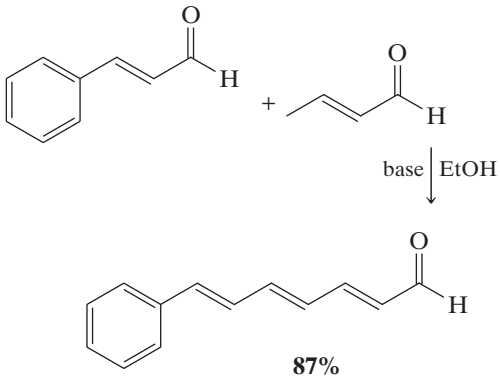


16.29 The hydrogen atoms of the γ carbon of crotonaldehyde are appreciably acidic ($pK_a \cong 20$).



Crotonaldehyde

(a) Write resonance structures that will explain this fact.
(b) Write a mechanism that accounts for the following reaction:



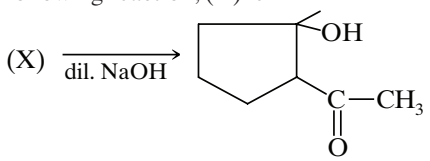
87%

ADDITIONAL OBJECTIVE QUESTIONS

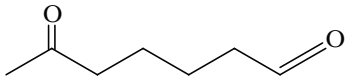
Single Correct Choice Type

1. Mixed aldol reactions require
(a) only one of the reactants to be able to form an enolate.
(b) one of the reactants to be more reactive towards the nucleophile.
(c) much stronger bases.
(d) (b) and (c).

2. In the following reaction, (X) is



(a)



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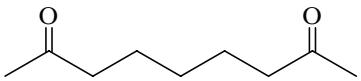

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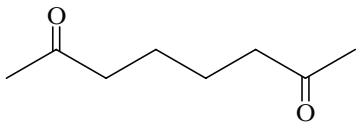

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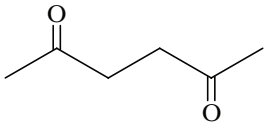

3. If formaldehyde and potassium hydroxide are heated, then we get

(a) acetylene. **(b)** methane.
(c) methyl alcohol. **(d)** ethyl formate.

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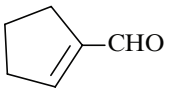
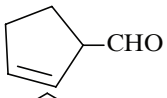
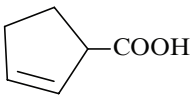
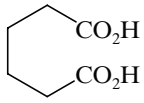
4. Cyclohexene on ozonolysis followed by reaction with zinc dust and water gives compound E, on further treatment with aqueous KOH followed by heating yields compound F. The compound F is

(a) 

(b) 

(c) 

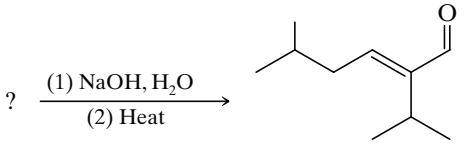
(d) 

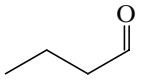
5. In Cannizzaro reaction given below, the slowest step is

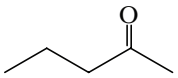
$$2PhCHO \xrightarrow{OH^-} PhCH_2OH + PhCO_2^-$$

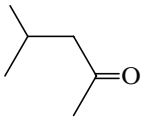
(a) the abstraction of proton from the carboxylic group.
(b) the deprotonation of $PhCH_2OH$.
(c) the attack of OH^- at the carboxyl group.
(d) the transfer of hydride to the carbonyl group.

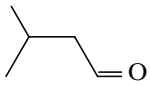
6. What starting material is required for the following reaction?



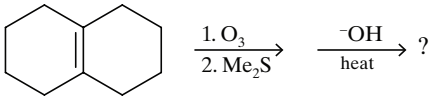
(a) 

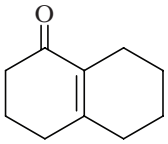
(b) 

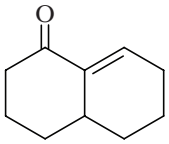
(c) 

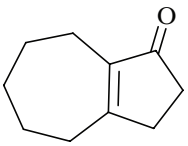
(d) 

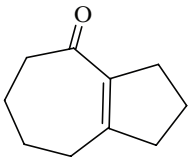
7. Choose the product of the following reaction sequence.



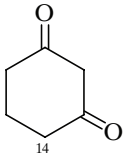
(a) 

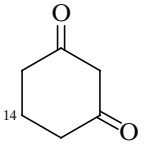
(b) 

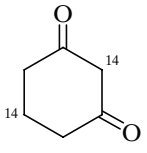
(c) 

(d) 

8. Which of the following compounds give $^{14}CHI_3$ as a product when treated with I_2 in presence of NaOH?

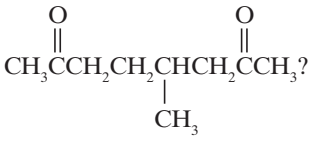
(a) 

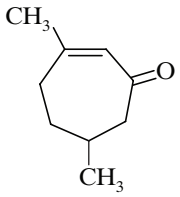
(b) 

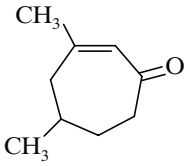
(c) 

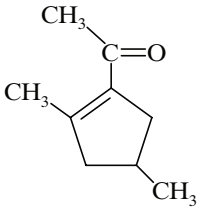
(d) All of these

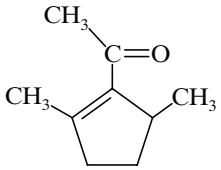
9. What compound results from the aldol cyclization of



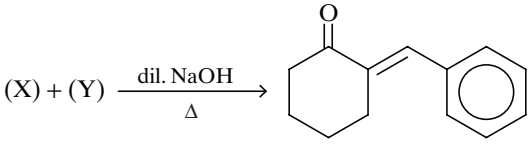
(a) 

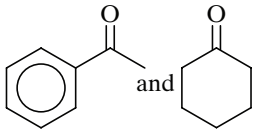
(b) 

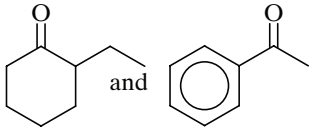
(c) 

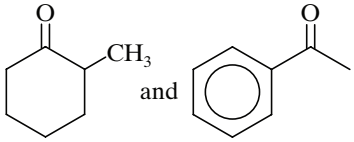
(d) 

10. In the following reaction, (X) and (Y) are



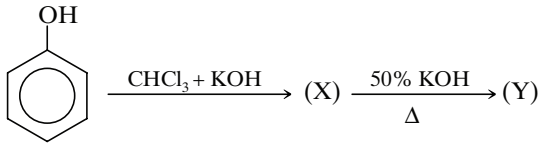
(a) 

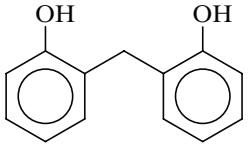
(b) 

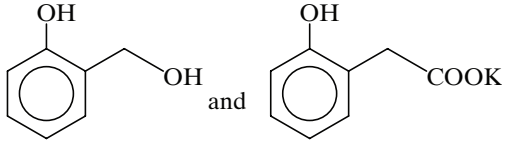
(c) 

(d) None

11. The end product of the following reaction is/are:



(a) 

(b) 

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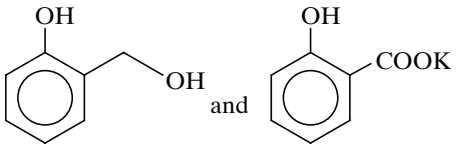
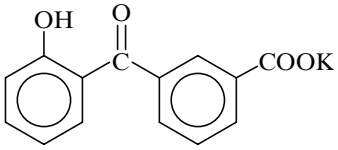
(c) 

(d) 

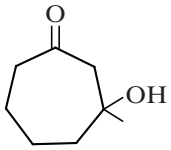
12. The Cannizzaro reaction is not given by

(a) trimethyl acetaldehyde. **(b)** acetaldehyde.
(c) benzaldehyde. **(d)** formaldehyde.

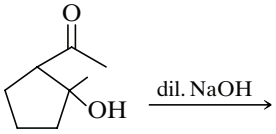
13. Benzyl alcohol is obtained from benzaldehyde by

(a) Fittig's reaction. **(b)** Cannizaro's reaction.
(c) Kolbe's reaction. **(d)** Wurtz's reaction.

14. This compound (X) is obtained from



(X)

(a) 

(b) $CH_3-\overset{O}{\overset{\|}{C}}-(CH_2)_4-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow{\text{dil. NaOH}}$

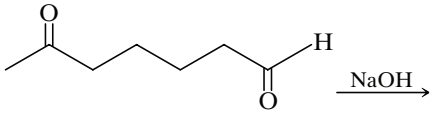
(c) $CH_3-\overset{O}{\overset{\|}{C}}-(CH_2)_5-\overset{O}{\overset{\|}{C}}-H \xrightarrow{\text{dil. NaOH}}$

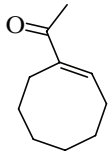
(d) Both (a) and (b)

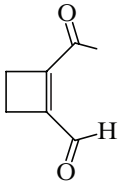
15. A mixture of benzaldehyde and formaldehyde on heating with aqueous NaOH solution gives

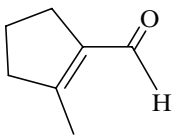
(a) benzyl alcohol and sodium formate.
(b) sodium benzoate and methyl alcohol.
(c) sodium benzoate and sodium formate.
(d) benzyl alcohol and methyl alcohol.

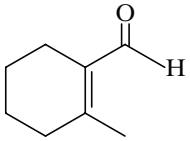
16. Predict the product of the following reaction.



(a) 

(b) 

(c) 

(d) 

17. Which reagents would you use to synthesize this compound by an aldol condensation?

$C_6H_5CH=CHC(=O)C_6H_5$

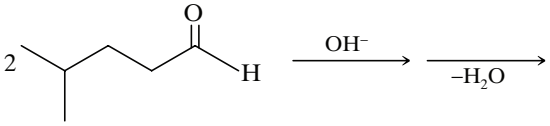
(a) C_6H_5CHO and $C_6H_5CH_2CHO$

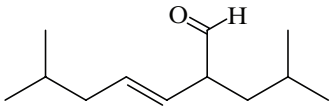
(b) $C_6H_5CH_2CHO$ and $C_6H_5COCH_3$

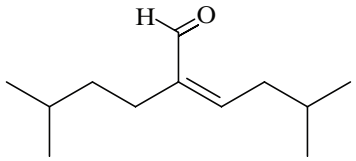
(c) $C_6H_5CH=CHCHO$ and C_6H_5OH

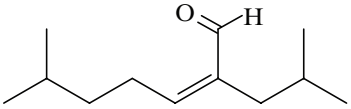
(d) $C_6H_5COCH_3$ and C_6H_5CHO

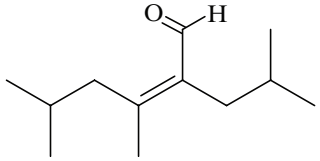
18. Predict the product of the following aldol condensation.



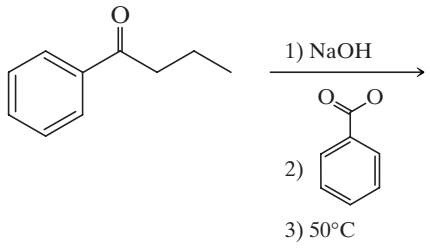
(a) 

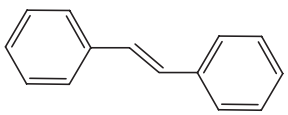
(b) 

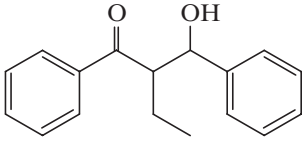
(c) 

(d) 

19. What is the product of the following reaction?



(I) 

(II) 

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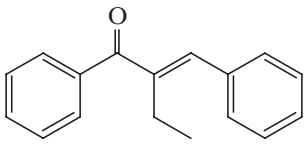
(III)



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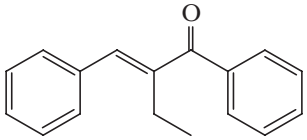


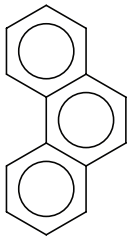
(a) (I) **(b)** (II)
(c) (III) and (IV) **(d)** (III) and (I)

20. Which of these is not among the reaction products when a crossed aldol addition occurs between ethanol and butanal?

(a) $CH_3CH(OH)CH_2C(H)=O$ **(b)** $CH_3CH_2CH_2CH(OH)CH(CH_3)CH_2C(H)=O$

(c) $CH_3CH(OH)CH(CH_2CH_3)C(H)=O$ **(d)** $CH_3CH_2CH_2CH(OH)CH_2C(H)=O$

21.

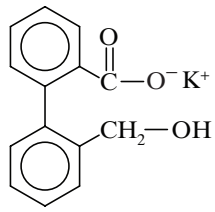


(A)

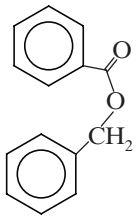
$\xrightarrow[\text{(Selective) Ozonolysis}]{O_3,\ Zn}$ (B) $\xrightarrow{\text{Conc. KOH}}$ (C) $\xrightarrow[\Delta]{H^+}$ (D)

Compound (D) is

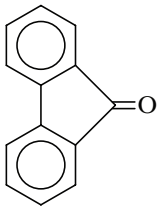
(a)



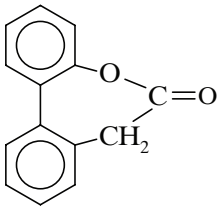
(b)



(c)



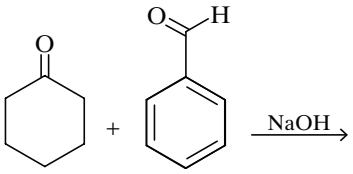
(d)



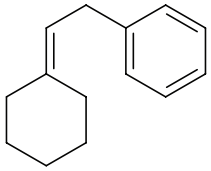
22. Acid catalyzed aldol condensation involves
(a) carbanion. **(b)** enolate ion.
(c) enol. **(d)** both (a) and (b).

23. Which is the only one of these compounds which cannot self-condense in the presence of dilute aqueous alkali?
(a) Phenylethanal **(b)** Propanal
(c) 3-Methylpentanal **(d)** 2,2-Dimethylpropanal

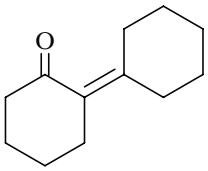
24. Predict the major product of the following reaction.



(a)



(b)



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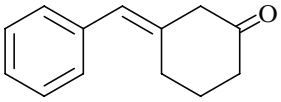
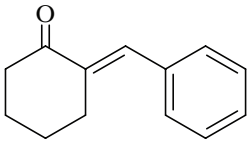
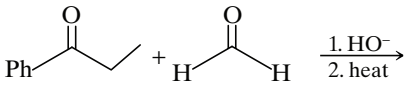


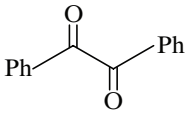
(d)



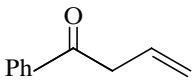
25. Choose the major product of the following aldol reaction.



(a)



(b)



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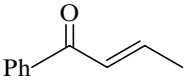
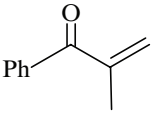
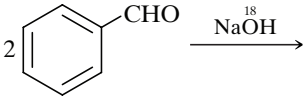


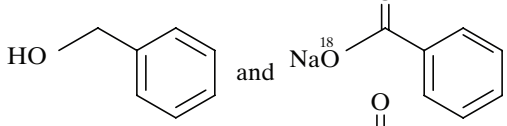
(d)



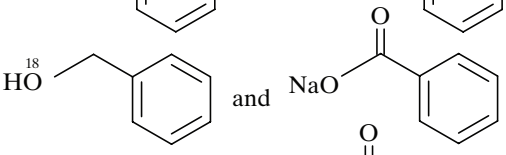
26. The product of the following reaction are



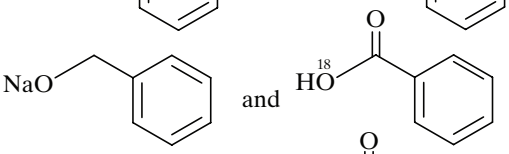
(a)



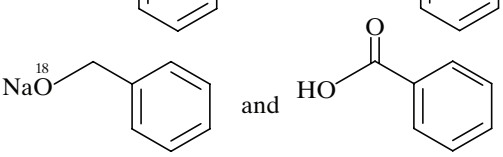
(b)



(c)



(d)



Linked Comprehension Type

Paragraph for Questions 1 to 3

A tertiary alcohol H upon acid-catalyzed dehydration gives a product I. Ozonolysis of I leads to compounds J and K.

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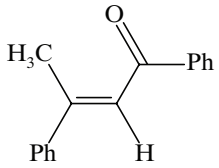
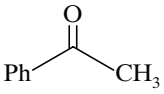
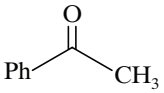
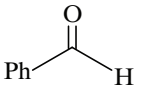
Compound J upon reaction with KOH gives benzyl alcohol and a compound L, whereas K on reaction with KOH gives only M:

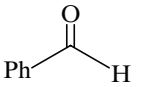
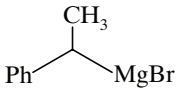
M = 

1. Compound H is formed by the reaction of

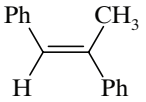
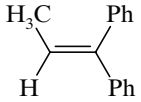
(a)  + PhMgBr

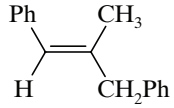
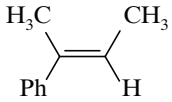
(b)  + $PhCH_2MgBr$

(c)  + $PhCH_2MgBr$

(d)  + 

2. The structure of compound I is

(a)  **(b)** 

(c)  **(d)** 

3. The structures of compounds J, K and L, respectively, are

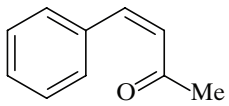
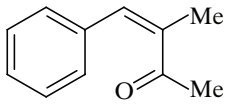
(a) $PhCOCH_3$, $PhCH_2COCH_3$ and $PhCH_2COO^-K^+$
(b) PhCHO, $PhCH_2CHO$ and $PhCOO^-K^+$
(c) $PhCOCH_3$, $PhCH_2CHO$ and $CH_3COO^-K^+$
(d) PhCHO, $PhCOCH_3$ and $PhCOO^-K^+$

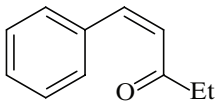
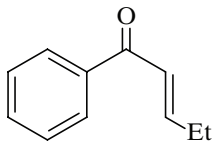
Paragraph for Questions 4 to 6

A carbonyl compound P, which gives positive iodoform test, undergoes reaction with MeMgBr followed by dehydration to give an olefin Q. Ozonolysis of Q leads to a dicarbonyl compound R, which undergoes intramolecular aldol reaction to give predominantly S.

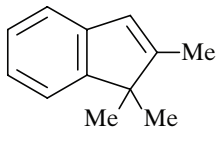
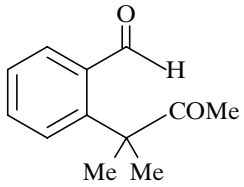
$$P \xrightarrow[(2)\ H^+, H_2O \\ (3)\ H_2SO_4, \Delta]{(1)\ MeMgBr} Q \xrightarrow[(2)\ Zn, H_2O]{(1)\ O_3} R \xrightarrow[(2)\ \Delta]{(1)\ OH^-} S$$

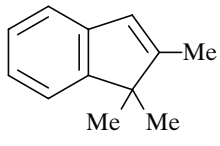
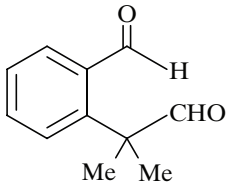
4. The structure of the carbonyl compound P is

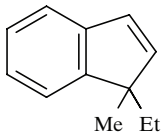
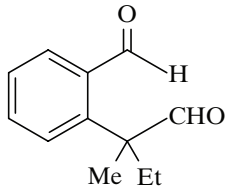
(a)  **(b)** 

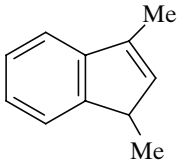
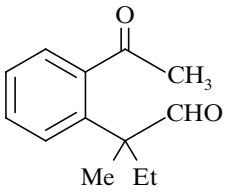
(c)  **(d)** 

5. The structures of the products Q and R, respectively, are

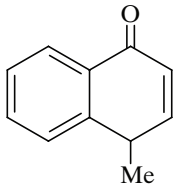
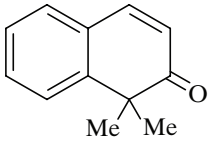
(a)  

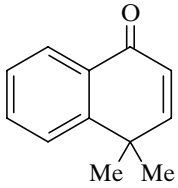
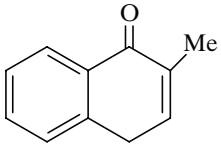
(b)  

(c)  

(d)  

6. The structure of the product S is

(a)  **(b)** 

(c)  **(d)** 

Paragraph for Questions 7 to 9

$$A \xrightarrow{O_3} B + C \xrightarrow{\text{conc. KOH}} \text{Benzyl alcohol + Salt of benzoic acid}$$

$$B \xrightarrow{\text{dil. KOH}} CH_3-\underset{OH}{CH}-CH_2-\overset{O}{\overset{\|}{C}}-H \xrightarrow{HCN} D \xrightarrow[\Delta]{H_3O^+} E$$

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7. Structure of A is

(a) $H_2C=CH-CHO$

(b) $Ph-CH=CH-CH_3$

(c) $Ph-\underset{\displaystyle CH_3}{\underset{|}{CH}}=CH_2-CH_3$

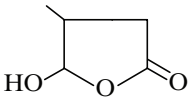
(d) $Ph-CH_2-\underset{\displaystyle CH_3}{\underset{|}{C}}=CH_3$

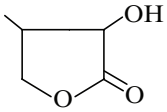
8. Structure of B and C can be differentiated by

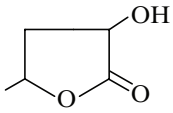
(a) Tollens' reagent **(b)** Fehling solution

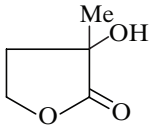
(c) 2,4-DNP **(d)** $NaHSO_3$

9. Structure of E is

(a) 

(b) 

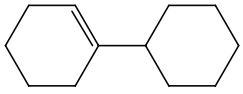
(c) 

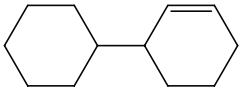
(d) 

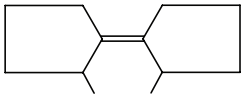
Paragraph for Questions 10 to 12

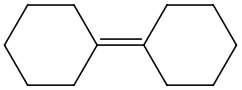
An organic compound A ($C_{12}H_{20}$) decolorizes bromine water, and on reductive ozonolysis produces two molecules of B ($C_6H_{10}O$). Compound B on aldol condensation followed by dehydration of product gives C ($C_{12}H_{18}O$), which on reduction with N_2H_4/OH_2 regenerates A. Compound B on reduction with Zn(Hg)/HCl produces D (C_6H_{12}), which on monochlorination gives E ($C_6H_{11}Cl$) as the sole product.

10. Structure of compound A is

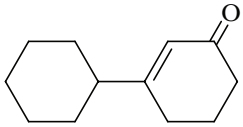
(a) 

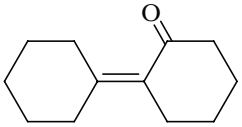
(b) 

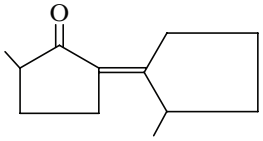
(c) 

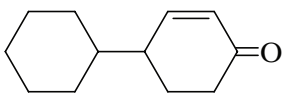
(d) 

11. Structure of compound C is

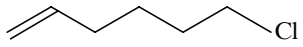
(a) 

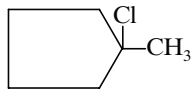
(b) 

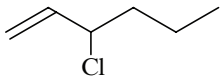
(c) 

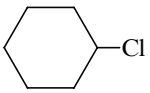
(d) 

12. Structure of compound E is

(a) 

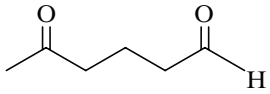
(b) 

(c) 

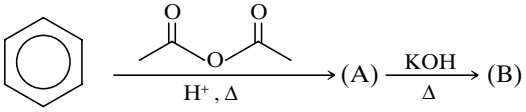
(d) 

Integer Type

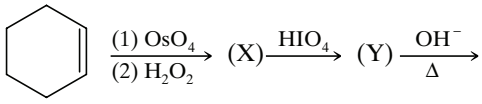
1. Total number of intramolecular aldol condensation products possible from given compound is (excluding stereoisomer).



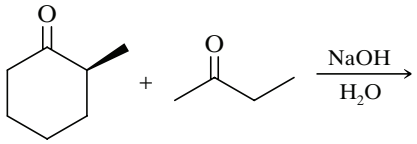
2. Find number of π bond present in compound B.



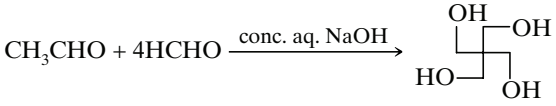
3. Number of possible intramolecular aldol products possible (excluding stereoisomers) in the following reaction is ____.



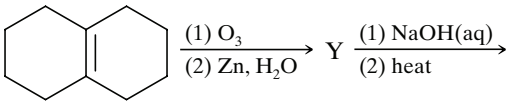
4. Total number of different cross aldol condensation products (only structural) obtained when a mixture of (*S*)-2-methyl cyclohexanone and 2-butanone is treated with aqueous sodium hydroxide is ____.



5. The number of aldol reaction(s) that occurs in the given transformation is ____.



6. In the scheme given below, the total number of intramolecular aldol condensation products formed from Y is ____.



ANSWER KEY

Single Correct Choice Type

1. (d)	**2.** (c)	**3.** (c)	**4.** (a)	**5.** (d)
6. (d)	**7.** (d)	**8.** (c)	**9.** (c)	**10.** (d)

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11. (c) **12.** (b) **13.** (b) **14.** (b) **15.** (a)
16. (c) **17.** (d) **18.** (c) **19.** (c) **20.** (b)
21. (b) **22.** (c) **23.** (d) **24.** (d) **25.** (d)
26. (a)

Linked Comprehension Type

1. (b) **2.** (a) **3.** (d) **4.** (b) **5.** (a)
6. (b) **7.** (b) **8.** (b) **9.** (c) **10.** (d)
11. (b) **12.** (d)

Integer Type

1. (3) **2.** (8) **3.** (1) **4.** (3) **5.** (3)
6. (1)

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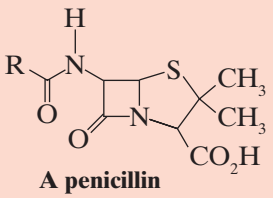
17

Carboxylic Acids and Their Derivatives

Nucleophilic Addition–Elimination at the Acyl Carbon



A penicillin

Contents

17.1 | Introduction
17.2 | Nomenclature and Physical Properties
17.3 | Preparation of Carboxylic Acids
17.4 | Acyl Substitution: Nucleophilic Addition–Elimination at the Acyl Carbon
17.5 | Acyl Chlorides
17.6 | Carboxylic Acid Anhydrides
17.7 | Esters
17.8 | Amides
17.9 | Derivatives of Carbonic Acid
17.10 | Decarboxylation of Carboxylic Acids
17.11 | Chemical Tests for Acyl Compounds
17.12 | Summary of the Reactions of Carboxylic Acids and Their Derivatives

17.1 | INTRODUCTION

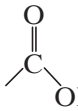
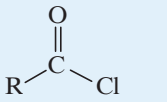
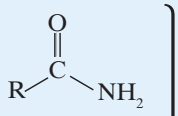
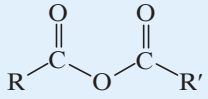
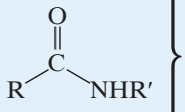
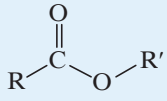
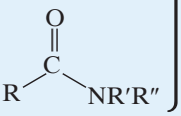
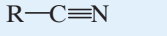
The carboxyl group, , is one of the most widely occurring functional groups in chemistry and biochemistry. Not only are carboxylic acids themselves important, but the carboxyl group is the parent group of a large family of related compounds called **acyl compounds** or **carboxylic acid derivatives**, shown in Table 17.1.

Table 17.1 Carboxylic Acid Derivatives

Structure	Name	Structure	Name
	Acyl (or acid) chloride		Amide
	Acid anhydride		
	Ester		
	Nitrile		

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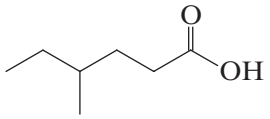
17.2 | NOMENCLATURE AND PHYSICAL PROPERTIES

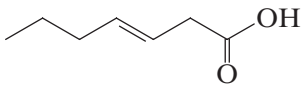
17.2A Carboxylic Acids

- Systematic or substitutive names for carboxylic acids are obtained by dropping the final *-e* of the name of the alkane corresponding to the longest chain in the acid and by adding *-oic acid*. The carboxyl carbon atom is assigned number 1.

The following examples show how this is done:



4-Methylhexanoic acid



(*E*)-3-Heptenoic acid
[or (*E*)-hept-3-enoic acid]

Many carboxylic acids have common names that are derived from Latin or Greek words that indicate one of their natural sources. Methanoic acid is called formic acid (*formica*, Latin: ant). Ethanoic acid is called acetic acid (*acetum*, Latin: vinegar). Butanoic acid is one compound responsible for the odor of rancid butter, so its common name is butyric acid (*butyrum*, Latin: butter). Pentanoic acid, as a result of its occurrence in valerian, a perennial herb, is named valeric acid. Hexanoic acid is one compound associated with the odor of goats, hence its common name, caproic acid (*caper*, Latin: goat). Octadecanoic acid takes its common name, stearic acid, from the Greek word *stear*, for tallow.

Most of these common names have been used for a long time and some are likely to remain in common usage, so it is helpful to be familiar with them. In this text we shall refer to methanoic acid and ethanoic acid as formic acid and acetic acid, respectively. However, in almost all other instances we shall use IUPAC systematic or substitutive names.

Carboxylic acids are polar substances. Their molecules can form strong hydrogen bonds with each other and with water. As a result, carboxylic acids generally have high boiling points, and low-molecular-weight carboxylic acids show appreciable solubility in water. As the length of the carbon chain increases, water solubility declines.

17.2B Carboxylate Salts

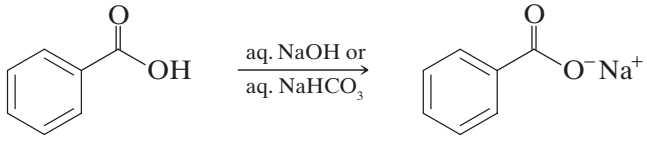
Salts of carboxylic acids are named as *-ates*; in both common and systematic names, *-ate* replaces *-ic acid*. The name of the cation precedes that of the carboxylate anion. Thus, CH_3CO_2Na is sodium acetate or sodium ethanoate.

Sodium and potassium salts of most carboxylic acids are readily soluble in water. This is true even of the long-chain carboxylic acids. Sodium or potassium salts of long-chain carboxylic acids are the major ingredients of soap.

17.2C Acidity of Carboxylic Acids

Most unsubstituted carboxylic acids have K_a values in the range of 10^{-4}–10^{-5} ($pK_a = 4$–5). The pK_a of water is about 16, and the apparent pK_a of H_2CO_3 is about 7. These relative acidities mean that carboxylic acids react readily with aqueous solutions of sodium hydroxide and sodium bicarbonate to form soluble sodium salts. We can use solubility tests, therefore, to distinguish water-insoluble carboxylic acids from water-insoluble phenols (Chapter 21) and alcohols.

- Water-insoluble carboxylic acids dissolve in either aqueous sodium hydroxide or aqueous sodium bicarbonate.



Benzoic acid
water insoluble

Sodium benzoate
water soluble

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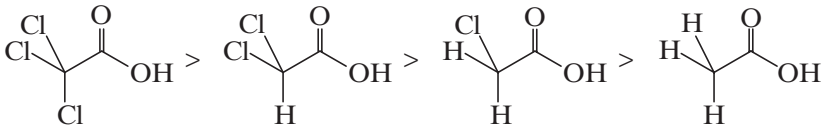
- Water-insoluble phenols (Section 19.5) dissolve in aqueous sodium hydroxide but (except for some nitrophenols) do not dissolve in aqueous sodium bicarbonate.
- Water-insoluble alcohols do not dissolve in either aqueous sodium hydroxide or sodium bicarbonate.

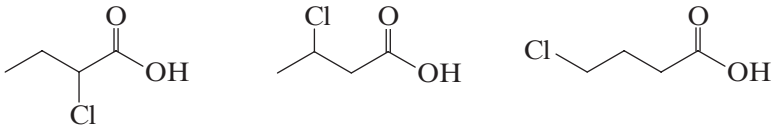
Carboxylic acids having electron-withdrawing groups are more acidic than unsubstituted acids. The chloroacetic acids, for example, show the following order of acidities:



pK_a **0.70** **1.48** **2.86** **4.76**

- In general, the more delocalization of charge in the conjugate base, the more stable is the anion, and the stronger the acid.

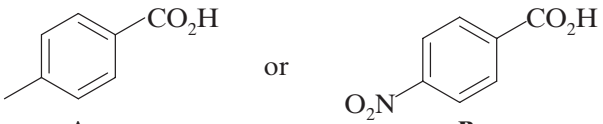
Since inductive effects are not transmitted very effectively through covalent bonds, the acid-strengthening effect decreases as the distance between the electron-withdrawing group and the carboxyl group increases. Of the chlorobutanoic acids that follow, the strongest acid is 2-chlorobutanoic acid:



2-Chlorobutanoic acid ($pK_a = 2.85$) **3-Chlorobutanoic acid** ($pK_a = 4.05$) **4-Chlorobutanoic acid** ($pK_a = 4.50$)

Solved Problem 17.1

Which carboxylic acid would you expect to be stronger, **A** or **B**?



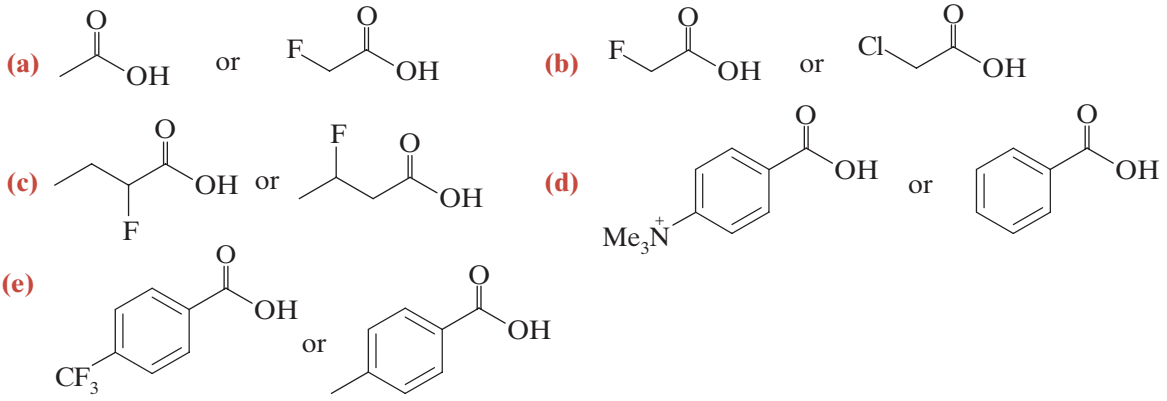
A **B**

Answer

The electron-withdrawing effect of the nitro group would help stabilize the conjugate base of **B**, whereas the electron-donating effect of the methyl group in **A** would destabilize its conjugate base. Therefore, **B** is expected to be the stronger acid.

Practice Problem 17.1

Which acid of each pair shown here would you expect to be stronger?



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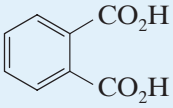
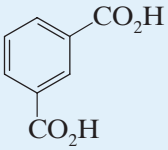
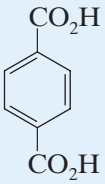
17.2D Dicarboxylic Acids

Dicarboxylic acids are named as **alkanedioic acids** in the IUPAC systematic or substitutive system. Most simple dicarboxylic acids have common names (Table 17.2).

Table 17.2 Dicarboxylic Acids

Structure	Common Name	mp (°C)	pK_a (at 25 °C)	
			pK_{a1}	pK_{a2}
$HO_2C—CO_2H$	Oxalic acid	189 dec	1.2	4.2
$HO_2CCH_2CO_2H$	Malonic acid	136	2.9	5.7
$HO_2C(CH_2)_2CO_2H$	Succinic acid	187	4.2	5.6
$HO_2C(CH_2)_3CO_2H$	Glutaric acid	98	4.3	5.4
$HO_2C(CH_2)_4CO_2H$	Adipic acid	153	4.4	5.6
cis-$HO_2C—CH{=}CH—CO_2H$	Maleic acid	131	1.9	6.1
trans-$HO_2C—CH{=}CH—CO_2H$	Fumaric acid	287	3.0	4.4
	Phthalic acid	206–208 dec	2.9	5.4
	Isophthalic acid	345–348	3.5	4.6
	Terephthalic acid	Sublimes	3.5	4.8

Solved Problem 17.2

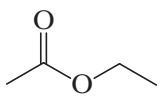
Suggest explanations for the following. **(a)** The pK_{a1} for all of the dicarboxylic acids in Table 17.2 is smaller than the pK_a for a monocarboxylic acid with the same number of carbon atoms. **(b)** The difference between pK_{a1} and pK_{a2} for dicarboxylic acids of the type $HO_2C(CH_2)_nCO_2H$ decreases as n increases.

Answer

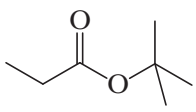
(a) The carboxyl group is electron-withdrawing; thus, in a dicarboxylic acid such as those in Table 17.2, one carboxylic acid group increases the acidity of the other. **(b)** As the distance between the carboxyl groups increases, the acid-strengthening, inductive effect decreases.

17.2E Esters

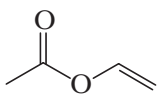
The names of esters are derived from the names of the alcohol (with the ending **-yl**) and the acid (with the ending **-ate** or **-oate**). The portion of the name derived from the alcohol comes first:



Ethyl acetate or ethyl ethanoate



***tert*-Butyl propanoate**



Vinyl acetate or ethenyl ethanoate

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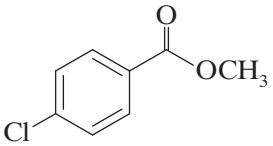
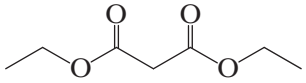


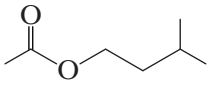
Methyl *p*-chlorobenzoate



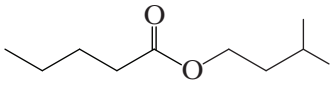
Diethyl malonate

Esters are polar compounds, but, lacking a hydrogen attached to oxygen, their molecules cannot form strong hydrogen bonds to each other. As a result, esters have boiling points that are lower than those of acids and alcohols of comparable molecular weight. The boiling points of esters are about the same as those of comparable aldehydes and ketones.

Unlike the low-molecular-weight acids, esters usually have pleasant odors, some resembling those of fruits, and these are used in the manufacture of synthetic flavors:



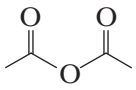
Isopentyl acetate
(used in synthetic banana flavor)



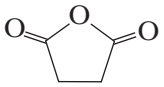
Isopentyl pentanoate
(used in synthetic apple flavor)

17.2F Carboxylic Anhydrides

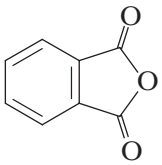
Most anhydrides are named by dropping the word **acid** from the name of the carboxylic acid and then adding the word **anhydride**:



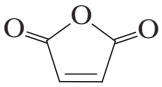
Acetic anhydride
(ethanoic anhydride)
mp –73 °C



Succinic anhydride
mp 121 °C



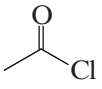
Phthalic anhydride
mp 131 °C



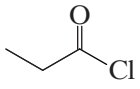
Maleic anhydride
mp 53 °C

17.2G Acyl Chlorides

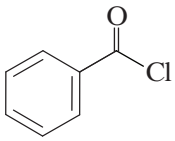
Acyl chlorides are also called **acid chlorides**. They are named by dropping **-ic acid** from the name of the acid and then adding **-yl chloride**. Examples are



Acetyl chloride
(ethanoyl chloride)
mp –112 °C; bp 51 °C



Propanoyl chloride
mp –94 °C; bp 80 °C



Benzoyl chloride
mp –1 °C; bp 197 °C

Acyl chlorides and carboxylic anhydrides have boiling points in the same range as esters of comparable molecular weight.

17.2H Amides

Amides that have no substituent on nitrogen are named by dropping **-ic acid** from the common name of the acid (or *-oic acid* from the substitutive name) and then adding **-amide**. Alkyl groups on the nitrogen atom of amides are named as substituents, and the named substituent is prefaced by *N*- or *N*,*N*-. Examples are

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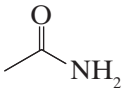
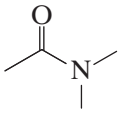
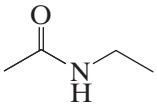


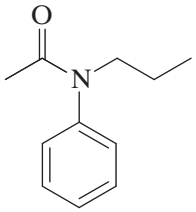
Acetamide (ethanamide) mp 82 °C; bp 221 °C



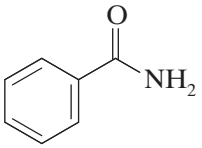
***N*,*N*-Dimethylacetamide mp –20 °C; bp 166 °C**



***N*-Ethylacetamide bp 205 °C**



***N*-Phenyl-*N*-propylacetamide mp 49 °C; bp 266 °C at 712 torr**



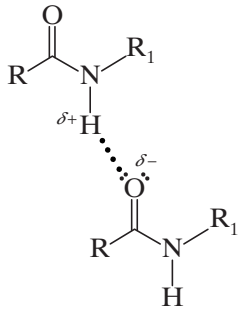
Benzamide mp 130 °C; bp 290 °C

- Amides with nitrogen atoms bearing one or two hydrogen atoms are able to form strong hydrogen bonds to each other.

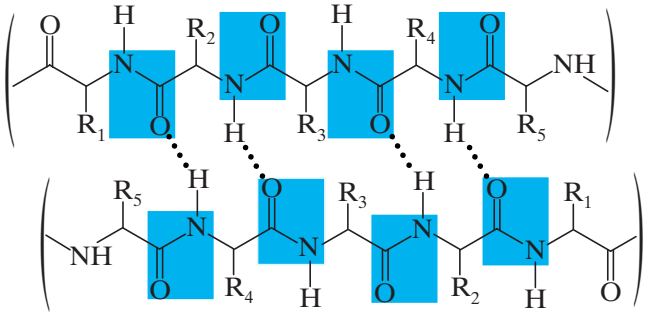
Such amides have high melting points and boiling points. On the other hand, molecules of *N*,*N*-disubstituted amides cannot form strong hydrogen bonds to each other, and they have lower melting points and boiling points. The melting and boiling data given above illustrate this trend.

- Hydrogen bonding between amide groups plays a key role in the way proteins and peptides fold to achieve their overall shape (Chapter 21).

Proteins and peptides (short proteins) are polymers of amino acids joined by amide groups. One feature common to the structure of many proteins is the β sheet, shown below:



Hydrogen bonding between amide molecules



Hydrogen bonding between amide groups of peptide chains. This interaction between chains (called a β sheet) is important to the structure of many proteins.

17.2I Nitriles

Carboxylic acids can be converted to nitriles and vice versa. In IUPAC substitutive nomenclature, acyclic nitriles are named by adding the suffix *-nitrile* to the name of the corresponding hydrocarbon. The carbon atom of the —C≡N group is assigned number 1. Additional examples of nitriles were presented in Section 2.10 with other functional groups of organic molecules. The name acetonitrile is an acceptable common name for CH_3CN, and acrylonitrile is an acceptable common name for $CH_2{=}CHCN$:



Ethanenitrile (acetonitrile)

Propenenitrile (acrylonitrile)

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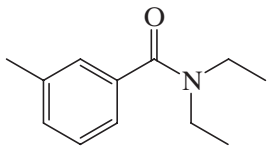
Solved Problem 17.3

N,*N*-Diethyl-3-methylbenzamide (also called *N*,*N*-diethyl-*m*-toluamide, or DEET) is used in many insect repellants. Write its structure.

Answer



DEET

Practice Problem 17.2

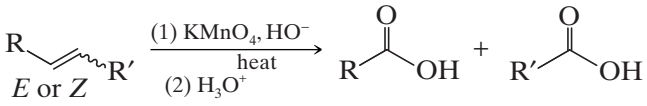
Write structural formulas for the following:

(a) Methyl propanoate
(b) Ethyl *p*-nitrobenzoate
(c) Dimethyl malonate
(d) *N*,*N*-Dimethylbenzamide
(e) Pentanenitrile
(f) Dimethyl phthalate
(g) Dipropyl maleate
(h) *N*,*N*-Dimethylformamide
(i) 2-Bromopropanoyl bromide
(j) Diethyl succinate

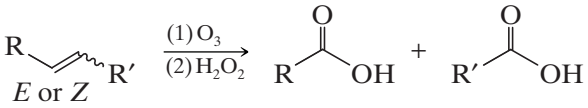
17.3 | PREPARATION OF CARBOXYLIC ACIDS

Most of the methods for the preparation of carboxylic acids have been presented previously:

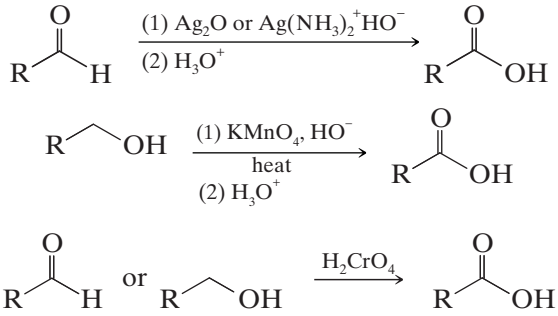
1. **By oxidation of alkenes.** We learned in Section 8.17A that alkenes can be oxidized to carboxylic acids with hot alkaline $KMnO_4$:



Alternatively, ozonides (Section 8.16B) can be subjected to an oxidative workup that yields carboxylic acids:



2. **By oxidation of aldehydes and primary alcohols.** Aldehydes can be oxidized to carboxylic acids with mild oxidizing agents such as $Ag(NH_3)_2^+HO^-$ (Section 15.12B). Primary alcohols can be oxidized with $KMnO_4$. Aldehydes and primary alcohols are oxidized to carboxylic acids with chromic acid (H_2CrO_4) in aqueous acetone (the Jones oxidation; Section 11.4C).



3. **By benzylic oxidation of alkylbenzenes.** Primary and secondary alkyl groups (but not 3° groups) directly attached to a benzene ring are oxidized by $KMnO_4$ to a $—CO_2H$ group (Section 14.13C):

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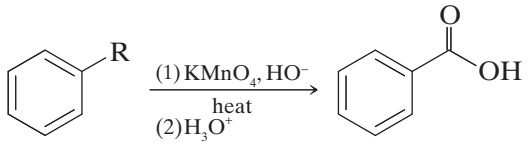
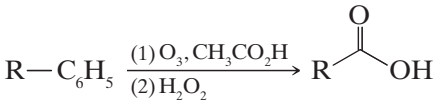
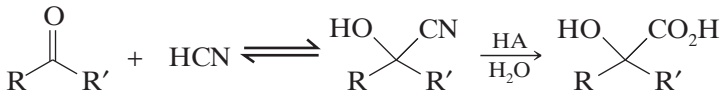


4. **By oxidation of the benzene ring.** The benzene ring of an alkylbenzene can be converted to a carboxyl group by ozonolysis, followed by treatment with hydrogen peroxide (Section 14.13D):

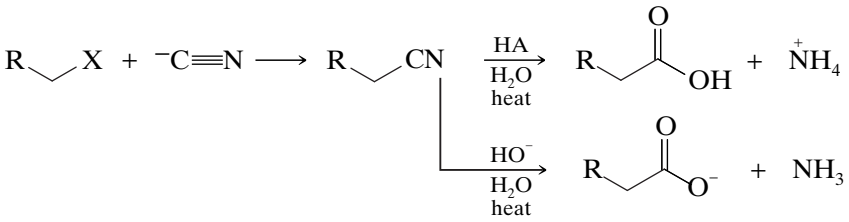


5. **By hydrolysis of cyanohydrins and other nitriles.** We saw, in Section 15.9, that aldehydes and ketones can be converted to **cyanohydrins** and that these can be hydrolyzed to α-hydroxy acids. In the hydrolysis the –CN group is converted to a $-CO_2H$ group. The mechanism of nitrile hydrolysis is discussed in Section 17.8H:

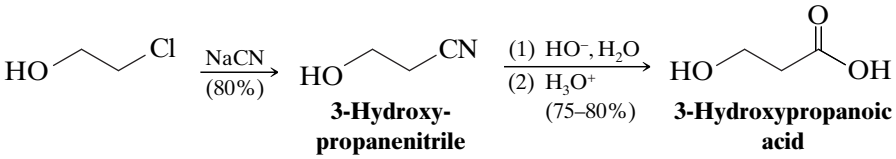


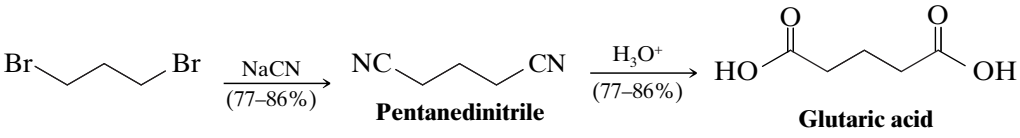
Nitriles can also be prepared by nucleophilic substitution reactions of alkyl halides with sodium cyanide. Hydrolysis of the nitrile yields a carboxylic acid *with a chain one carbon atom longer* than the original alkyl halide:

General Reaction



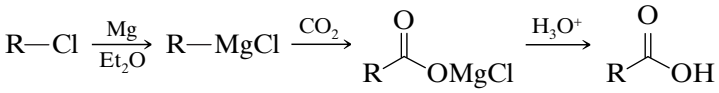
Specific Examples



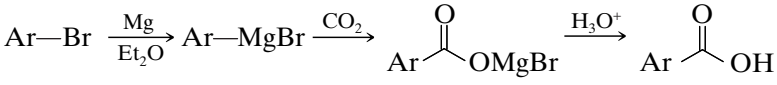


This synthetic method is generally limited to the use of *primary alkyl halides*. The cyanide ion is a relatively strong base, and the use of a secondary or tertiary alkyl halide leads primarily to an alkene (through E2 elimination) rather than to a nitrile (through S_N2 substitution). Aryl halides (except for those with ortho and para nitro groups) do not react with sodium cyanide.

6. **By carbonation of Grignard reagents.** Grignard reagents react with carbon dioxide to yield magnesium carboxylates. Acidification produces carboxylic acids:



or



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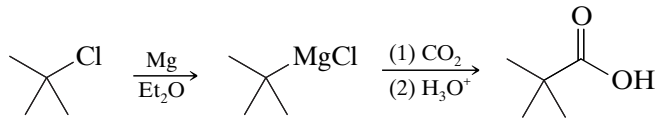
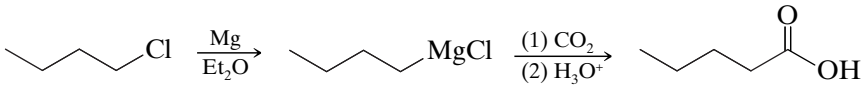
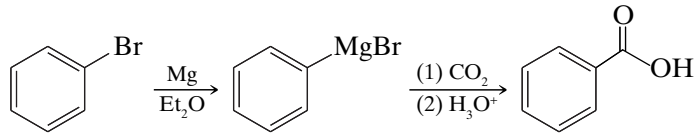
This synthesis of carboxylic acids is applicable to primary, secondary, tertiary, allyl, benzyl, and aryl halides, provided they have no groups incompatible with a Grignard reaction (see Section 12.8B):



***tert*-Butyl chloride** **2,2-Dimethylpropanoic acid (79–80% overall)**



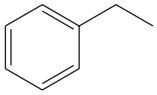
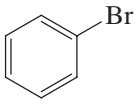
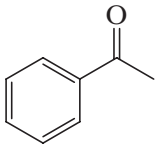
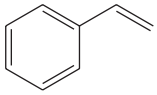
Butyl chloride **Pentanoic acid (80% overall)**



Bromobenzene **Benzoic acid (85%)**

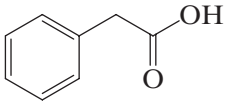
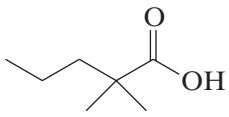
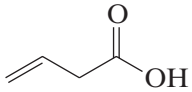
Practice Problem 17.3

Show how each of the following compounds could be converted to benzoic acid:

(a)  **(b)**  **(c)**  **(d)**  **(e)** Benzyl alcohol **(f)** Benzaldehyde

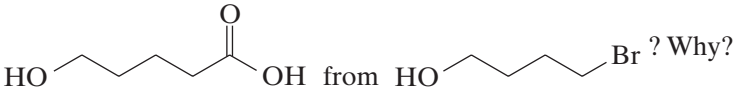
Practice Problem 17.4

Show how you would prepare each of the following carboxylic acids through a Grignard synthesis:

(a)  **(b)**  **(c)**  **(d)** 4-Methylbenzoic acid **(e)** Hexanoic acid

Practice Problem 17.5

(a) Which of the carboxylic acids in Practice Problem 17.4 could be prepared by a nitrile synthesis as well? **(b)** Which synthesis, Grignard or nitrile, would you choose to prepare



17.4 | ACYL SUBSTITUTION: NUCLEOPHILIC ADDITION–ELIMINATION AT THE ACYL CARBON

The reactions of carboxylic acids and their derivatives are characterized by **nucleophilic addition–elimination** at their acyl (carbonyl) carbon atoms. The result is a substitution at the acyl carbon. Key to this mechanism is formation of a **tetrahedral intermediate** that returns to a carbonyl group after the elimination of a leaving group. We shall encounter many reactions of this general type, as shown in the following box.

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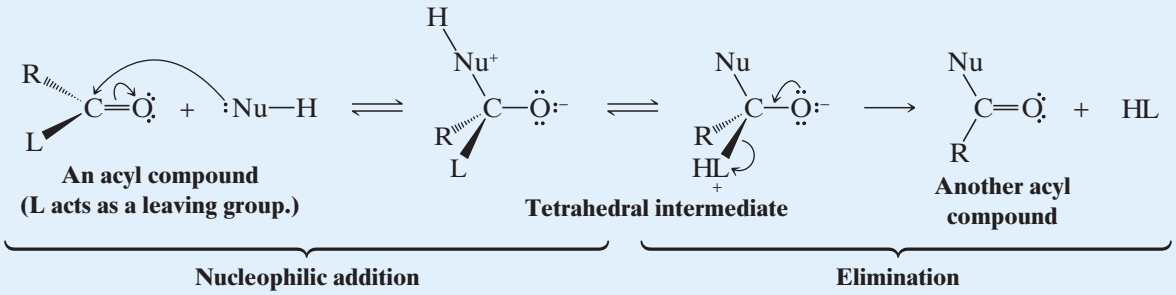
A MECHANISM FOR THE REACTION — Acyl Substitution by Nucleophilic Addition–Elimination



- The initial step in an acyl substitution reaction is nucleophilic addition at the carbonyl carbon atom. This step is facilitated by the relative steric openness of the carbonyl carbon atom and the ability of the carbonyl oxygen atom to accommodate an electron pair of the carbon–oxygen double bond.
- In the second step the tetrahedral intermediate eliminates a leaving group (**L** in the mechanism above); this **elimination** leads to regeneration of thecarbon–oxygen double bond and to a substitution product.

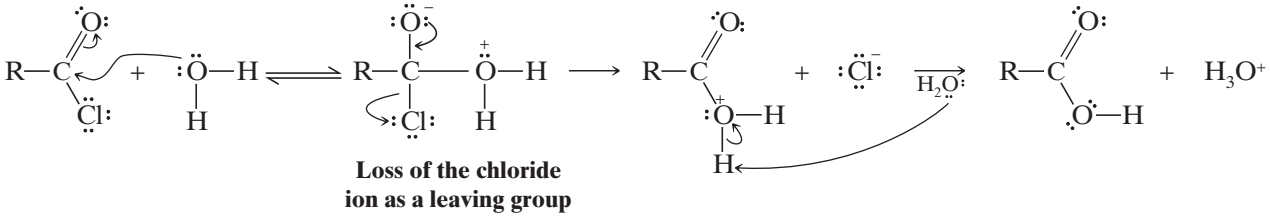
The overall process, therefore, is **acyl substitution** by a **nucleophilic addition–elimination** mechanism.

Acyl compounds react as they do because they all have good, or reasonably good, leaving groups (or they can be protonated to form good leaving groups) attached to the carbonyl carbon atom.

- Acyl substitution requires a leaving group at the carbonyl carbon.

An acyl chloride, for example, generally reacts by losing a *chloride ion*—a very weak base and thus a very good leaving group. The reaction of an acyl chloride with water is an example.

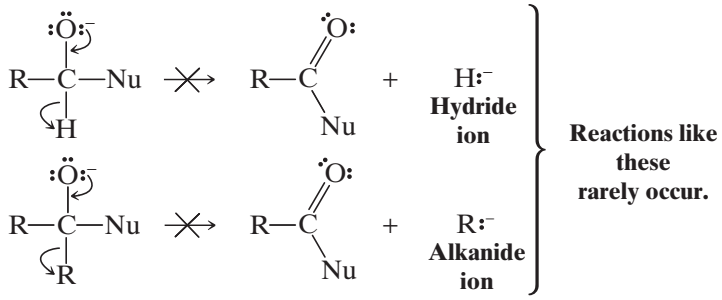
Specific Example



An acid anhydride generally reacts by losing *a carboxylate anion* or a molecule of a *carboxylic acid*—both are weak bases and good leaving groups.

As we shall see later, esters generally undergo nucleophilic addition–elimination by losing a molecule of an *alcohol* (Section 17.7B), acids react by losing a molecule of *water* (Section 17.7A), and amides react by losing a molecule of *ammonia* or of an *amine* (Section 17.8F). All of the molecules lost in these reactions are weak bases and are reasonably good leaving groups.

For an aldehyde or ketone to react by nucleophilic addition–elimination, the tetrahedral intermediate would need to eject a hydride ion ($H:^-$) or an alkanide ion ($R:^-$). Both are *very powerful bases*, and both are therefore *very poor leaving groups*:



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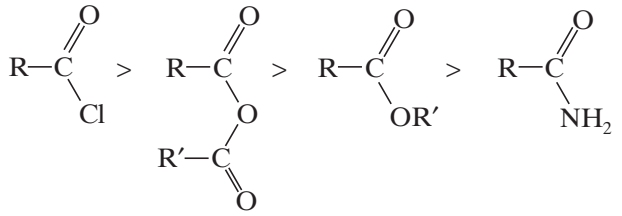
[The haloform reaction (Section 16.3C) is one of the rare instances in which an alkanide anion can act as a leaving group, but then only, as we shall see, because the leaving group is a weakly basic trihalomethyl anion.]

17.4A Relative Reactivity of Acyl Compounds

Of the acid derivatives that we study in this chapter, acyl chlorides are the most reactive toward nucleophilic addition–elimination, and amides are the least reactive. In general, the overall order of reactivity is



Acyl chloride **Acid anhydride** **Ester** **Amide**

The green groups in the structures above can be related to the green **L** group in the Mechanism for the Reaction box at the beginning of Section 17.4.

- The general order of reactivity of acid derivatives can be explained by taking into account the basicity of the leaving groups.

When acyl chlorides react, the leaving group is a *chloride ion*. When acid anhydrides react, the leaving group is a carboxylic acid or a carboxylate ion. When esters react, the leaving group is an alcohol, and when amides react, the leaving group is an amine (or ammonia). Of all of these bases, chloride ions are the *weakest bases* and acyl chlorides are the *most reactive* acyl compounds. Amines (or ammonia) are the *strongest bases* and so amides are the *least reactive* acyl compounds.

17.4B Synthesis of Acid Derivatives

As we begin now to explore the syntheses of carboxylic acid derivatives, we shall find that in many instances one acid derivative can be synthesized through a nucleophilic addition–elimination reaction of another. The order of reactivities that we have presented gives us a clue as to which syntheses are practical and which are not. In general, ***less reactive acyl compounds can be synthesized from more reactive ones, but the reverse is usually difficult and, when possible, requires special reagents.***

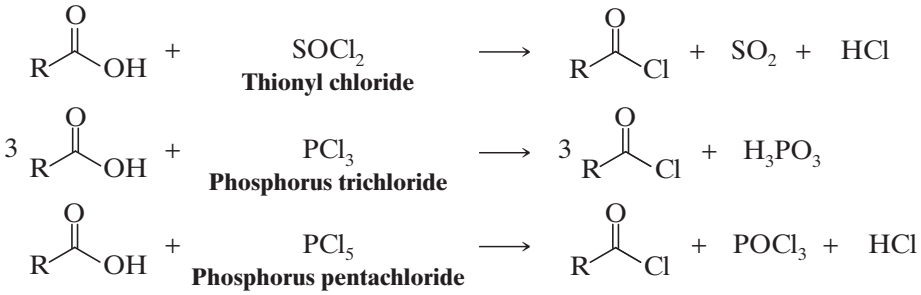
- Synthesis of acid derivatives by acyl substitution requires that the reactant have a better leaving group at the acyl carbon than the product.

17.5 | ACYL CHLORIDES

17.5A Synthesis of Acyl Chlorides

Since acyl chlorides are the most reactive of the acid derivatives, we must use special reagents to prepare them. We use other acid chlorides, *the acid chlorides of inorganic acids*: PCl_5 (an acid chloride of phosphoric acid), PCl_3 (an acid chloride of phosphorous acid), and $SOCl_2$ (an acid chloride of sulfurous acid). All of these reagents react with carboxylic acids to give acyl chlorides in good yield:

General Reactions



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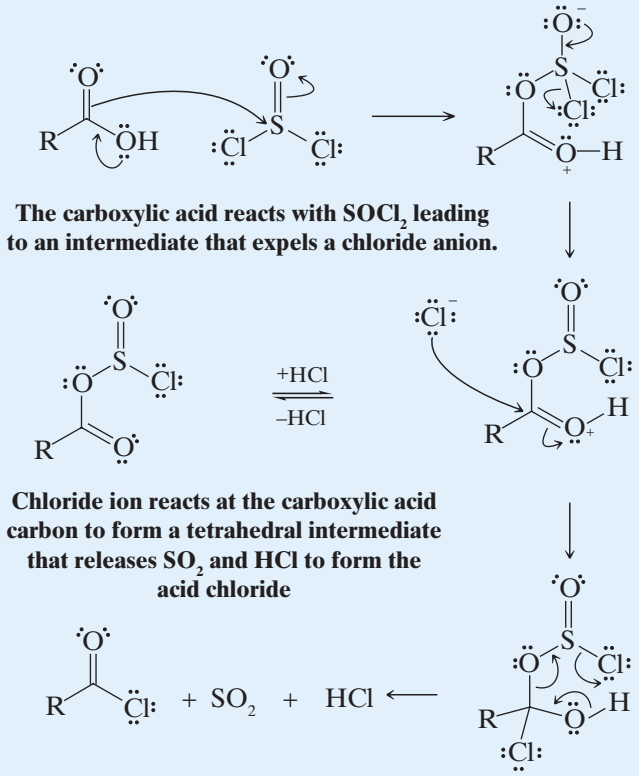
These reactions all involve nucleophilic addition–elimination by a chloride ion on a highly reactive intermediate: a protonated acyl chlorosulfite, a protonated acyl chlorophosphite, or a protonated acyl chlorophosphate. These intermediates contain even better acyl leaving groups than the acyl chloride product. Thionyl chloride, for example, reacts with a carboxylic acid in the following way:

A MECHANISM FOR THE REACTION — Synthesis of Acyl Chlorides Using Thionyl Chloride



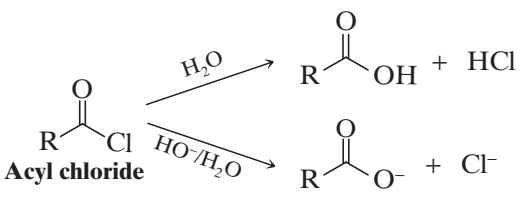
17.5B Reactions of Acyl Chlorides

Because acyl chlorides are the most reactive of the acyl derivatives, they are easily converted to less reactive ones.

- Often the best synthetic route to an anhydride, an ester, or an amide is synthesis of an acyl chloride from the carboxylic acid and then conversion of the acyl chloride to the desired acyl derivative.

The scheme given in Fig. 17.1 illustrates how this can be done. We examine these reactions in detail in Sections 17.6–17.8.

Acyl chlorides also react with water and (even more rapidly) with aqueous base, but these reactions are usually not carried out deliberately because they destroy the useful acyl chloride reactant by regenerating either the carboxylic acid or its salt:



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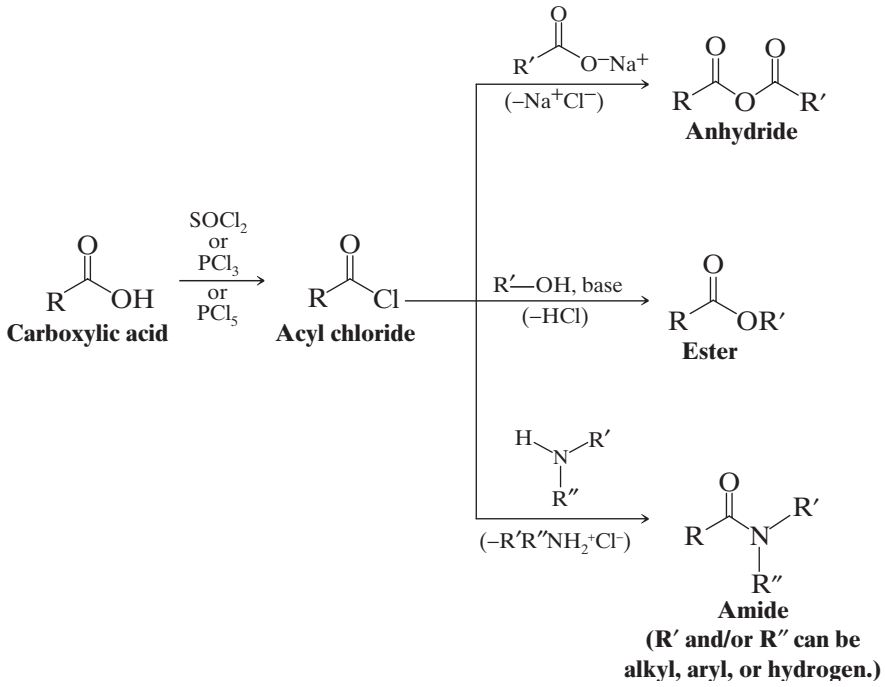
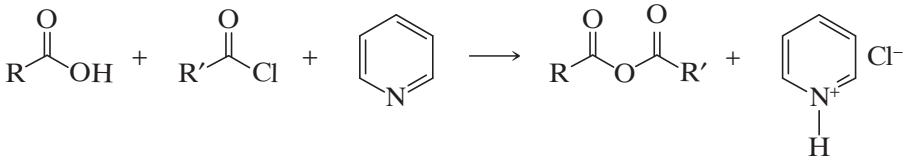


Figure 17.1 Preparation of an acyl chloride and reactions of acyl chlorides.

17.6 | CARBOXYLIC ACID ANHYDRIDES

17.6A Synthesis of Carboxylic Acid Anhydrides

Carboxylic acids react with acyl chlorides in the presence of pyridine to give carboxylic acid anhydrides. Pyridine deprotonates the carboxylic acid, enhancing its nucleophilicity.

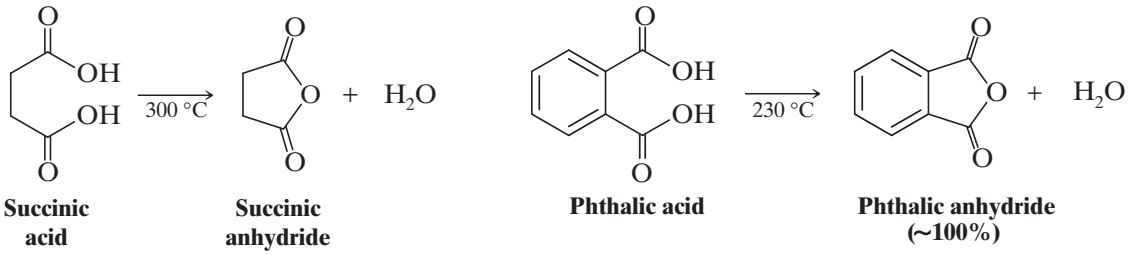


This method is frequently used in the laboratory for the preparation of anhydrides. The method is quite general and can be used to prepare mixed anhydrides ($R \neq R'$) or symmetric anhydrides ($R = R'$).

Sodium salts of carboxylic acids also react with acyl chlorides to give anhydrides:



Cyclic anhydrides can sometimes be prepared simply by heating the appropriate dicarboxylic acid. This method succeeds, however, only when anhydride formation leads to a five- or six-membered ring:



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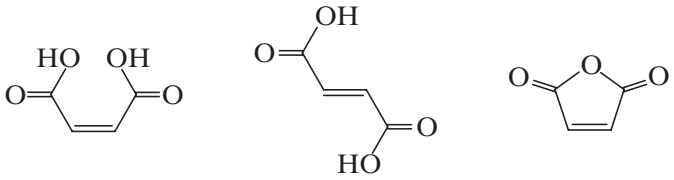
Practice Problem 17.6

When maleic acid is heated to 200 °C, it loses water and becomes maleic anhydride. Fumaric acid, a diastereomer of maleic acid, requires a much higher temperature before it dehydrates; when it does, it also yields maleic anhydride. Provide an explanation for these observations.



Maleic acid **Fumaric acid** **Maleic anhydride**

17.6B Reactions of Carboxylic Acid Anhydrides

Because carboxylic acid anhydrides are highly reactive, they can be used to prepare esters and amides (Fig. 17.2). We study these reactions in detail in Sections 17.7 and 17.8.

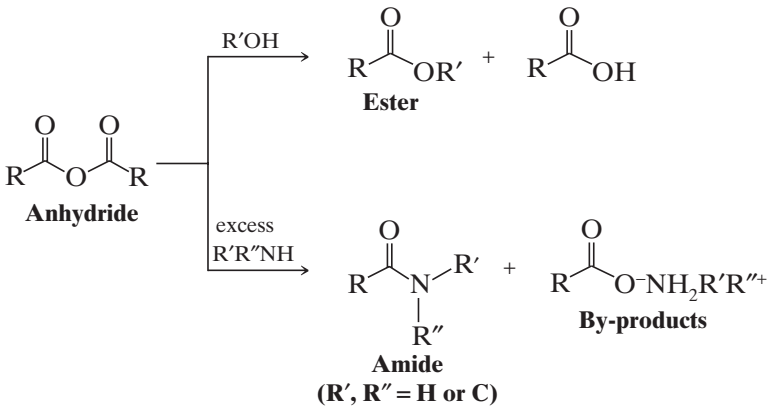
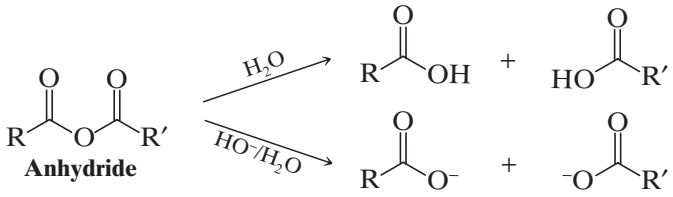


Figure 17.2 Reactions of carboxylic acid anhydrides.

Carboxylic acid anhydrides also undergo hydrolysis:

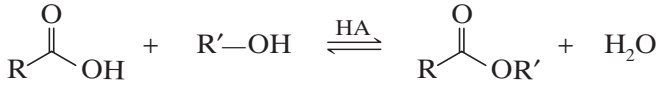


17.7 | ESTERS

17.7A Synthesis of Esters: Esterification

Carboxylic acids react with alcohols to form esters through a condensation reaction known as **esterification**:

General Reaction



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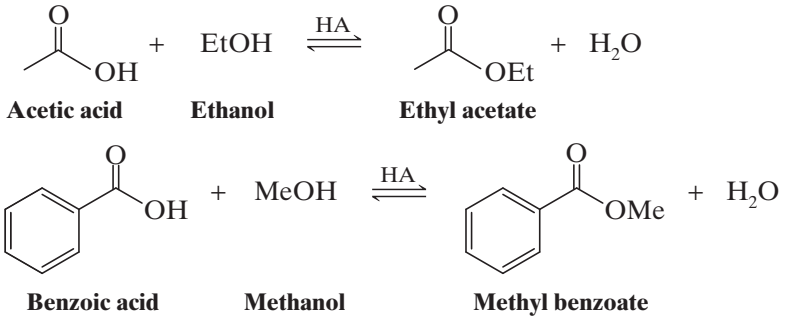
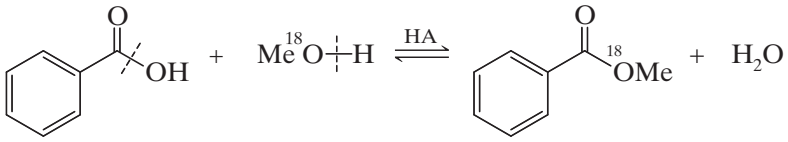
Specific Examples



- Acid-catalyzed esterifications, such as these examples, are called Fischer esterifications.

Fischer esterifications proceed very slowly in the absence of strong acids, but they reach equilibrium within a matter of a few hours when an acid and an alcohol are refluxed with a small amount of concentrated sulfuric acid or hydrogen chloride. Since the position of equilibrium controls the amount of the ester formed, the use of an excess of either the carboxylic acid or the alcohol increases the yield based on the limiting reagent. Just which component we choose to use in excess will depend on its availability and cost. The yield of an esterification reaction can also be increased by removing water from the reaction mixture as it is formed.

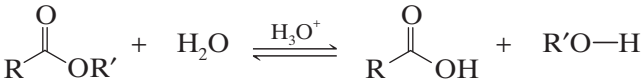
When benzoic acid reacts with methanol that has been labeled with ^{18}O, the labeled oxygen appears in the ester. This result reveals just which bonds break in the esterification:



The results of the labeling experiment and the fact that esterifications are acid catalyzed are both consistent with the mechanism that follows. This mechanism is typical of acid-catalyzed nucleophilic addition–elimination reactions at acyl carbon atoms.

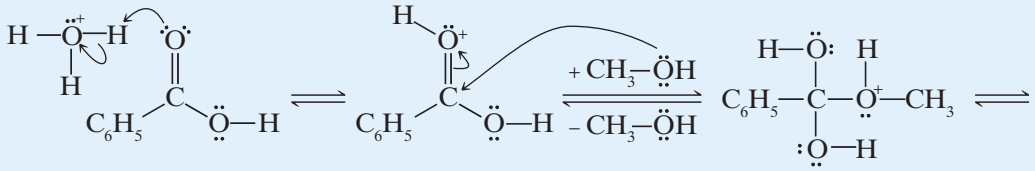
If we follow the forward reactions in this mechanism, we have the mechanism for the *acid-catalyzed esterification of an acid*. If, however, we follow the reverse reactions, we have the mechanism for the *acid-catalyzed hydrolysis of an ester*:

Acid-Catalyzed Ester Hydrolysis



Which result we obtain will depend on the conditions we choose. If we want to esterify an acid, we use an excess of the alcohol and, if possible, remove the water as it is formed. If we want to hydrolyze an ester, we use a large excess of water; that is, we reflux the ester with dilute aqueous HCl or dilute aqueous H_2SO_4.

A MECHANISM FOR THE REACTION — Acid-Catalyzed Esterification



The carboxylic acid accepts a proton from the strong acid catalyst.

The alcohol attacks the protonated carbonyl group to give a tetrahedral intermediate.

A proton is lost at one oxygen atom and gained at another.

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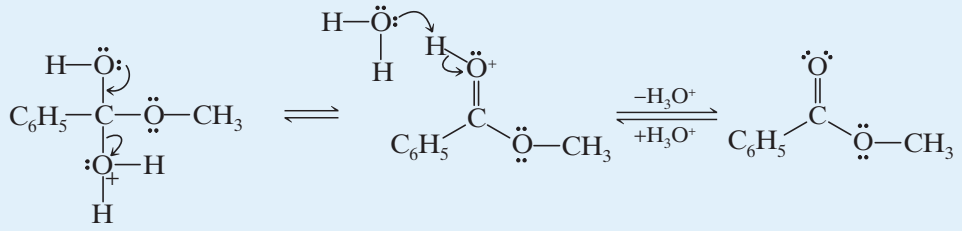


Practice Problem 17.7

Where would you expect to find the labeled oxygen if you carried out an acid-catalyzed hydrolysis of methyl benzoate in ^{18}O-labeled water? Write a detailed mechanism to support your answer.

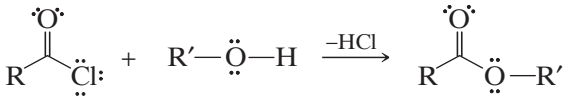
Steric factors strongly affect the rates of acid-catalyzed hydrolyses of esters. Large groups near the reaction site, whether in the alcohol component or the acid component, slow both reactions markedly. Tertiary alcohols, for example, react so slowly in acid-catalyzed esterifications that they usually undergo elimination instead. However, they can be converted to esters safely through the use of acyl chlorides and anhydrides in the ways that follow.

Esters from Acyl Chlorides

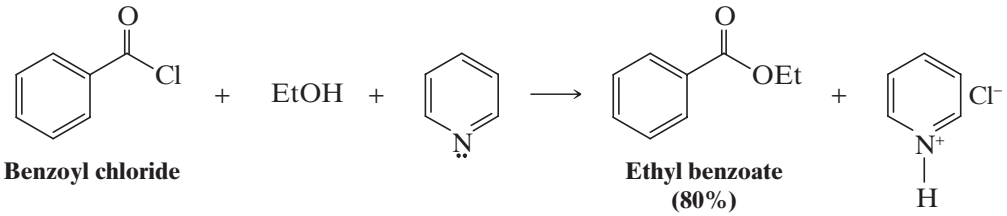
- The reaction of acyl chlorides with alcohols is one of the best ways to synthesize an ester.

The reaction of an acyl chloride with an alcohol to form an ester occurs rapidly and does not require an acid catalyst. Pyridine is often added to the reaction mixture to react with the HCl that forms. (Pyridine may also react with the acyl chloride to form an acylpyridinium ion, an intermediate that is even more reactive toward the nucleophile than the acyl chloride.)

General Reaction



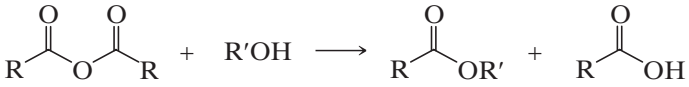
Specific Example



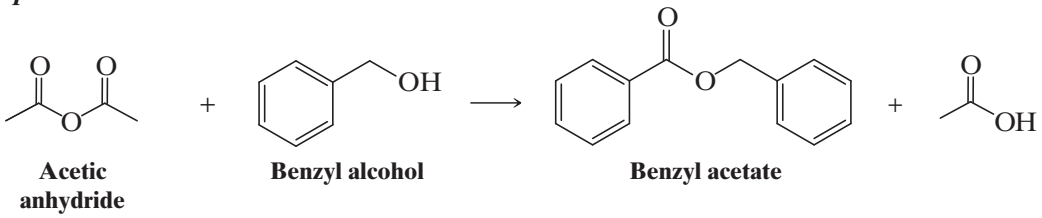
Esters from Carboxylic Acid Anhydrides

- Carboxylic acid anhydrides also react with alcohols to form esters in the absence of an acid catalyst.

General Reaction



Specific Example



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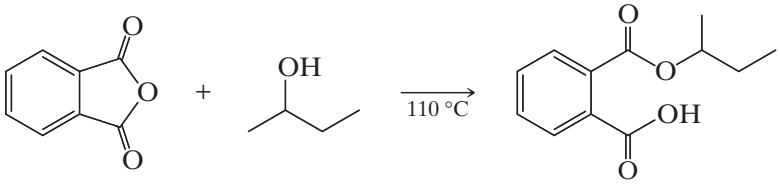
- Ester synthesis is often accomplished best by the reaction of an alcohol with an acyl chloride or anhydride. These reagents avoid the use of a strong acid, as is needed for acid-catalyzed esterification. A strong acid may cause side reactions depending on what other functional groups are present.

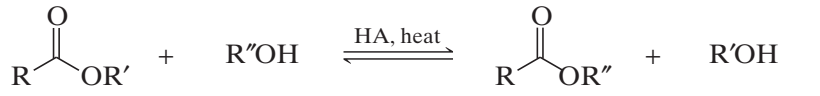
Cyclic anhydrides react with one molar equivalent of an alcohol to form compounds that are *both esters and acids*:



Phthalic anhydride **sec-Butyl alcohol** ***sec*-Butyl hydrogen phthalate (97%)**

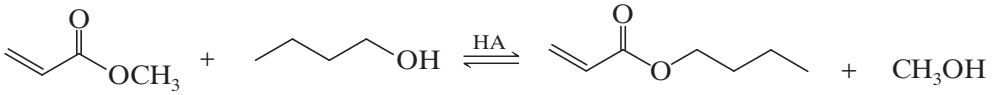
Practice Problem 17.8

Esters can also be synthesized by **transesterification**:



High-boiling ester **High-boiling alcohol** **Higher boiling ester** **Lower boiling alcohol**

In this procedure we shift the equilibrium to the right by allowing the low-boiling alcohol to distill from the reaction mixture. The mechanism for transesterification is similar to that for an acid-catalyzed esterification (or an acid-catalyzed ester hydrolysis). Write a detailed mechanism for the following transesterification:

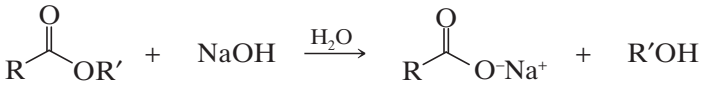


Methyl acrylate **Butyl alcohol** **Butyl acrylate (94%)** **Methanol**

17.7B Base-Promoted Hydrolysis of Esters: Saponification

- Esters undergo *base-promoted hydrolysis* as well as acid hydrolysis.

Base-promoted hydrolysis is called **saponification**, from the Latin word *sapo*, for soap. Refluxing an ester with aqueous sodium hydroxide, for example, produces an alcohol and the sodium salt of the acid:

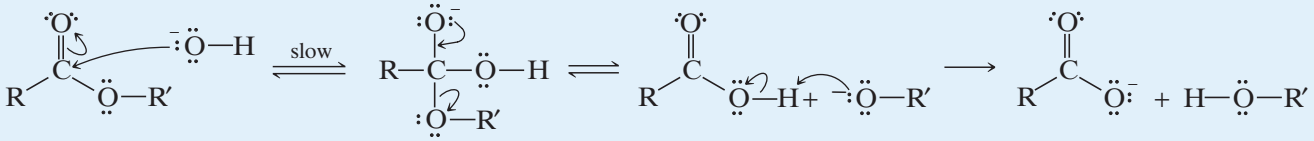


Ester **Sodium carboxylate** **Alcohol**

The carboxylate ion is very unreactive toward nucleophilic substitution because it is negatively charged. Base-promoted hydrolysis of an ester, as a result, is an essentially irreversible reaction.

The mechanism for base-promoted hydrolysis of an ester also involves a nucleophilic addition–elimination at the acyl carbon.

A MECHANISM FOR THE REACTION — Base-Promoted Hydrolysis of an Ester



A hydroxide ion attacks the carbonyl carbon atom. **The tetrahedral intermediate expels an alkoxide ion.** **Transfer of a proton leads to the products of the reaction.**

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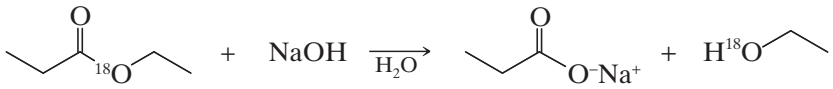
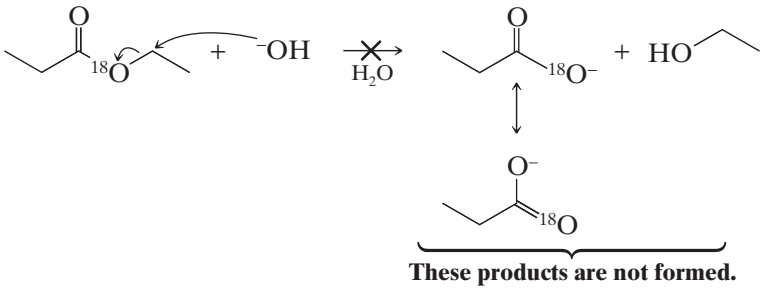
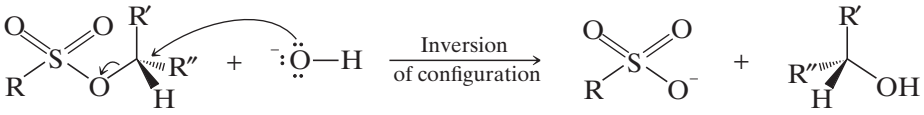
Evidence for this mechanism comes from studies done with isotopically labeled esters. When ethyl propanoate labeled with ^{18}O in the ether-type oxygen of the ester (below) is subjected to hydrolysis with aqueous NaOH, all of the ^{18}O shows up in the ethanol that is produced. None of the ^{18}O appears in the propanoate ion:



This labeling result is completely consistent with the mechanism given above (outline the steps for yourself and follow the labeled oxygen through to the products). If the hydroxide ion had attacked the alkyl carbon instead of the acyl carbon, the alcohol obtained would not have been labeled. Attack at the alkyl carbon is almost never observed.



Although nucleophilic attack at the alkyl carbon seldom occurs with esters of carboxylic acids, it is the preferred mode of attack with esters of sulfonic acids (e.g., tosylates, mesylates, and triflates; Section 10.9).

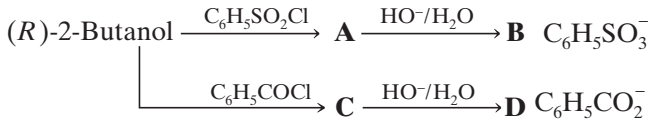


An alkyl sulfonate

This mechanism is preferred with alkyl sulfonates.

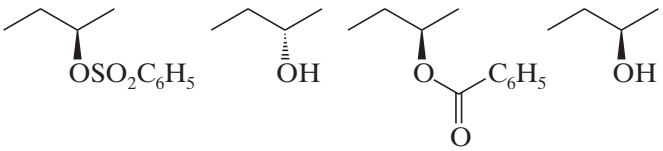
Solved Problem 17.4

Give stereochemical formulas for **A–D**. [*Hint*: **B** and **D** are enantiomers of each other.]



Answer

Compound **A** is a benzenesulfonate ester, which forms with retention of configuration from (*R*)-2-butanol. **B** is the S_N2 product formed by reaction with hydroxide, which occurs with **inversion** of configuration. **C** is a benzoate ester, formation of which does not affect the configuration at the chirality center. Saponification of **C** to form **D** does not affect the chirality center either, since it is an acyl substitution reaction.



A **B** **C** **D**

17.7C Lactones

Carboxylic acids whose molecules have a hydroxyl group on a γ or δ carbon undergo an intramolecular esterification to give cyclic esters known as γ- or δ-*lactones*. The reaction is acid catalyzed:

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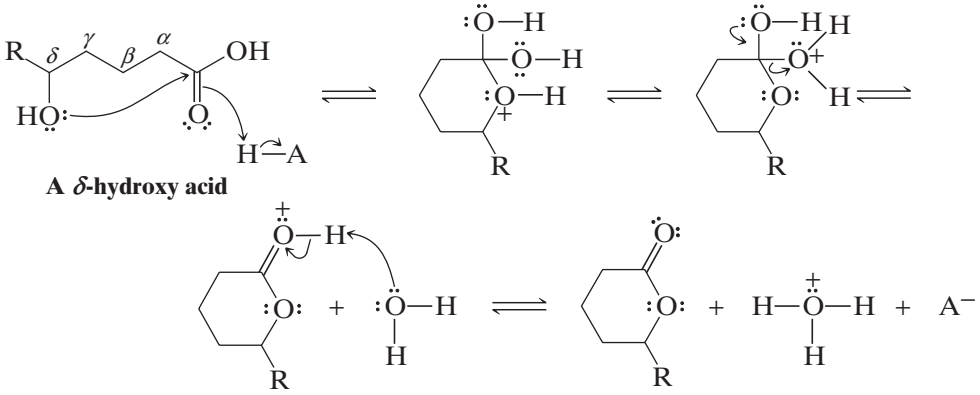
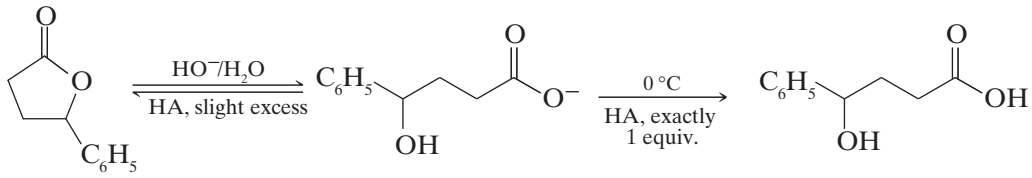


A δ-hydroxy acid

A δ-lactone

Lactones are hydrolyzed by aqueous base just as other esters are. Acidification of the sodium salt, however, may lead spontaneously back to the γ- or δ-lactone, particularly if excess acid is used:



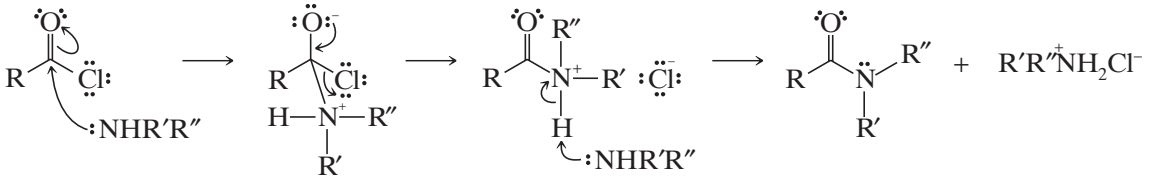
17.8 | AMIDES

17.8A Synthesis of Amides

Amides can be prepared in a variety of ways, starting with acyl chlorides, acid anhydrides, esters, carboxylic acids, and carboxylate salts. All of these methods involve nucleophilic addition–elimination reactions by ammonia or an amine at an acyl carbon. As we might expect, acid chlorides are the most reactive and carboxylate anions are the least.

17.8B Amides from Acyl Chlorides

Primary amines, secondary amines, and ammonia all react rapidly with acid chlorides to form amides. An excess of ammonia or amine is used to neutralize the HCl that would be formed otherwise:



Reactant
Ammonia; R′, R″ = H
1° Amine; R′ = H, R″ = alkyl, aryl
2° Amine; R′, R″ = alkyl, aryl

Product
Unsubstituted amide; R′, R″ = H
***N*-Substituted amide; R′ = H, R″ = alkyl, aryl**
***N*,*N*-Disubstituted amide; R′, R″ = alkyl, aryl**

- The reaction of an amine with an acyl chloride is one of the most widely used laboratory methods for the synthesis of amides, because acyl chlorides are themselves easily prepared from carboxylic acids.

The reaction between an acyl chloride and an amine (or ammonia) usually takes place at room temperature (or below) and produces the amide in high yield.

Acyl chlorides also react with tertiary amines by a nucleophilic addition–elimination reaction. The acylammonium ion that forms, however, is not stable in the presence of water or any hydroxylic solvent:

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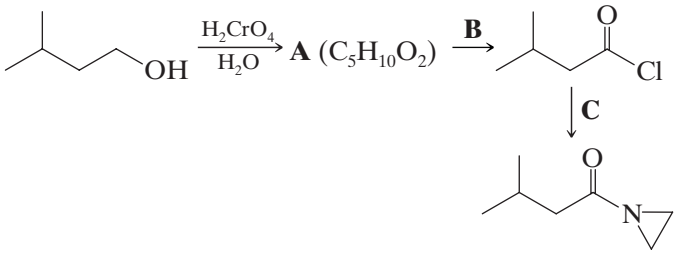
Acyl chloride **3° Amine** **Acylammonium chloride**

Acylpyridinium ions are probably involved as intermediates in those reactions of acyl chlorides that are carried out in the presence of pyridine.

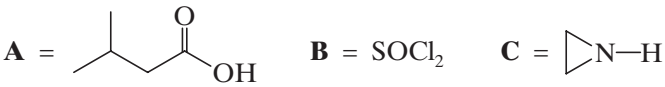
Solved Problem 17.5

Provide the missing compounds, **A**–**C**, in the following synthesis.



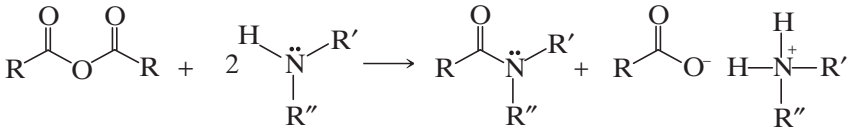
Answer

The first reaction is a chromic acid oxidation, leading to $C_5H_{10}O_2$, which is consistent with the carboxylic acid derived from 3-methyl-1-butanol. **B** must be a reagent by which we can prepare an acid chloride. The final product is an amide, thus **C** must be the appropriate amine. Compounds **A**–**C**, therefore, are as follows:



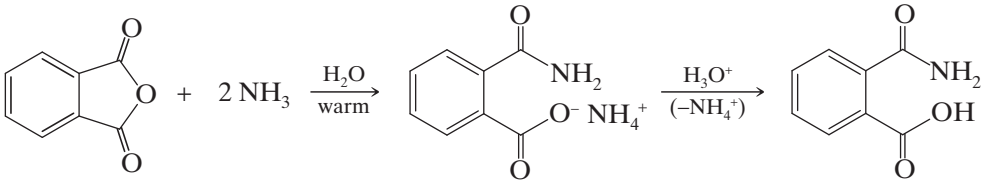
17.8C Amides from Carboxylic Anhydrides

Acid anhydrides react with ammonia and with primary and secondary amines to form amides through reactions that are analogous to those of acyl chlorides:



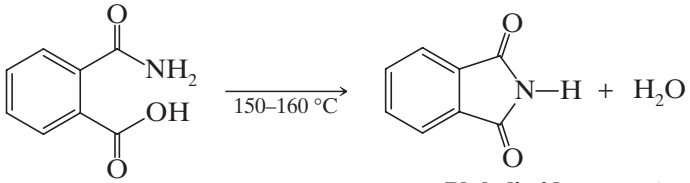
R′, R″ can be H, alkyl, or aryl.

Cyclic anhydrides react with ammonia or an amine in the same general way as acyclic anhydrides; however, the reaction yields a product that is both an amide and an ammonium salt. Acidifying the ammonium salt gives a compound that is both an amide and an acid:



Phthalic anhydride **Ammonium phthalamate (94%)** **Phthalamic acid (81%)**

Heating the amide acid causes dehydration to occur and gives an *imide*. Imides contain the linkage —C—NH—C—.



Phthalamic acid **Phthalimide (~100%)**

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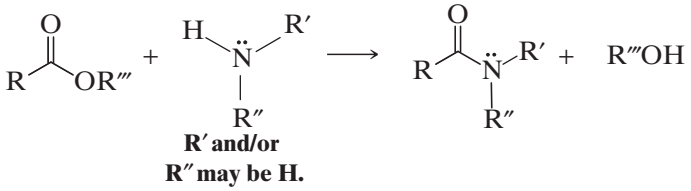
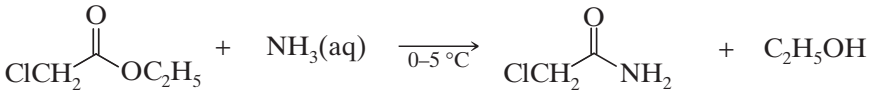
17.8D Amides from Esters

Esters undergo nucleophilic addition–elimination at their acyl carbon atoms when they are treated with ammonia (called *ammonolysis*) or with primary and secondary amines. These reactions take place much more slowly than those of acyl chlorides and anhydrides, but they can still be synthetically useful:



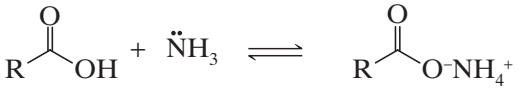
R′ and/or R″ may be H.



Ethyl chloroacetate **Chloroacetamide (62–87%)**

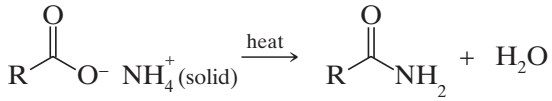
17.8E Amides from Carboxylic Acids and Ammonium Carboxylates

Carboxylic acids react with aqueous ammonia to form ammonium salts:



An ammonium carboxylate

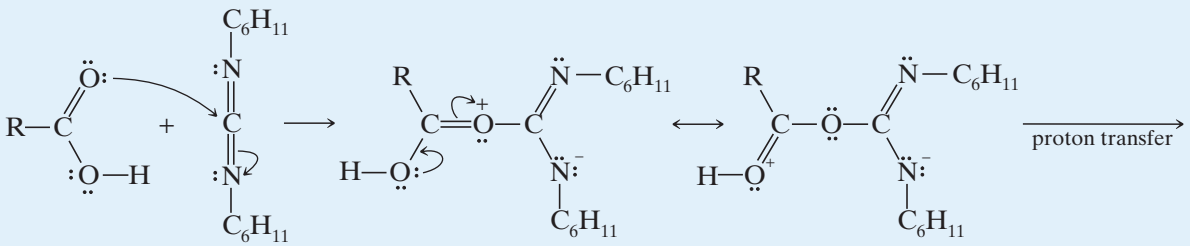
Because of the low reactivity of the carboxylate ion toward nucleophilic addition–elimination, further reaction does not usually take place in aqueous solution. However, if we evaporate the water and subsequently heat the dry salt, dehydration produces an amide:



This is generally a poor method for preparing amides. A much better method is to convert the acid to an acyl chloride and then treat the acyl chloride with ammonia or an amine (Section 17.8B).

Amides are of great importance in biochemistry. The linkages that join individual amino acids together to form proteins are primarily amide linkages. As a consequence, much research has been done to find convenient and mild ways for amide synthesis. Dialkylcarbodiimides (R—N═C═N—R), such as diisopropylcarbodiimide and dicyclohexylcarbodiimide (DCC), are especially useful reagents for amide synthesis. Dialkylcarbodiimides promote amide formation by reacting with the carboxyl group of an acid and activating it toward nucleophilic addition–elimination.

A MECHANISM FOR THE REACTION — DCC-Promoted Amide Synthesis



Dicyclohexylcarbodiimide (DCC)

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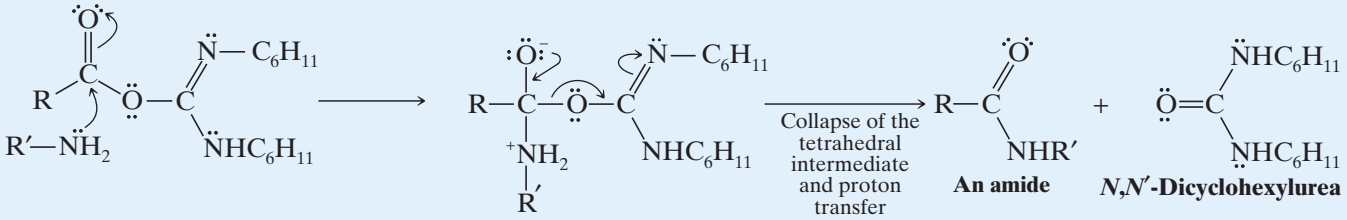
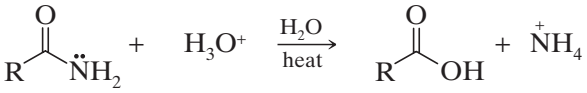


The intermediate in this synthesis does not need to be isolated, and both steps take place at room temperature. Amides are produced in very high yield.

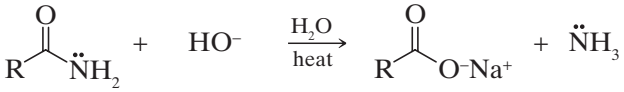
17.8F Hydrolysis of Amides

- Amides undergo hydrolysis when they are heated with aqueous acid or aqueous base.

Acidic Hydrolysis



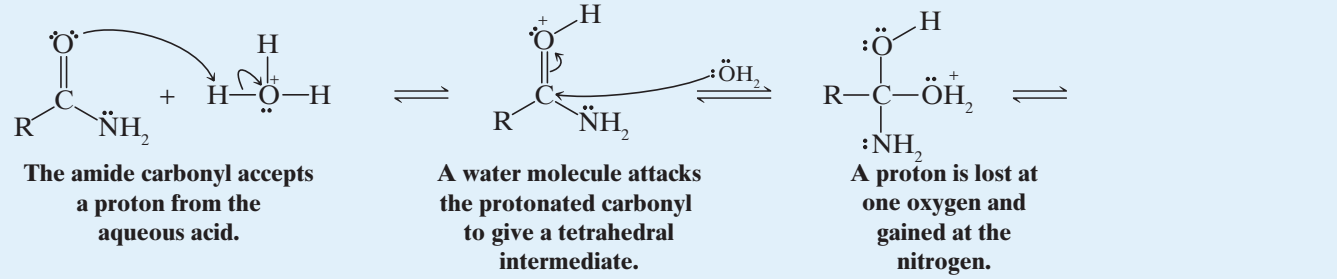
Basic Hydrolysis



N-Substituted amides and *N*,*N*-disubstituted amides also undergo hydrolysis in aqueous acid or base. Amide hydrolysis by either method takes place more slowly than the corresponding hydrolysis of an ester. Thus, amide hydrolyses generally require the forcing conditions of heat and strong acid or base.

The mechanism for acid hydrolysis of an amide is similar to that given in Section 17.7A for the acid hydrolysis of an ester. Water acts as a nucleophile and attacks the protonated amide. The leaving group in the acidic hydrolysis of an amide is ammonia (or an amine).

A MECHANISM FOR THE REACTION — Acidic Hydrolysis of an Amide



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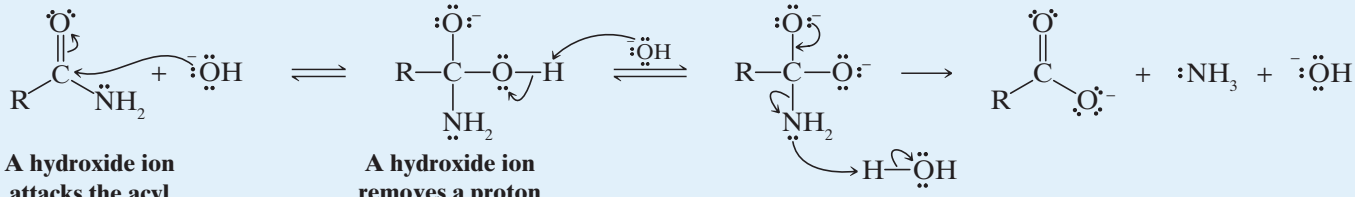
There is evidence that in basic hydrolyses of amides, hydroxide ions act both as nucleophiles and as bases.

A MECHANISM FOR THE REACTION — Basic Hydrolysis of an Amide



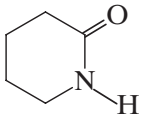
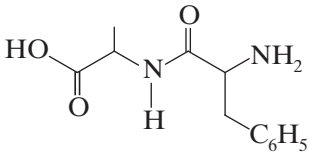
A hydroxide ion attacks the acyl carbon of the amide.

A hydroxide ion removes a proton to give a dianion.

The dianion loses a molecule of ammonia (or an amine); this step is synchronized with a proton transfer from water due to the basicity of NH_2^-.

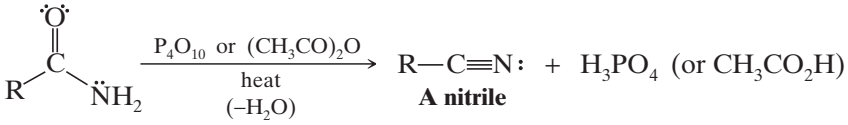
Practice Problem 17.9

What products would you obtain from acidic and basic hydrolysis of each of the following amides?

(a) *N*,*N*-Diethylbenzamide **(b)**  **(c)**  (a dipeptide)

17.8G Nitriles from the Dehydration of Amides

Amides react with P_4O_{10} (a compound that is often called phosphorus pentoxide and written P_2O_5) or with boiling acetic anhydride to form nitriles:



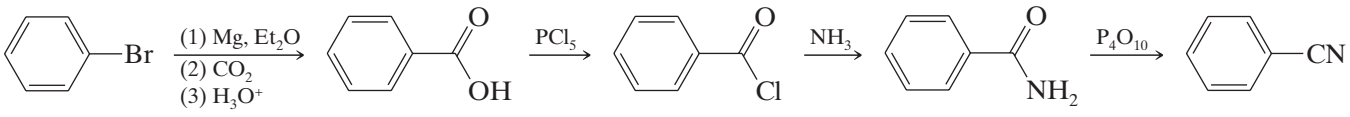
A nitrile

This is a useful synthetic method for preparing nitriles that are not available by nucleophilic substitution reactions between alkyl halides and cyanide ion.

Solved Problem 17.6

At first glance the conversion of bromobenzene to benzenenitrile looks simple—just carry out a nucleophilic substitution using cyanide ion as the nucleophile. Then we remember that bromobenzene does not undergo either an S_N1 or an S_N2 reaction (Section 6.14A). The conversion can be accomplished, however, though it involves several steps. Outline possible steps.

Answer



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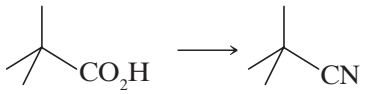
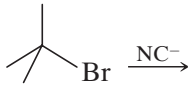
Practice Problem 17.10

(a) Provide the reagents required to accomplish the following transformation.

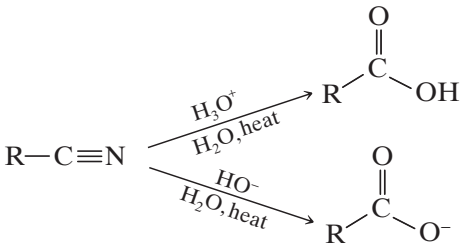


(b) What product would you likely obtain if you attempted to synthesize the nitrile above by the following method?



17.8H Hydrolysis of Nitriles

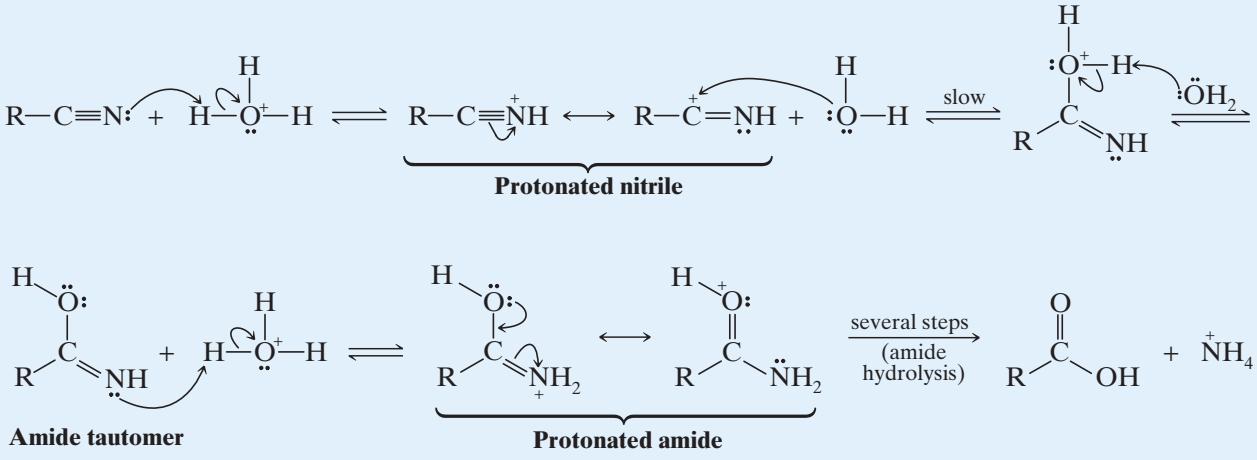
- Nitriles are related to carboxylic acids because complete hydrolysis of a nitrile produces a carboxylic acid or a carboxylate anion (Sections 15.9 and 17.3):



The mechanisms for these hydrolyses are related to those for the acidic and basic hydrolyses of amides.

In **acidic hydrolysis** of a nitrile the first step is protonation of the nitrogen atom. This protonation (in the following sequence) enhances polarization of the nitrile group and makes the carbon atom more susceptible to nucleophilic attack by the weak nucleophile, water. The loss of a proton from the oxygen atom then produces a tautomeric form of an amide. Gain of a proton at the nitrogen atom gives a **protonated amide**, and from this point on the steps are the same as those given for the acidic hydrolysis of an amide in Section 17.8F. (In concentrated H_2SO_4 the reaction stops at the protonated amide, and this is a useful way of making amides from nitriles.)

A MECHANISM FOR THE REACTION — Acidic Hydrolysis of a Nitrile



In **basic hydrolysis**, a hydroxide ion attacks the nitrile carbon atom, and subsequent protonation leads to the amide tautomer. Further attack by the hydroxide ion leads to hydrolysis in a manner analogous to that for the basic hydrolysis of an amide (Section 17.8F). (Under the appropriate conditions, amides can be isolated when nitriles are hydrolyzed.)

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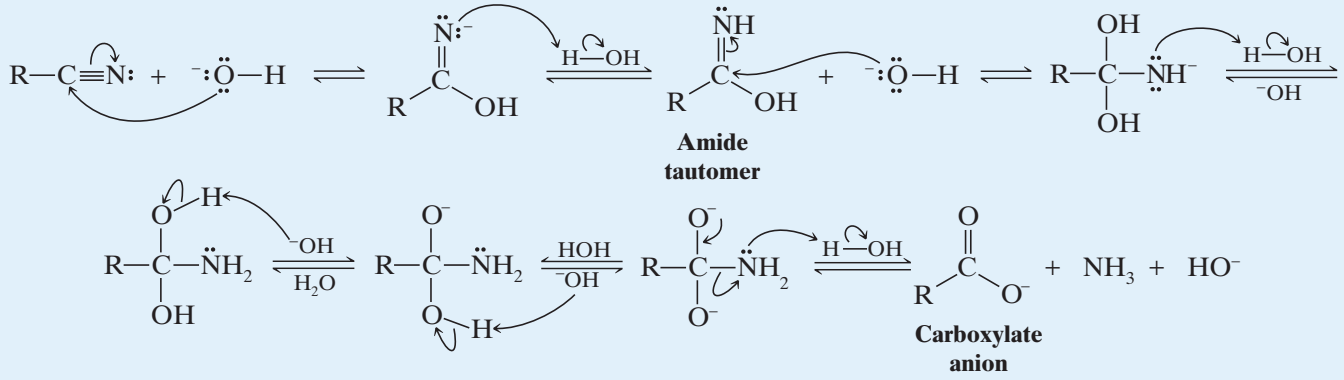
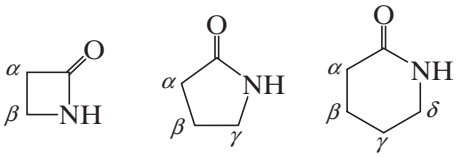
A MECHANISM FOR THE REACTION — Basic Hydrolysis of a Nitrile



17.8I Lactams

Cyclic amides are called **lactams**. The size of the lactam ring is designated by Greek letters in a way that is analogous to lactone nomenclature (Section 17.7C):

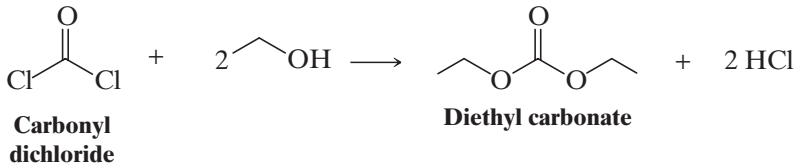


γ-Lactams and δ-lactams often form spontaneously from γ- and δ-amino acids. β-Lactams, however, are highly reactive; their strained four-membered rings open easily in the presence of nucleophilic reagents.

17.9 | DERIVATIVES OF CARBONIC ACID

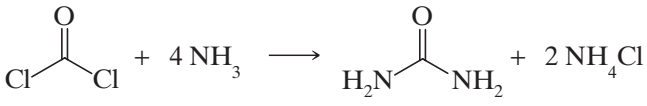
Carbonic acid, HO–C(=O)–OH, is an unstable compound that decomposes spontaneously to produce carbon dioxide and water and, therefore, cannot be isolated. However, many acyl chlorides, esters, and amides that are derived from carbonic acid are stable compounds that have important applications.

Carbonyl dichloride (ClCOCl), a highly toxic compound that is also called *phosgene*, can be thought of as the diacyl chloride of carbonic acid. Carbonyl dichloride reacts by nucleophilic addition–elimination with two molar equivalents of an alcohol to yield a **dialkyl carbonate**:



A tertiary amine is usually added to the reaction to neutralize the hydrogen chloride that is produced.

Carbonyl dichloride reacts with ammonia to yield **urea**



Urea is the end product of the metabolism of nitrogen-containing compounds in most mammals and is excreted in the urine.

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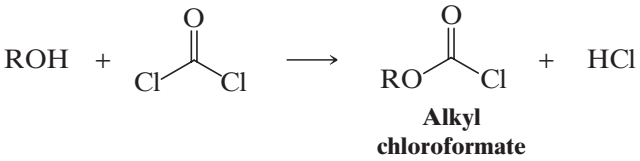
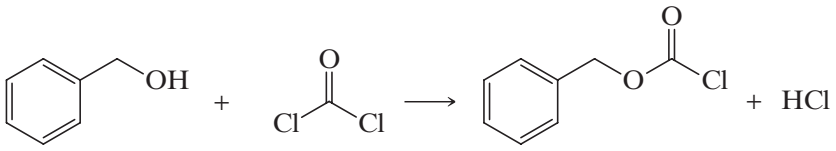
17.9A Alkyl Chloroformates and Carbamates (Urethanes)

Treating carbonyl dichloride with one molar equivalent of an alcohol leads to the formation of an alkyl chloroformate:



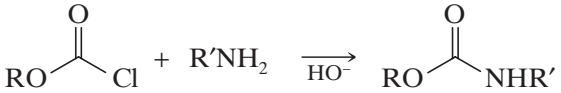
Alkyl chloroformate

Specific Example



Benzyl chloroformate

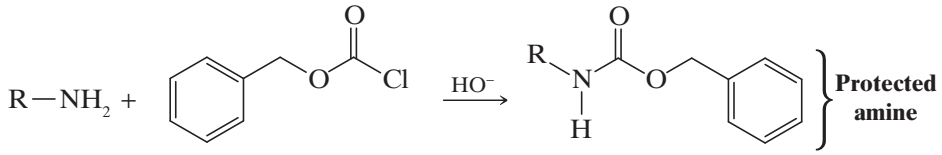
Alkyl chloroformates react with ammonia or amines to yield compounds called *carbamates* or *urethanes*:



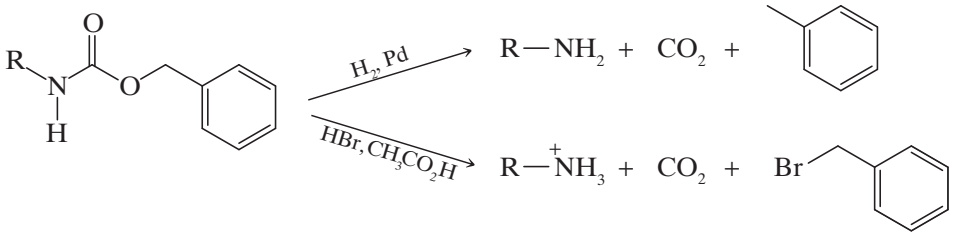
A carbamate (or urethane)

Benzyl chloroformate is used to install an amino protecting (blocking) group called the benzyloxycarbonyl group. One advantage of the benzyloxycarbonyl group is that it can be removed under mild conditions. Treating the benzyloxycarbonyl derivative with hydrogen and a catalyst or with cold HBr in acetic acid removes the protecting group:

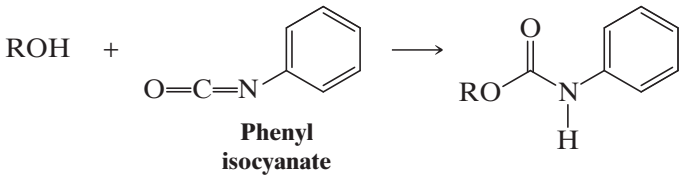
Protection



Deprotection



Carbamates can also be synthesized by allowing an alcohol to react with an isocyanate, R—N=C=O. (Carbamates tend to be nicely crystalline solids and are useful derivatives for identifying alcohols.) The reaction is an example of nucleophilic addition to the acyl carbon:



Phenyl isocyanate

The insecticide called *Sevin* is a carbamate made by allowing 1-naphthol to react with methyl isocyanate:

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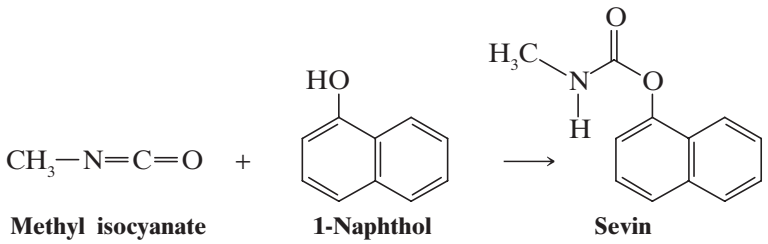


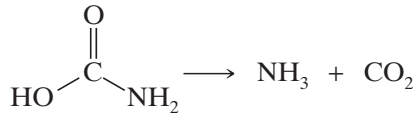
Methyl isocyanate **1-Naphthol** **Sevin**

A tragic accident that occurred at Bhopal, India, in 1984 was caused by leakage of methyl isocyanate from a manufacturing plant. Methyl isocyanate is a highly toxic gas, and more than 1800 people living near the plant lost their lives.

Although alkyl chloroformates (ROCOCl), dialkyl carbonates (ROCOOR), and carbamates ($ROCONH_2$, ROCONHR, etc.) are stable, chloroformic acid (HOCOCl), alkyl hydrogen carbonates (ROCOOH), and carbamic acid ($HOCONH_2$) are not. These latter compounds decompose spontaneously to liberate carbon dioxide:

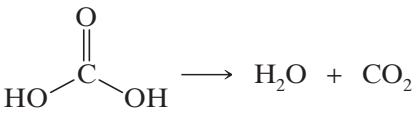


Chloroformic acid (unstable) **An alkyl hydrogen carbonate (unstable)**



A carbamic acid (unstable)

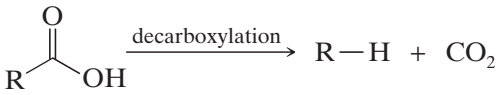
This instability is a characteristic that these compounds share with their functional parent, carbonic acid:



Carbonic acid (unstable)

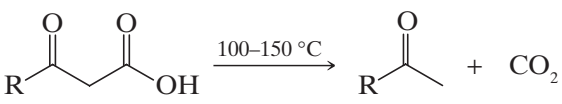
17.10 | DECARBOXYLATION OF CARBOXYLIC ACIDS

The reaction whereby a carboxylic acid loses CO_2 is called a **decarboxylation**:



Although the unusual stability of carbon dioxide means that decarboxylation of most acids is exothermic, in practice the reaction is not always easy to carry out because the reaction is very slow. Special groups usually have to be present in the molecule for decarboxylation to be rapid enough to be synthetically useful.

- Carboxylic acids that have a carbonyl group one carbon removed from the carboxylic acid group, called **β-keto acids**, decarboxylate readily when they are heated to 100–150 °C. Some β-keto acids even decarboxylate slowly at room temperature.



A β-keto acid

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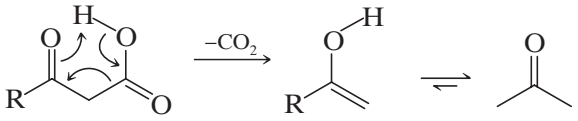
There are two reasons for this ease of decarboxylation:

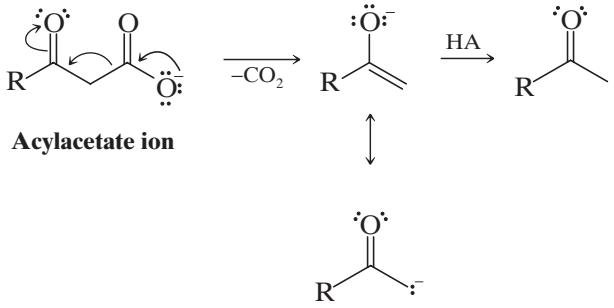
1. When the acid itself decarboxylates, it can do so through a six-membered cyclic transition state:



β-Keto acid **Enol** **Ketone**

This reaction produces an enol (alk**en**e-alcoh**ol**) directly and avoids an anionic intermediate. The enol then tautomerizes to a methyl ketone.

2. When the carboxylate anion decarboxylates, it forms a resonance-stabilized anion:



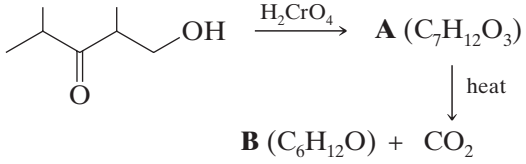
Acylacetate ion

Resonance-stabilized anion

This type of anion is much more stable than simply $RCH_2:^-$, the anion that would have been produced by decarboxylation in the absence of a β-carbonyl group. It is known as an enolate.

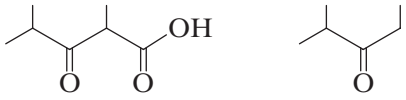
Solved Problem 17.7

Provide structures for **A** and **B**.



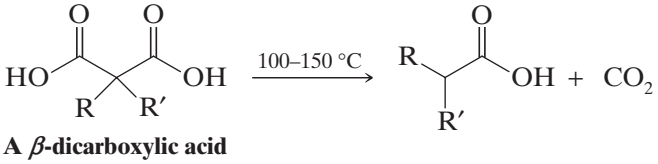
Answer

H_2CrO_4 oxidizes a primary alcohol to a carboxylic acid, which is consistent with the formula provided for **A**. Because **A** is a β-ketocarboxylic acid, it decarboxylates on heating to form **B**.



A **B**

β-Dicarboxylic acids (1,3-dicarboxylic acids, also called malonic acids) decarboxylate readily for reasons similar to β-keto acids.



A β-dicarboxylic acid

β-Dicarboxylic acids undergo decarboxylation so readily that they do not form cyclic anhydrides (Section 17.6A).

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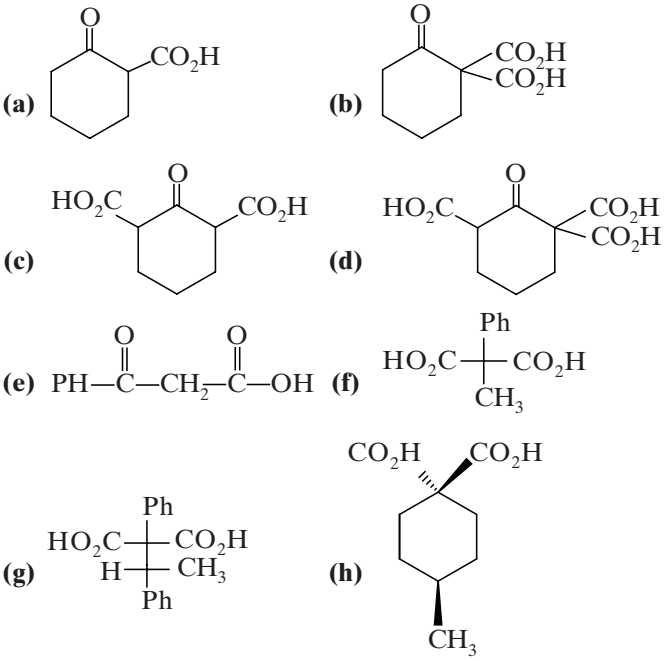
17.10A Decarboxylation of Carboxyl Radicals

Although the carboxylate ions (RCO_2^-) of simple aliphatic acids do not decarboxylate readily, carboxyl radicals ($RCO_2\cdot$) do. They decarboxylate by losing CO_2 and producing alkyl radicals:

$$RCO_2\cdot \longrightarrow R\cdot + CO_2$$

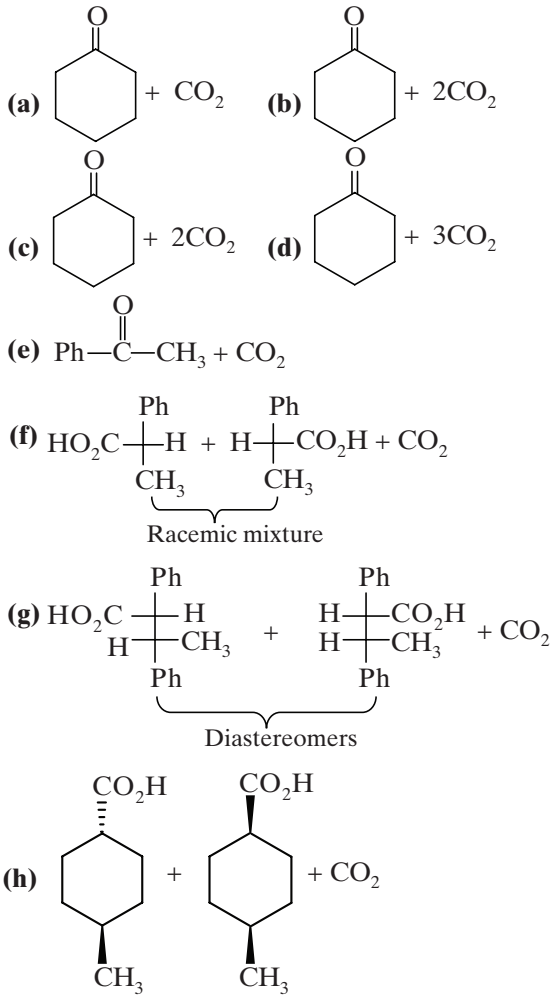
Solved Problem 17.8

Identify the product obtained when following acids undergo prolonged heating.



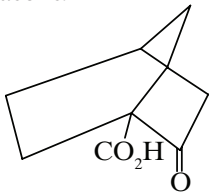
Answer

The products obtained prolonged heating of the given acids are as follows:



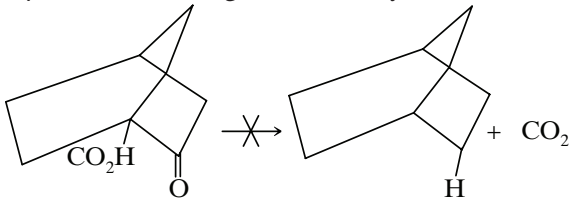
Solved Problem 17.9

Following β-ketoacid will not undergo decarboxylation on heating. Give reasons.



Answer

The carbon at bridge head position cannot be sp^2 hybridized according to Bredt's rule. This rule is violated if the given β-ketoacid undergoes decarboxylation on heating.



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Practice Problem 17.11

Using decarboxylation reactions, outline a synthesis of each of the following from appropriate starting materials:

(a) 2-Hexanone
(b) 2-Methylbutanoic acid
(c) Cyclohexanone
(d) Pentanoic acid

17.11 | CHEMICAL TESTS FOR ACYL COMPOUNDS

Carboxylic acids are weak acids, and their acidity helps us to detect them. Aqueous solutions of water-soluble carboxylic acids give an acid test with blue litmus paper. Water insoluble carboxylic acids dissolve in aqueous sodium hydroxide and aqueous sodium bicarbonate. The latter reagent helps us distinguish carboxylic acids from most phenols. Except for the di- and trinitrophenols, phenols do not dissolve in aqueous sodium bicarbonate.

When carboxylic acids dissolve in aqueous sodium bicarbonate, they also cause the evolution of carbon dioxide.

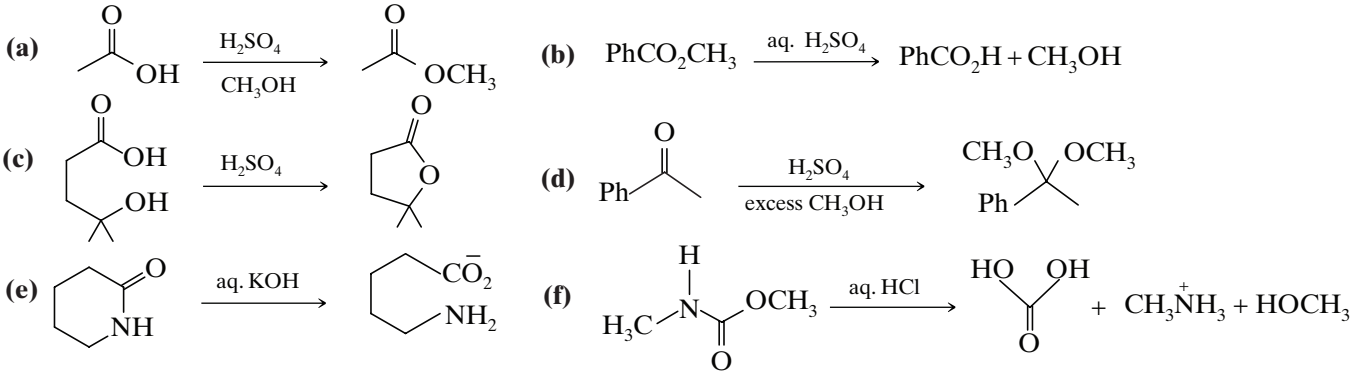
Acyl chlorides hydrolyze in water, and the resulting chloride ion gives a precipitate when treated with aqueous silver nitrate. Acid anhydrides dissolve when heated briefly with aqueous sodium hydroxide.

Esters and amides hydrolyze slowly when they are refluxed with sodium hydroxide. An ester produces a carboxylate anion and an alcohol; an amide produces a carboxylate anion and an amine or ammonia. The hydrolysis products, the acid and the alcohol or amine, can be isolated and identified. Since base-promoted hydrolysis of an unsubstituted amide produces ammonia, this ammonia can often be detected by holding moist red litmus paper in the vapors above the reaction mixture.

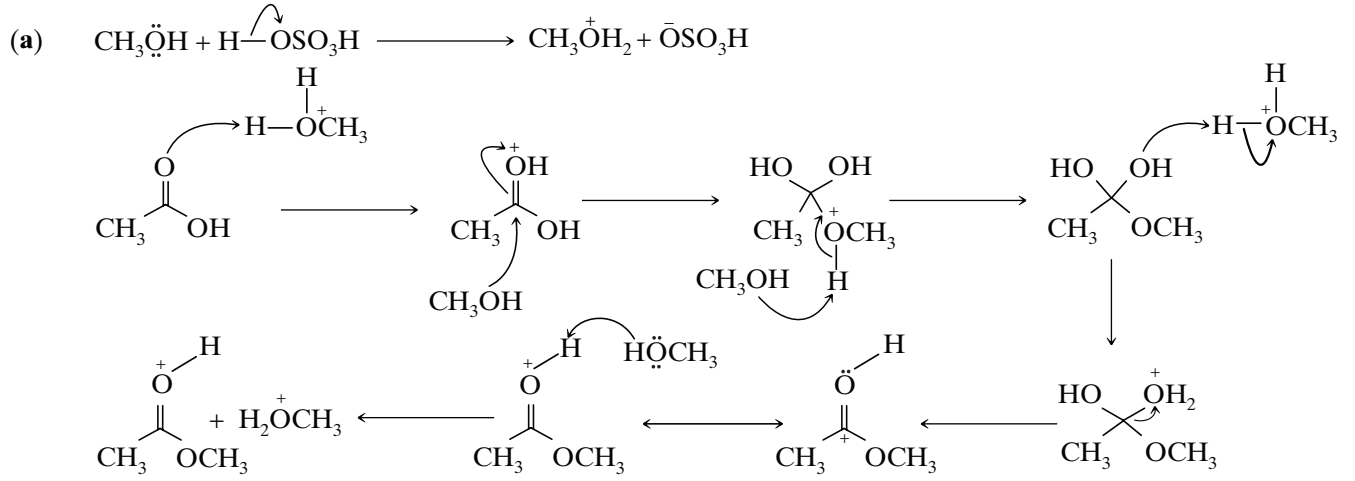
Amides can be distinguished from amines with dilute HCl. Most amines dissolve in dilute HCl, whereas most amides do not.

Solved Problem 17.10

Provide detailed curved arrow mechanisms for the following reactions:



Answer



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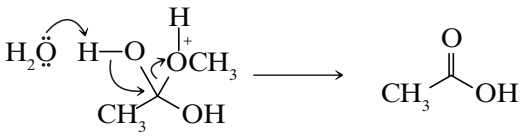
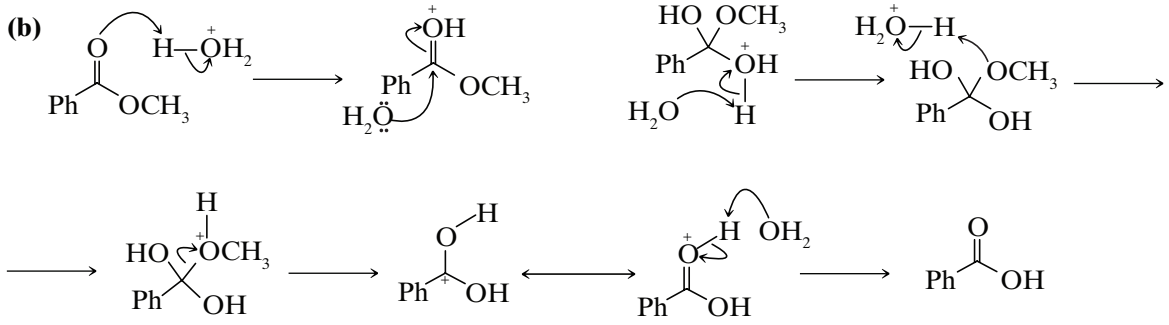
The last two steps of this mechanism show loss of water in an E_1 fashion. An E_2-type of dehydration is also acceptable, as explained below.

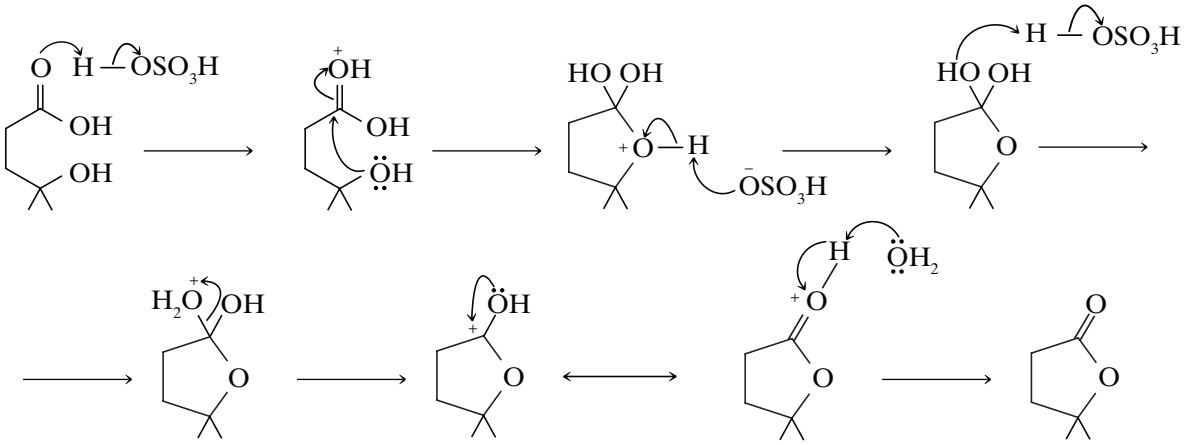


(b)

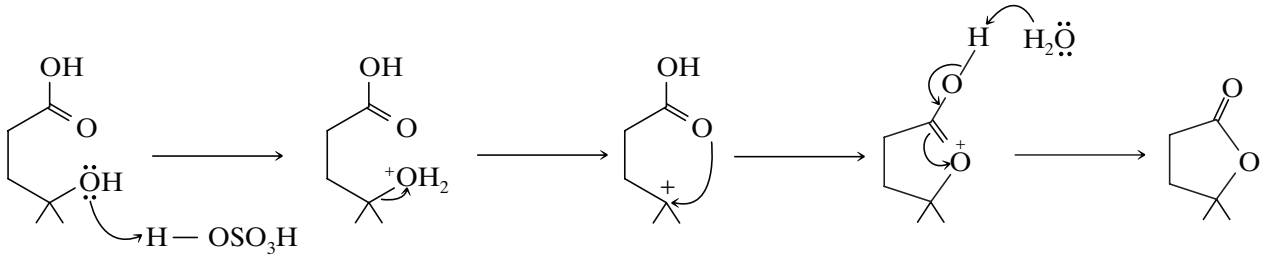


(c) Two reasonable mechanisms can be written for this reaction: a traditional Fischer esterification or a carbonyl carbon cation capture mechanism. Both are acceptable, although the traditional Fischer esterification mechanism is probably the minor pathway as an alcohol is more basic than a carboxylic acid.

Fischer esterification mechanism is as follows:



Mechanism involving carbocation capture of carbonyl:



The carbocation captures the carbonyl oxygen of the OC–CH_2 group instead of the OH oxygen, because it leads to the more stable oxonium ion intermediate. The resulting oxonium ion enjoys resonance stabilization; whereas the oxonium ion formed by OH capture does not.

This carbocation–carbonyl capture mechanism for acid-catalyzed esterification of a carboxylic acid can only be a possibility when the carbocation derived from the alcohol is sufficiently stable (secondary or better).

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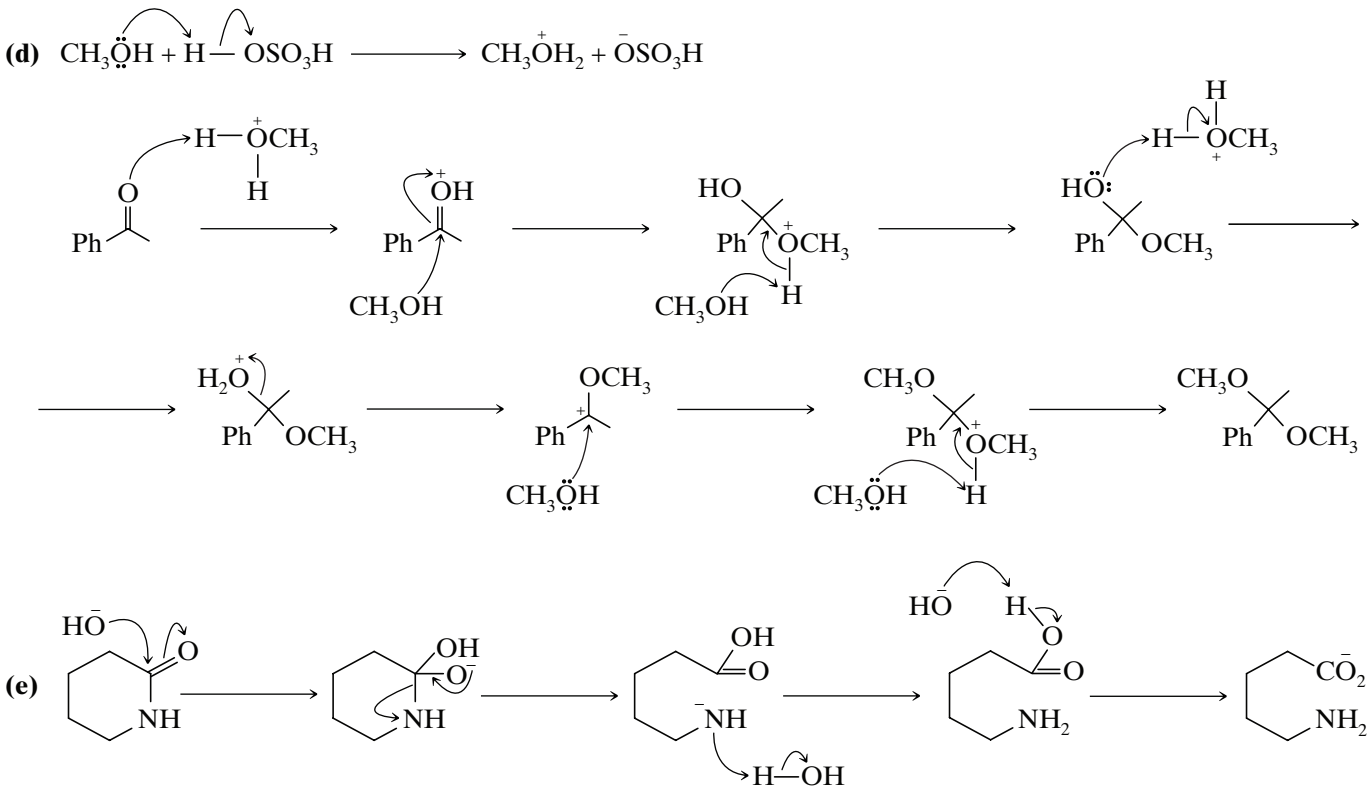
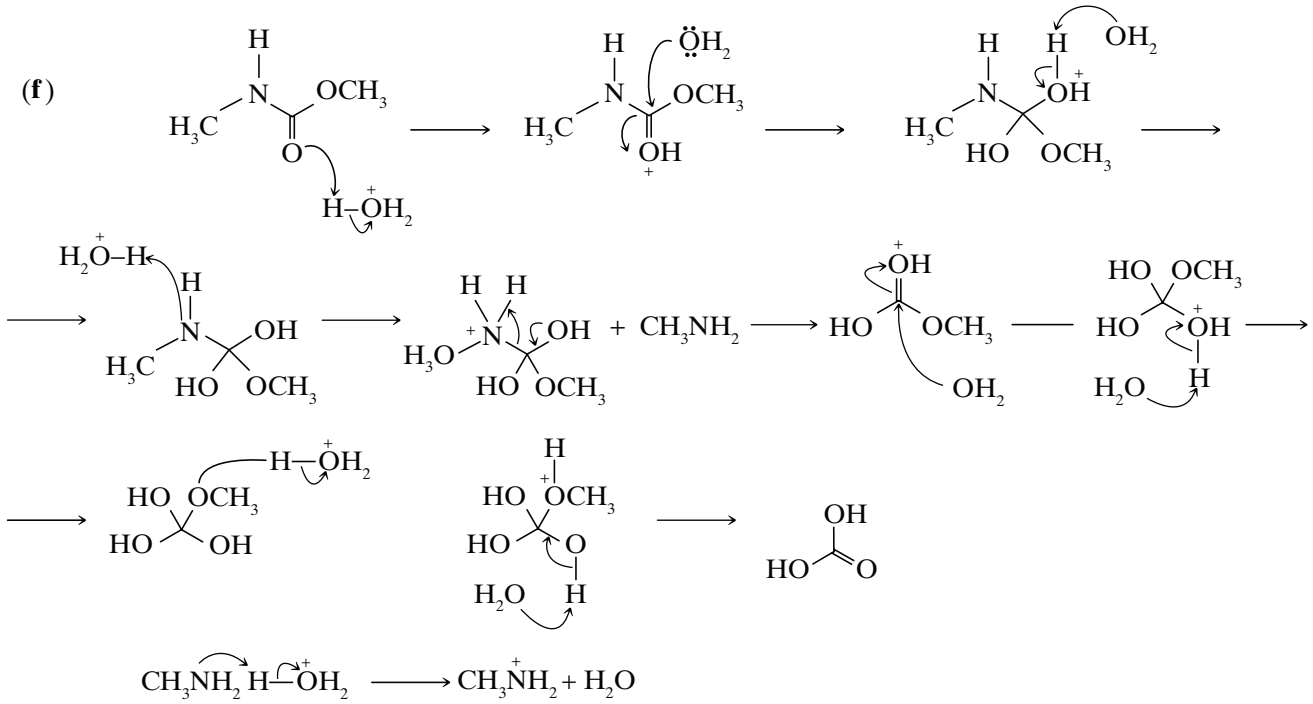


Fragmentation of the tetrahedral intermediate with an amide anion leaving group (in this case RNH) is the obvious rate determining step, because an amide anion is a poor leaving group. (An amide anion is a poorer leaving group than a hydroxide ion.) One could combine this step with the nitrogen anion protonation to avoid having an amide anion leaving group. This is reasonable, as the solvent is water, and the amine will be hydrogen bonded before it departs. However, in this reaction, the amide anion leaving group problem cannot be solved by protonation with H_3O^+ because H_3O^+ is simply not present. The reaction medium is strongly basic, so any strong acid such as hydronium ion will be immediately neutralized.



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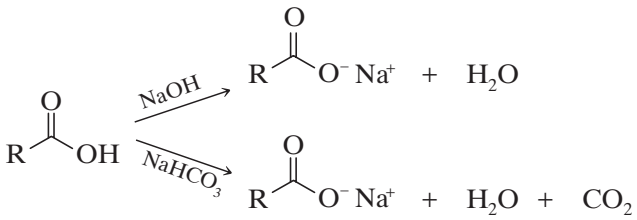
In the fourth mechanism step, the nitrogen atom is protonated in preference to the oxygen atoms because nitrogen is less electronegative, and thus more readily willing to share its lone pair.

17.12 | SUMMARY OF THE REACTIONS OF CARBOXYLIC ACIDS AND THEIR DERIVATIVES

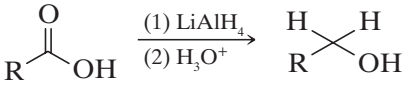
The reactions of carboxylic acids and their derivatives are summarized here. Many (but not all) of the reactions in this summary are acyl substitution reactions (they are principally the reactions referenced to Sections 17.5 and beyond). As you use this summary, you will find it helpful to also review Section 17.4, which presents the general nucleophilic addition–elimination mechanism for acyl substitution. It is instructive to relate aspects of the specific acyl substitution reactions below to this general mechanism. In some cases proton transfer steps are also involved, such as to make a leaving group more suitable by prior protonation or to transfer a proton to a stronger base at some point in a reaction, but in all acyl substitution the essential nucleophilic addition–elimination steps are identifiable.

Reactions of Carboxylic Acids

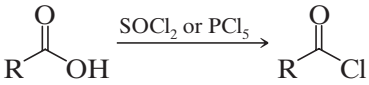
1. As acids (discussed in Sections 3.12 and 17.2C):



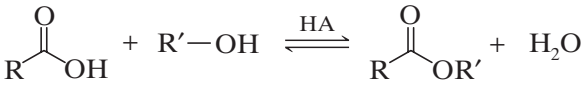
2. Reduction (discussed in Section 11.3):



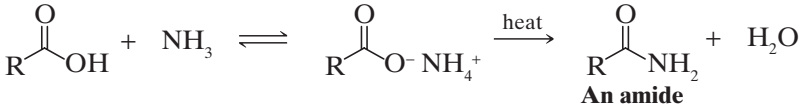
3. Conversion to acyl chlorides (discussed in Section 17.5):



4. Conversion to esters (Fischer esterification) or lactones (discussed in Section 17.7A):

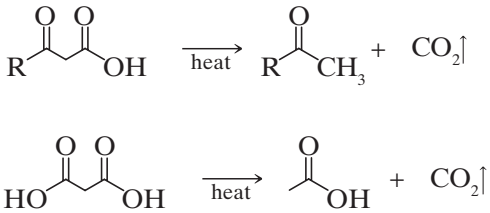


5. Conversion to amides (discussed in Section 17.8E, but a very limited method):



An amide

6. Decarboxylation (discussed in Section 17.10):



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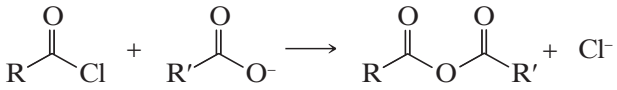
Reactions of Acyl Chlorides

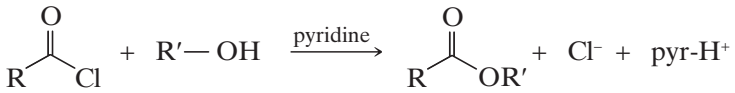
1. Conversion (hydrolysis) to acids (discussed in Section 17.5B):



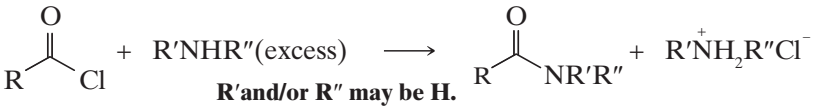
2. Conversion to anhydrides (discussed in Section 17.6A):



3. Conversion to esters (discussed in Section 17.7A):

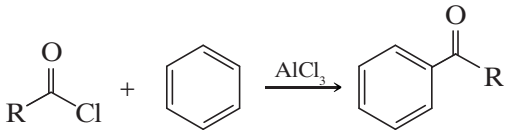


4. Conversion to amides (discussed in Section 17.8B):

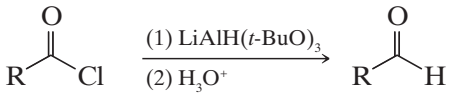


R′and/or R″ may be H.

5. Conversion to ketones (Friedel–Crafts acylation, Sections 14.7–14.9):

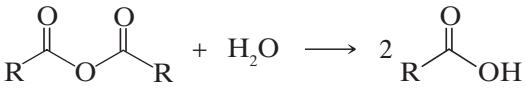


6. Conversion to aldehydes (discussed in Section 15.4C):

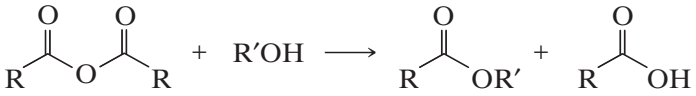


Reactions of Acid Anhydrides

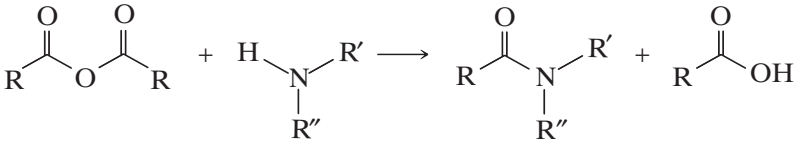
1. Conversion (hydrolysis) to acids (discussed in Section 17.6B):



2. Conversion to esters (discussed in Sections 17.6B and 17.7A):



3. Conversion to amides (discussed in Section 17.8C):



R′ and/or R″ may be H.

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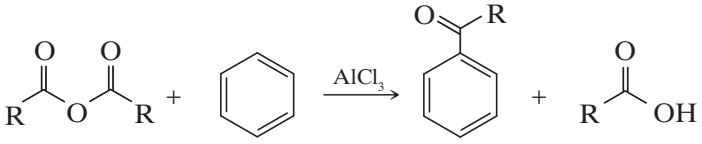
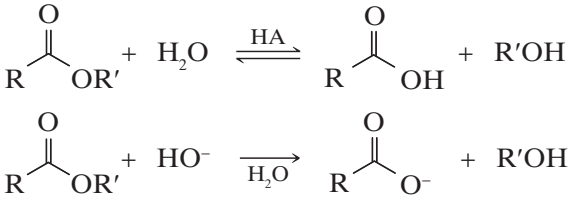
4. Conversion to aryl ketones (Friedel–Crafts acylation, Sections 14.7–14.9):

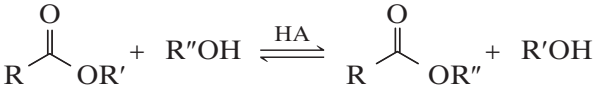


Reactions of Esters

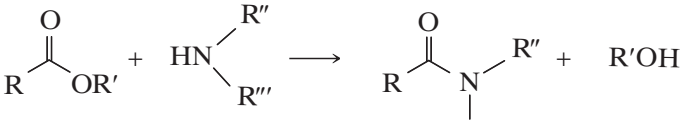
1. Hydrolysis (discussed in Section 17.7B):



2. Conversion to other esters: transesterification (discussed in Practice Problem 17.8):

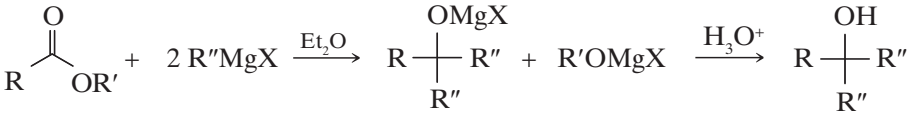


3. Conversion to amides (discussed in Section 17.8D):

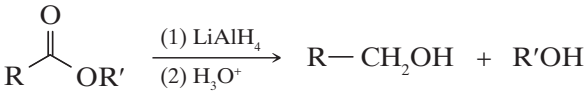


R″ and/or R‴ may be H.

4. Reaction with Grignard reagents (discussed in Section 11.8):

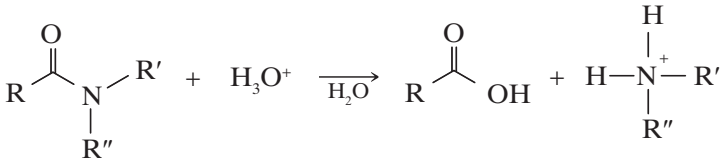


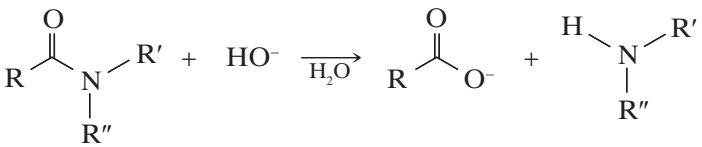
5. Reduction (discussed in Section 11.3):



Reactions of Amides

1. Hydrolysis (discussed in Section 17.8F):





R, R′, and/or R″ may be H.

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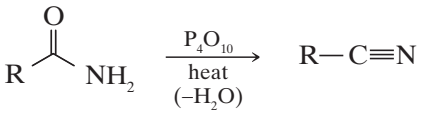
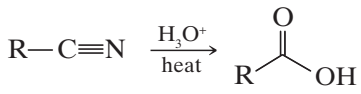
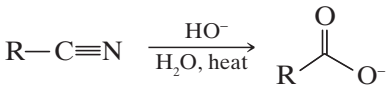
2. Conversion to nitriles: dehydration (discussed in Section 17.8G):



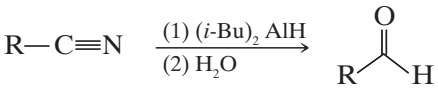
Reactions of Nitriles

1. Hydrolysis to a carboxylic acid or carboxylate anion (Section 17.8H):

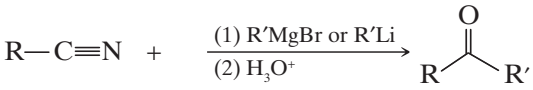




2. Reduction to an aldehyde with $(i\text{-Bu})_2AlH$ (DIBAL-H, Section 15.4C):



3. Conversion to a ketone by a Grignard or organolithium reagent (Section 15.5B):



REVIEW PROBLEMS

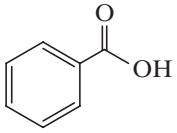
Structure and Nomenclature

17.12 Write a structural formula for each of the following compounds:

- **(a)** Octanoic acid
- **(b)** Propanamide
- **(c)** *N*,*N*-Diethylhexanamide
- **(d)** 2-Methyl-4-hexenoic acid
- **(e)** Butanedioic acid
- **(f)** 1,2-Benzenedioic acid (phthalic acid)
- **(g)** 1,4-Benzenedioic acid (terephthalic acid)
- **(h)** Acetic anhydride
- **(i)** Isobutyl propanoate
- **(j)** Benzyl acetate
- **(k)** Ethanoyl chloride (acetyl chloride)
- **(l)** 2-Methylpropanenitrile
- **(m)** Ethyl 3-oxobutanoate (ethyl acetoacetate)
- **(n)** Diethyl propanedioate (diethyl malonate)

17.13 Give an IUPAC systematic or common name for each of the following compounds:

(a)



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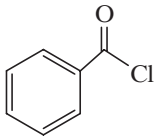

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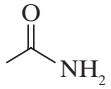

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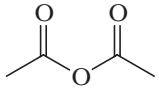

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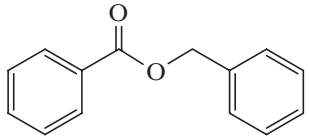

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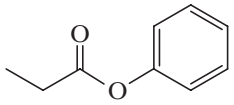

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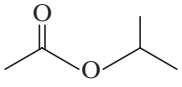

(h) CH_3CN

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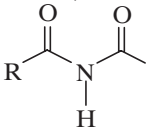
17.14 Amides are weaker bases than corresponding amines. For example, most water-insoluble amines (RNH_2) will dissolve in dilute aqueous acids (aqueous HCl, H_2SO_4, etc.) by forming water-soluble alkylaminium salts ($RNH_3^+X^-$). Corresponding amides ($RCONH_2$) *do not dissolve in dilute aqueous acids*, however. Propose an explanation for the much lower basicity of amides when compared to amines.

17.15 While amides are much less basic than amines, they are much stronger acids. Amides have pK_a values in the range 14–16, whereas for amines, pK_a = 33–35.

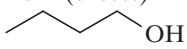
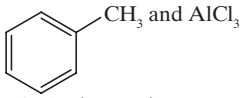
(a) What factor accounts for the much greater acidity of amides?

(b) Imides, that is, compounds with the structure , are even stronger acids than amides.

For imides, pK_a = 9–10, and as a consequence, water-insoluble imides dissolve in aqueous NaOH by forming soluble sodium salts. What extra factor accounts for the greater acidity of imides?

Functional Group Transformations

17.16 What major organic product would you expect to obtain when acetyl chloride reacts with each of the following?

(a) H_2O
(b) BuLi (excess)
(c) 
(d) NH_3 (excess)
(e) 
(f) LiAlH(*t*-BuO)$_3$
(g) NaOH/H_2O
(h) CH_3NH_2 (excess)
(i) $(CH_3)_2NH$ (excess)
(j) EtOH and pyridine
(k) $CH_3CO_2^-Na^+$
(l) CH_3CO_2H and pyridine

17.17 What major organic product would you expect to obtain when acetic anhydride reacts with each of the following?

(a) NH_3 (excess)
(b) H_2O
(c) $CH_3CH_2CH_2OH$
(d) $C_6H_6 + AlCl_3$
(e) $CH_3CH_2NH_2$ (excess)
(f) $(CH_3CH_2)_2NH$ (excess)

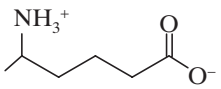
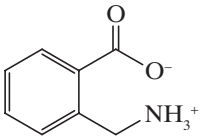
17.18 What products would you expect to obtain when ethyl propanoate reacts with each of the following?

(a) H_3O^+, H_2O
(b) HO^-, H_2O
(c) 1-Octanol, HCl
(d) CH_3NH_2
(e) $LiAlH_4$, then H_2O
(f) Excess C_6H_5MgBr, then H_2O, NH_4Cl

17.19 What products would you expect to obtain when propanamide reacts with each of the following?

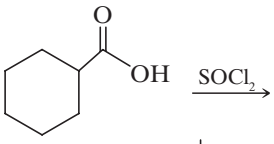
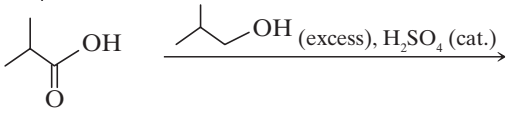
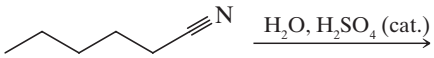
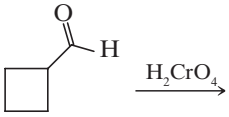
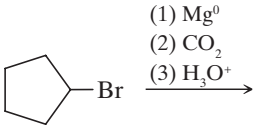
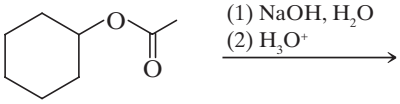
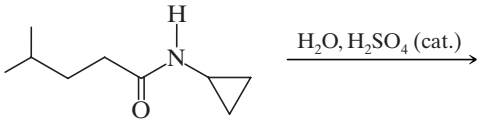
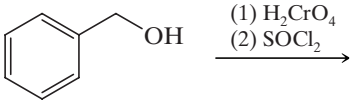
(a) H_3O^+, H_2O **(b)** HO^-, H_2O **(c)** P_4O_{10} and heat

17.20 What products would you expect to obtain when each of the following compounds is heated?

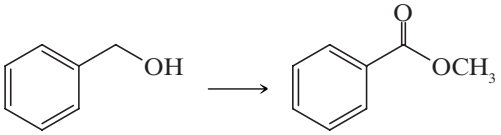
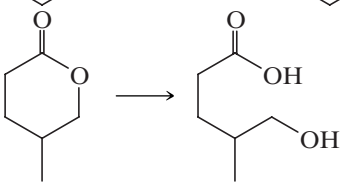
(a) 4-Hydroxybutanoic acid
(b) 3-Hydroxybutanoic acid
(c) 2-Hydroxybutanoic acid
(d) Glutaric acid
(e) 
(f) 

General Problems

17.21 Write structural formulas for the major organic products from each of the following reactions.

(a) 
(b) 
(c) 
(d) 
(e) 
(f) 
(g) 
(h) 

17.22 Indicate reagents that would accomplish each of following transformations. More than one reaction may be necessary in some cases.

(a) 
(b) 

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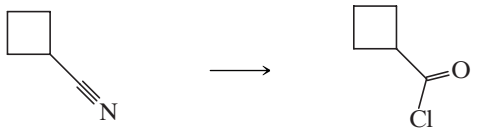
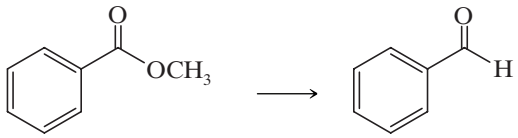
(c)



(d)



(e)



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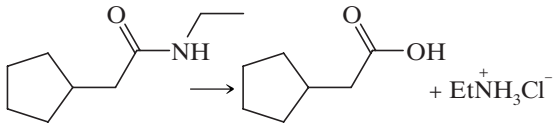
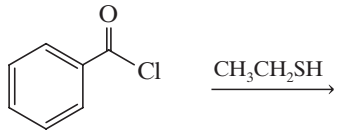
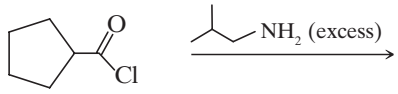


17.23 Write structural formulas for the major organic products from each of the following reactions.

(a)



(b)



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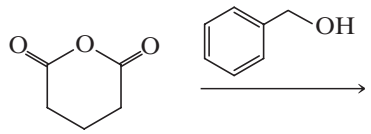

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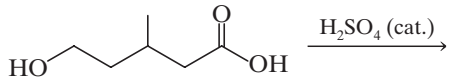

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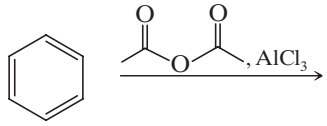
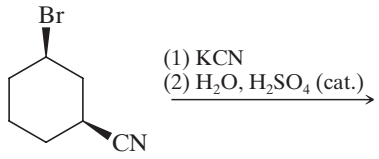


17.24 Write structural formulas for the major organic products from each of the following reactions.

(a)



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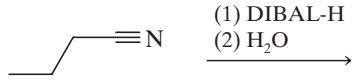

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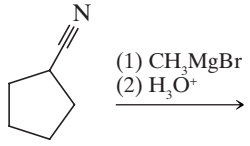

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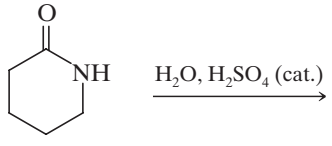

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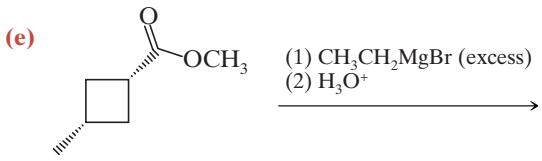
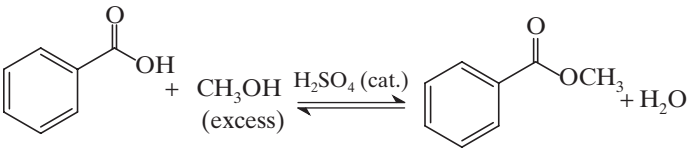


Mechanisms

17.25 Write detailed mechanisms for the acidic and basic hydrolysis of propanamide.

17.26 Provide a detailed mechanism for each of the following reactions.

(a)



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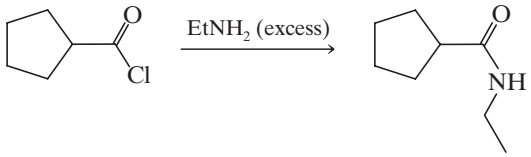

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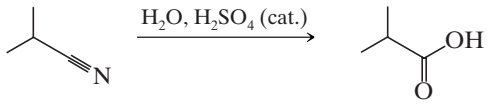


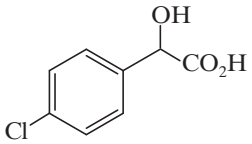
17.27 On heating, *cis*-4-hydroxycyclohexanecarboxylic acid forms a lactone but *trans*-4-hydroxycyclohexanecarboxylic acid does not. Explain.

Synthesis

17.28 Show how *p*-chlorotoluene could be converted to each of the following:

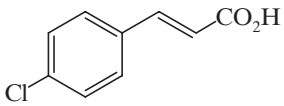
(a) *p*-Chlorobenzoic acid

(b)



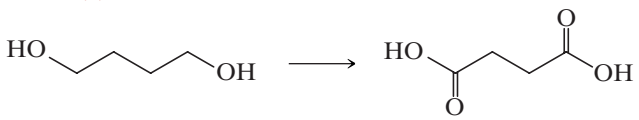
(c) *p*-Chlorophenylacetic acid

(d)



17.29 Indicate the reagents needed for each of the following syntheses. More than one step may be needed.

(a)



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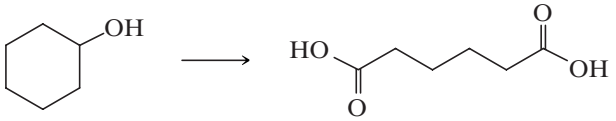

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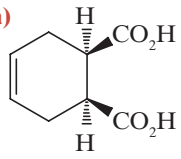
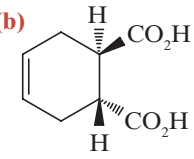
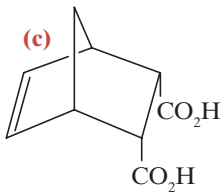
17.30 Show how pentanoic acid can be prepared from each of the following:
(a) 1-Pentanol **(b)** 1-Bromobutane (two ways)
(c) 5-Decene **(d)** Pentanal

17.31 The active ingredient of the insect repellent Off is *N*,*N*-diethyl-*m*-toluamide, *m*-$CH_3C_6H_4CON(CH_2CH_3)_2$. Outline a synthesis of this compound starting with 3-methylbenzoic acid (*m*-toluic acid).

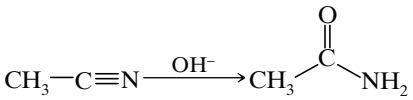
17.32 Starting with either *cis*- or *trans*-$HO_2C-CH=CH-CO_2H$ (i.e., either maleic or fumaric acid) and using any other needed compounds, outline syntheses of each of the following:

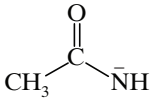
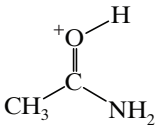
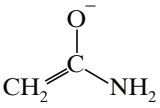
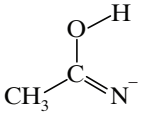
(a) 
(b) 
(c) 

ADDITIONAL OBJECTIVE QUESTIONS

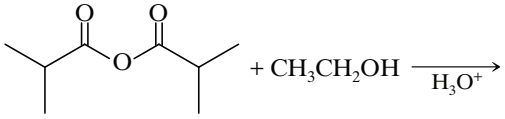
Single Correct Choice Type

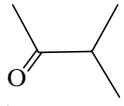
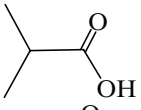
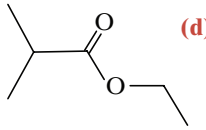
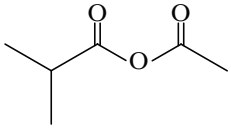
1. Choose the structure that is an intermediate in the base catalyzed hydrolysis of acetonitrile into acetamide.



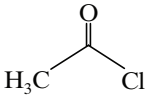
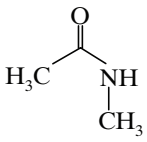
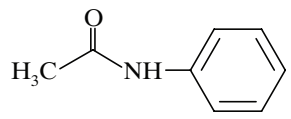
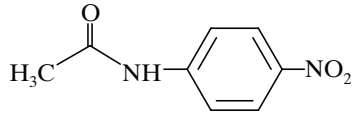
(a) 
(b) 
(c) 
(d) 

2. What is the major product of the following reaction?

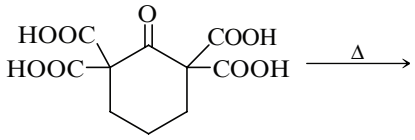
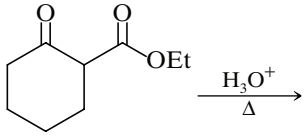
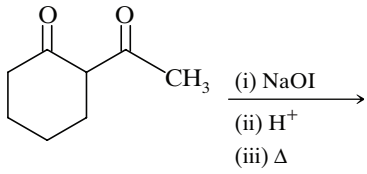
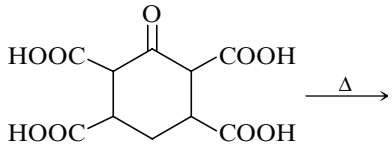


(a) 
(b) 
(c) 
(d) 

3. Which of the following are most reactive compounds for nucleophilic acyl substitution?

(a) 
(b) 
(c) 
(d) 

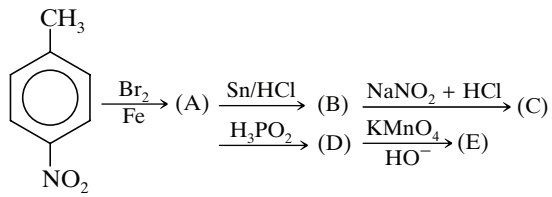
4. Which of the following reaction do not yield cyclohexanone as major product?

(a) 
(b) 
(c) 
(d) 

5. Which of the following carboxylic acids undergo decarboxylation easily?

(a) $C_6H_5CO-CH_2COOH$
(b) $C_6H_5CO-COCOOH$
(c) $C_6H_5CH_2(OH)-COOH$
(d) $C_6H_5CH_2(NH_2)-COOH$

6.



Product (E) is

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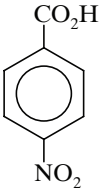
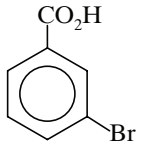
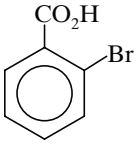
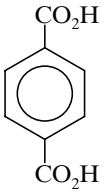
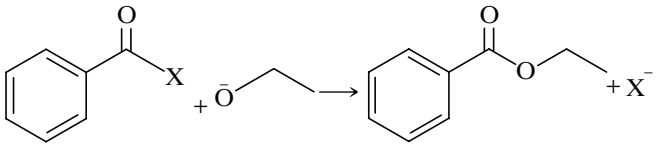
(a) 
(b) 
(c) 
(d) 

7. Choose the order that has the following benzoyl compounds correctly arranged with respect to increasing reactivity.



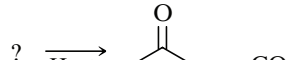
(i) X = OCH_3 **(ii)** X = Cl **(iii)** X = SCH_3
(a) (i) < (ii) < (iii) **(b)** (i) < (iii) < (ii)
(c) (ii) < (i) < (iii) **(d)** (ii) < (iii) < (i)

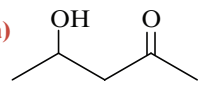
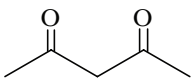
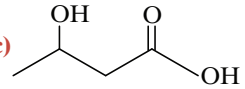
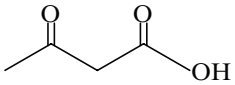
8. When propionic acid is treated with aqueous $NaHCO_3$, CO_2 is liberated. The 'C' of CO_2 comes from
(a) methyl group. **(b)** carboxylic acid group.
(c) methylene group. **(d)** bicarbonate.

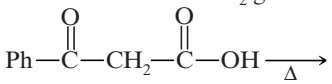
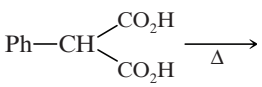
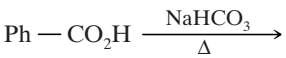
9. Which of the following carboxylic acids will have the largest K_a value?
(a) CH_3CO_2H **(b)** $ClCH_2CO_2H$
(c) $C_6H_5CO_2H$ **(d)** CF_3CO_2H

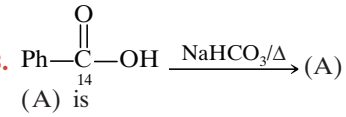
10. The reactivity of carboxylic acid derivatives from highest reactivity to lowest reactivity is
(a) acid anhydride > acid chloride > ester > amide
(b) acid chloride > acid anhydride > ester > amide
(c) acid anhydride > ester > amide > acid chloride
(d) amide > ester > acid anhydride > acid chloride

11. What starting material is required for the following reaction?

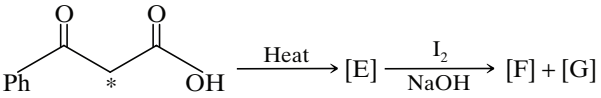


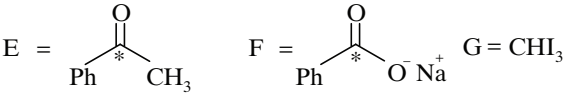
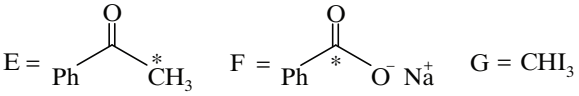
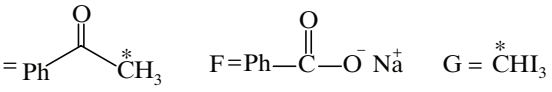
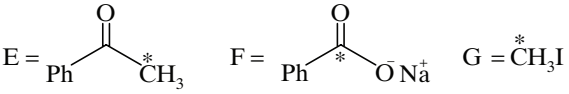
(a) 
(b) 
(c) 
(d) 

12. In which of the reaction CO_2 gas will evolve?
(a) 
(b) 
(c) 
(d) All

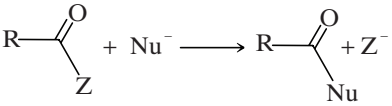
13. 
(A) is
(a) CO_2 **(b)** $^{14}CO_2$ **(c)** H_2 **(d)** NH_3

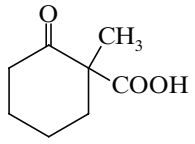
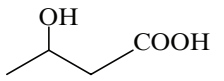
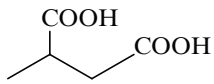
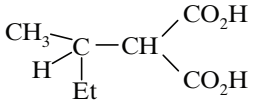
14. In the following reaction sequence, the correct structures of E, F and G are



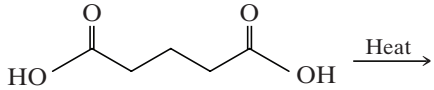
[* implies ^{13}C labeled carbon]
(a) 
(b) 
(c) 
(d) 

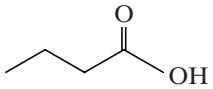
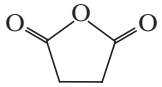
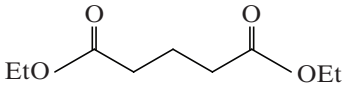
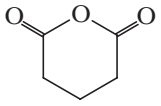
15. The product of mixing an acyl halide and an acid is
(a) an acid. **(b)** an amide.
(c) anhydride. **(d)** an aldehyde.

16. Rate of the reaction 
is fastest when Z is
(a) Cl **(b)** $OCOCH_3$ **(c)** OC_2H_5 **(d)** NH_2

17. Which of the following losses chirality when heated?
(a) 
(b) 
(c) 
(d) 

18. What is the product of the following reaction?



(a) 
(b) 
(c) 
(d) 

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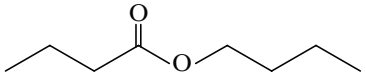
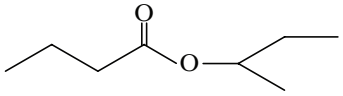
Linked Comprehension Type

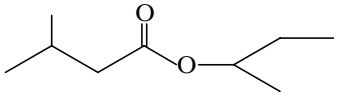
Paragraph for Questions 1 to 4

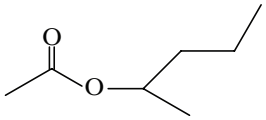
A neutral, resolvable organic compound A has molecular formula ($C_8H_{16}O_2$). A on treatment with $LiAlH_4$ gives isomeric B and C ($C_4H_{10}O$) of which only B is optically active. B on treatment with acidified dichromate solution gives D (C_4H_8O), which on refluxing with dilute NaOH followed by acidification of product gave E ($C_8H_{14}O$). E on heating with N_2H_4 in alkaline medium affords F (C_8H_{16}), which on treatment with $B_2H_6/H_2O_2/HO^-$ produced a resolvable G ($C_8H_{18}O$). G on treatment with acidified dichromate solution produced H ($C_8H_{16}O$), which on treatment with MCPBA produces A.

1. Compound (A) is

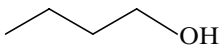
(a) 

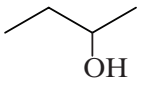
(b) 

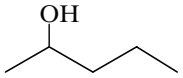
(c) 

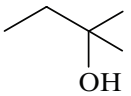
(d) 

2. Compound (B) is

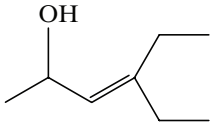
(a) 

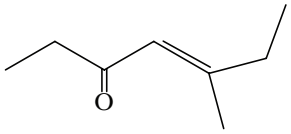
(b) 

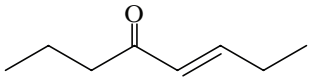
(c) 

(d) 

3. Compound (E) is

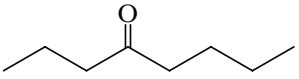
(a) 

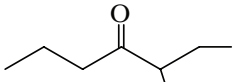
(b) 

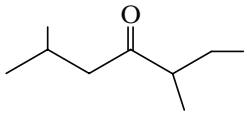
(c) 

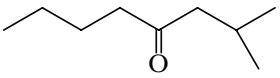
(d) None of these

4. Compound (H) is

(a) 

(b) 

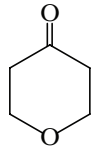
(c) 

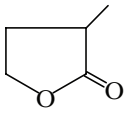
(d) 

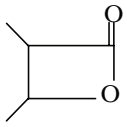
Paragraph for Questions 5 to 8

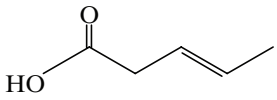
A neutral organic compound A ($C_5H_8O_2$) does not decolorize Bayer's reagent and on hydrolysis with dilute H_2SO_4 produces B ($C_5H_{10}O_3$), which is diastereomeric. B on heating with concentrated H_2SO_4 undergoes dehydration producing C ($C_5H_8O_2$), which shows geometrical isomerism. Also B on treatment with acidic dichromate solution produced D($C_5H_8O_3$), which is enantiomeric and gives a yellow precipitate with NaOI. D on gentle heating produces E (C_4H_8O),which is non-resolvable.

5. Compound (A) is

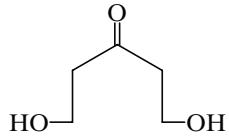
(a) 

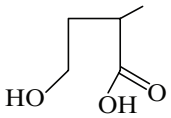
(b) 

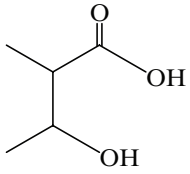
(c) 

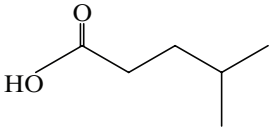
(d) 

6. Compound (B) is

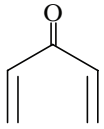
(a) 

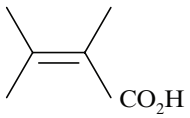
(b) 

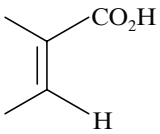
(c) 

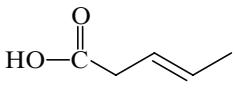
(d) 

7. Compound (C) is

(a) 

(b) 

(c) 

(d) 

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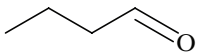
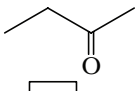
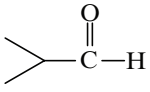
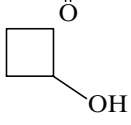
(a) 

(b) 

(c) 

(d) 

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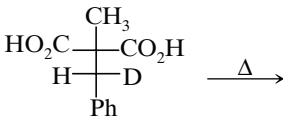
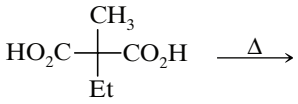
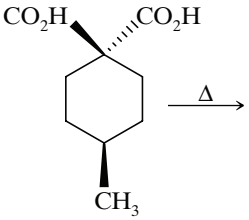
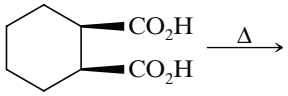
Matrix Match Type

1.

Column-I	Column-II
(a) 	**(p)** Diastereomers
(b) 	**(q)** Racemic mixture
(c) 	**(r)** Meso compound
(d) 	**(s)** CO_2 gas will evolve

ANSWER KEY

Single Correct Choice Type

1. (d)	**2.** (c)	**3.** (d)	**4.** (d)	**5.** (a)
6. (c)	**7.** (b)	**8.** (d)	**9.** (d)	**10.** (b)
11. (d)	**12.** (d)	**13.** (a)	**14.** (c)	**15.** (c)
16. (a)	**17.** (b)	**18.** (d)		

Linked Comprehension Type

1. (b)	**2.** (b)	**3.** (b)	**4.** (b)
5. (c)	**6.** (c)	**7.** (c)	**8.** (b)

Matrix Match Type

1. (a)→(p, s); (b)→(q, s); (c)→(p, s); (d)→(r)

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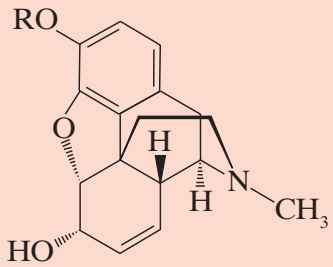
18

Amines



Morphine (R = H)
Codeine (R = CH_3)

Contents

18.1 | Nomenclature
18.2 | Physical Properties and Structure of Amines
18.3 | Basicity of Amines: Amine Salts
18.4 | Preparation of Amines
18.5 | Reactions of Amines
18.6 | Reactions of Amines with Nitrous Acid
18.7 | Replacement Reactions of Arenediazonium Salts
18.8 | Coupling Reactions of Arenediazonium Salts
18.9 | Reactions of Amines with Sulfonyl Chlorides
18.10 | Synthesis of Sulfa Drugs
18.11 | Eliminations Involving Ammonium Compounds
18.12 | The Cope Elimination
18.13 | Summary of Preparations and Reactions of Amines

18.1 | NOMENCLATURE

In common nomenclature most primary amines are named as *alkylamines*. In systematic nomenclature (blue names in parentheses below) they are named by adding the suffix *-amine* to the name of the chain or ring system to which the NH_2 group is attached with replacement of the final *-e*. Amines are classified as being **primary** (**1°**), **secondary** (**2°**), or **tertiary** (**3°**) on the basis of the number of organic groups attached to the nitrogen (Section 2.7).

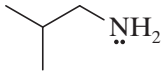
Primary Amines



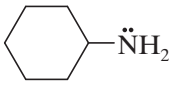
Methylamine (methanamine)



Ethylamine (ethanamine)



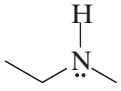
Isobutylamine (2-methyl-1-propanamine)



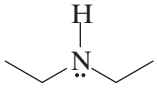
Cyclohexylamine (cyclohexanamine)

Most **secondary** and **tertiary amines** are named in the same general way. In common nomenclature we either designate the organic groups individually if they are different or use the prefixes di- or tri- if they are the same. In systematic nomenclature we use the locant *N* to designate substituents attached to a nitrogen atom.

Secondary Amines

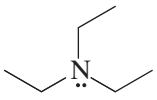


Ethylmethylamine (*N*-methylethanamine)

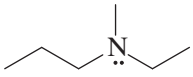


Diethylamine (*N*-ethylethanamine)

Tertiary Amines



Triethylamine (*N*,*N*-diethylethanamine)



Ethylmethylpropylamine (*N*-ethyl-*N*-methyl-1-propanamine)

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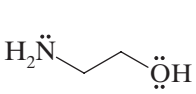
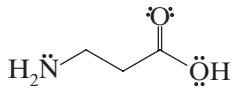
In the IUPAC system, the substituent —NH_2 is called the *amino* group. We often use this system for naming amines containing an OH group or a CO_2H group:



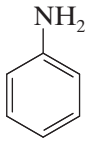
2-Aminoethanol



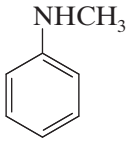
3-Aminopropanoic acid

18.1A Arylamines

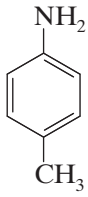
Some common **arylamines** have the following names:



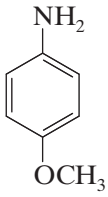
Aniline (benzenamine)



***N*-Methylaniline (*N*-methyl-benzenamine)**



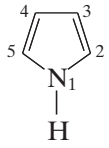
***p*-Toluidine (4-methyl-benzenamine)**



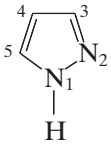
***p*-Anisidine (4-methoxy-benzenamine)**

18.1B Heterocyclic Amines

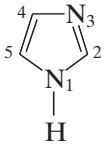
The important **heterocyclic amines** all have common names. In systematic replacement nomenclature the prefixes *aza-*, *diaza-*, and *triaza-* are used to indicate that nitrogen atoms have replaced carbon atoms in the corresponding hydrocarbon. A nitrogen atom in the ring (or the highest atomic weight heteroatom, as in the case of thiazole) is designated position 1 and numbering proceeds to give the lowest overall set of locants to the heteroatoms:



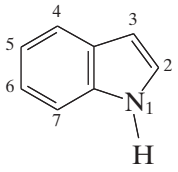
Pyrrole (1-azacyclopenta-2,4-diene)



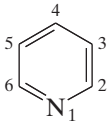
Pyrazole (1,2-diazacyclopenta-2,4-diene)



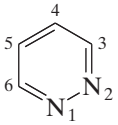
Imidazole (1,3-diazacyclopenta-2,4-diene)



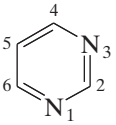
Indole (1-azaindene)



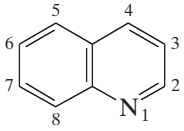
Pyridine (azabenzene)



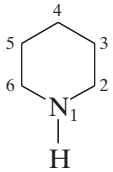
Pyridazine (1,2-diazabenzene)



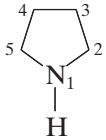
Pyrimidine (1,3-diazabenzene)



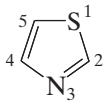
Quinoline (1-azanaphthalene)



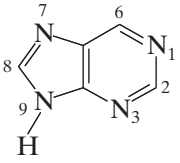
Piperidine (azacyclohexane)



Pyrrolidine (azacyclopentane)



Thiazole (1-thia-3-azacyclopenta-2,4-diene)



Purine

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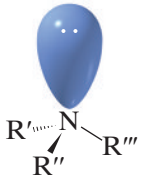
18.2 | PHYSICAL PROPERTIES AND STRUCTURE OF AMINES

18.2A Physical Properties

Amines are moderately polar substances; they have boiling points that are higher than those of alkanes but generally lower than those of alcohols of comparable molecular weight. Molecules of primary and secondary amines can form strong hydrogen bonds to each other and to water. Molecules of tertiary amines cannot form hydrogen bonds to each other, but they can form hydrogen bonds to molecules of water or other hydroxylic solvents. As a result, tertiary amines generally boil at lower temperatures than primary and secondary amines of comparable molecular weight, but all low-molecular-weight amines are very water soluble.

18.2B Structure of Amines

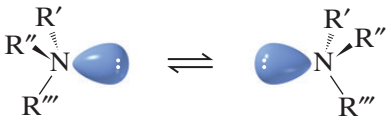
The nitrogen atom of most amines is like that of ammonia; it is approximately sp^3 hybridized. The three alkyl groups (or hydrogen atoms) occupy corners of a tetrahedron; the sp^3 orbital containing the unshared electron pair is directed toward the other corner. We describe the shape of the amine by the location of the atoms as being **trigonal pyramidal** However, if we were to consider the unshared electron pair as being a group we would describe the geometry of the amine as being tetrahedral.



Structure of an amine.

The bond angles are what one would expect of a tetrahedral structure; they are very close to 109.5°. The bond angles for trimethylamine, for example, are 108°.

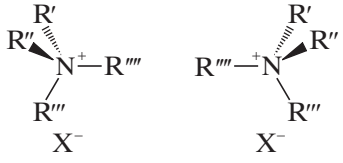
If the alkyl groups of a tertiary amine are all different, the amine will be chiral. There will be two enantiomeric forms of the tertiary amine, and, theoretically, we ought to be able to resolve (separate) these enantiomers. In practice, however, resolution is usually impossible because the enantiomers interconvert rapidly:



Interconversion of amine enantiomers

This interconversion occurs through what is called a **pyramidal** or **nitrogen inversion**. The barrier to the interconversion is about 25 kJ mol^{-1} for most simple amines, low enough to occur readily at room temperature. In the transition state for the inversion, the nitrogen atom becomes sp^2 hybridized with the unshared electron pair occupying a p orbital.

Ammonium salts cannot undergo nitrogen inversion because they do not have an unshared pair. Therefore, those **quaternary ammonium salts** with four different groups are chiral and can be resolved into separate (relatively stable) enantiomers:



Quaternary ammonium salts such as these can be resolved.

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18.3 | BASICITY OF AMINES: AMINE SALTS

- Amines are relatively weak bases. Most are stronger bases than water but are far weaker bases than hydroxide ions, alkoxide ions, and alkanide anions.

A convenient way to compare the **base strengths** of amines is to compare the pK_a values of their conjugate acids, the corresponding alkylaminium ions (Sections 3.7C and 18.3D).

$$RNH_3^+ + H_2O \rightleftharpoons RNH_2 + H_3O^+$$

$$K_a = \frac{[RNH_2][H_3O^+]}{[RNH_3^+]}$$

$$pK_a = -\log K_a$$

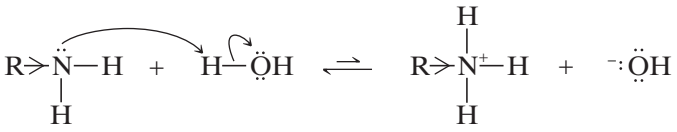
The equilibrium for an amine that is relatively more basic will lie more toward the left in the above chemical equation than for an amine that is less basic.

- The aminium ion of a more basic amine will have a larger pK_a than the aminium ion of a less basic amine.

When we compare aminium ion acidities in terms of this equilibrium, we see that most primary alkylaminium ions (RNH_3^+) are less acidic than ammonium ion (NH_4^+). In other words, primary alkylamines (RNH_2) are more basic than ammonia (NH_3):

	$H-\overset{+}{N}H_3$	$CH_3-\overset{+}{N}H_3$	$CH_3CH_2-\overset{+}{N}H_3$
Aminium ion pK_a	**9.26**	**10.64**	**10.75**

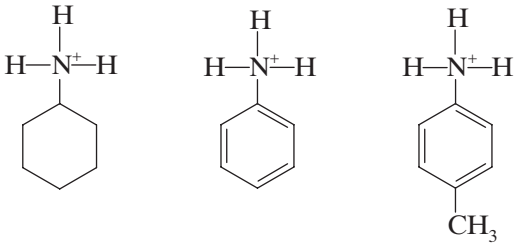
We can account for this on the basis of the electron-releasing ability of an alkyl group. An alkyl group releases electrons, and it *stabilizes* the alkylaminium ion that results from the acid–base reaction *by dispersing its positive charge*. It stabilizes the alkylaminium ion to a greater extent than it stabilizes the amine:



By releasing electrons, R → stabilizes the alkylaminium ion through dispersal of charge.

18.3A Basicity of Arylamines

- Aromatic amines are much weaker bases than alkylamines.



Aminium ion pK_a	**10.64**	**4.58**	**5.08**

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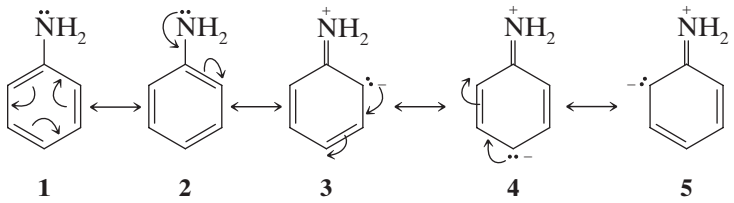
We can account for this effect, in part, on the basis of resonance contributions to the overall hybrid of an arylamine. For aniline, the following contributors are important:



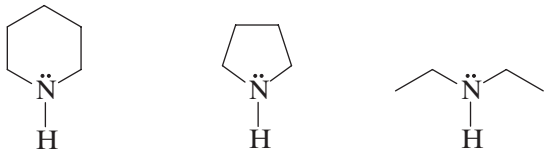
1 **2** **3** **4** **5**

Structures **1** and **2** are the Kekulé structures that contribute to any benzene derivative. Structures **3–5**, however, *delocalize* the unshared electron pair of the nitrogen over the ortho and para positions of the ring. This delocalization of the electron pair makes it less available to a proton, and *delocalization of the electron pair stabilizes aniline*.

Another important effect in explaining the lower basicity of aromatic amines is the **electron-withdrawing effect of a phenyl group**. Because the carbon atoms of a phenyl group are sp^2 hybridized, they are more electronegative (and therefore more electron withdrawing) than the sp^3-hybridized carbon atoms of alkyl groups. We shall discuss this effect further in Section 19.5A.

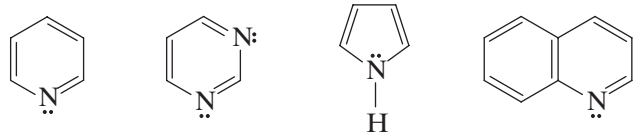
18.3B Basicity of Heterocyclic Amines

Nonaromatic heterocyclic amines have basicities that are approximately the same as those of acyclic amines:



	Piperidine	Pyrrolidine	Diethylamine
pK_a of corresponding aminium ion	**11.20**	**11.11**	**10.98**

In aqueous solution, aromatic heterocyclic amines such as pyridine, pyrimidine, and pyrrole are much weaker bases than nonaromatic amines or ammonia.



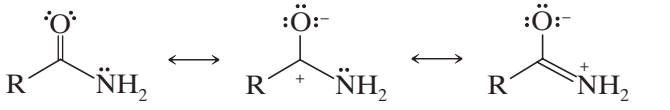
	Pyridine	Pyrimidine	Pyrrole	Quinoline
pK_a of corresponding aminium ion	**5.23**	**2.70**	**0.40**	**4.5**

18.3C Amines versus Amides

- Amides are far less basic than amines (even less basic than arylamines). The pK_a of the conjugate acid of a typical amide is about zero.

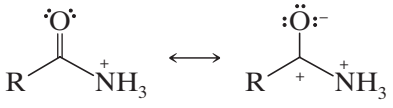
The lower basicity of amides when compared to amines can be understood in terms of resonance and inductive effects. An amide is stabilized by resonance involving the nonbonding pair of electrons on the nitrogen atom. However, an amide protonated on its nitrogen atom lacks this type of resonance stabilization. This is shown in the following resonance structures:

Amide



Larger resonance stabilization

N-Protonated Amide



Smaller resonance stabilization

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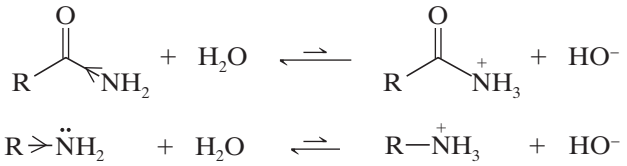
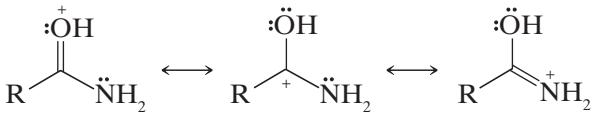
However, a more important factor accounting for amides being weaker bases than amines is the powerful electron-withdrawing effect of the carbonyl group of the amide.

Comparing the following equilibria, the reaction with the amide lies more to the left than the corresponding reaction with an amine. This is consistent with the amine being a stronger base than an amide.

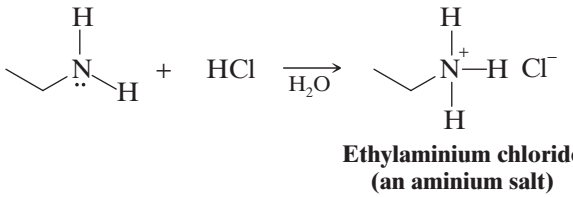


The nitrogen atoms of amides are so weakly basic that when an amide accepts a proton, it does so on its oxygen atom instead (see the mechanism for hydrolysis of an amide, Section 17.8F). Protonation on the oxygen atom occurs even though oxygen atoms (because of their greater electronegativity) are typically less basic than nitrogen atoms. Notice, however, that if an amide accepts a proton on its oxygen atom, resonance stabilization involving the nonbonding electron pair of the nitrogen atom is possible:

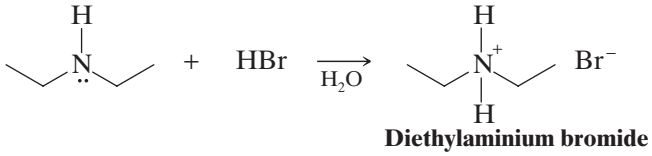


18.3D Aminium Salts and Quaternary Ammonium Salts

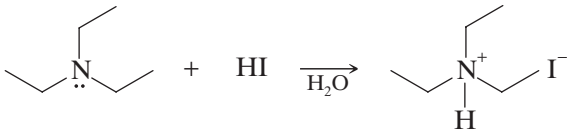
When primary, secondary, and tertiary amines act as bases and react with acids, they form compounds called **aminium salts**. In an aminium salt the positively charged nitrogen atom is attached to at least one hydrogen atom:



Ethylaminium chloride
(an aminium salt)

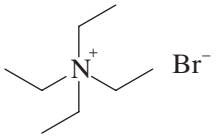


Diethylaminium bromide



Triethylaminium iodide

When the central nitrogen atom of a compound is positively charged *but is not attached to a hydrogen atom*, the compound is called a **quaternary ammonium salt**. For example,



Tetraethylammonium bromide
(a quaternary ammonium salt)

Quaternary ammonium halides—because they do not have an unshared electron pair on the nitrogen atom—cannot act as bases. Quaternary ammonium *hydroxides*, however, are strong bases. As solids, or in solution, they consist *entirely* of quaternary ammonium cations (R_4N^+) and hydroxide ions (HO^-); they are, therefore, strong bases—as

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strong as sodium or potassium hydroxide. Quaternary ammonium hydroxides react with acids to form quaternary ammonium salts:

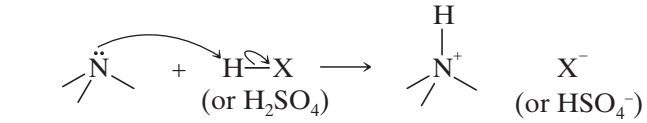
$$(CH_3)_4\overset{+}{N}OH^- + HCl \longrightarrow (CH_3)_4\overset{+}{N}Cl^- + H_2O$$

In Section 18.11A we shall see how quaternary ammonium salts can be used to form alkenes by a reaction called the *Hofmann elimination*.

18.3E Solubility of Amines in Aqueous Acids

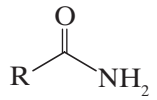
- Almost all alkylaminium chloride, bromide, iodide, and sulfate salts are soluble in water. Thus, primary, secondary, or tertiary amines that are not soluble in water will dissolve in dilute aqueous HCl, HBr, HI, and H_2SO_4.

Solubility in dilute acid provides a convenient chemical method for distinguishing amines from nonbasic compounds that are insoluble in water. Solubility in dilute acid also gives us a useful method for separating amines from nonbasic compounds that are insoluble in water. The amine can be extracted into aqueous acid (dilute HCl) and then recovered by making the aqueous solution basic and extracting the amine into ether or CH_2Cl_2.



Water-insoluble amine **Water-soluble aminium salt**

Because amides are far less basic than amines, water-insoluble amides *do not dissolve* in dilute aqueous HCl, HBr, HI, or H_2SO_4:



Water-insoluble amide (not soluble in aqueous acids)

18.4 | PREPARATION OF AMINES

In this section we discuss a variety of ways to synthesize amines. Some of these methods will be new to you, while others are methods you have studied earlier in the context of related functional groups and reactions. Later, in Chapter 21, you will see how some of the methods presented here, as well as some others for asymmetric synthesis, can be used to synthesize α-amino acids, the building blocks of peptides and proteins.

18.4A Through Nucleophilic Substitution Reactions

Alkylation of Ammonia Salts of primary amines can be prepared from ammonia and alkyl halides by nucleophilic substitution reactions. Subsequent treatment of the resulting aminium salts with a base gives primary amines:

$$\ddot{N}H_3 + R{-}X \longrightarrow R{-}\overset{+}{N}H_3\ X^- \xrightarrow{HO^-} RNH_2$$

- This method is of very limited synthetic application because multiple alkylations occur.

When ethyl bromide reacts with ammonia, for example, the ethylaminium bromide that is produced initially can react with ammonia to liberate ethylamine. Ethylamine can then compete with ammonia and react with ethyl bromide to give diethylaminium bromide. Repetitions of alkylation and proton transfer reactions ultimately produce some tertiary amines and even some quaternary ammonium salts if the alkyl halide is present in excess.

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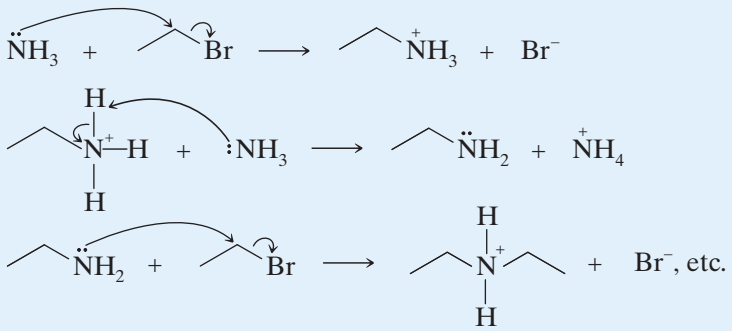
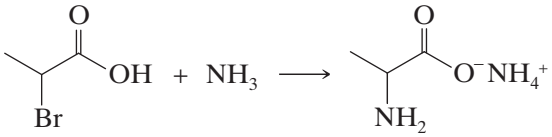
A MECHANISM FOR THE REACTION — Alkylation of NH_3

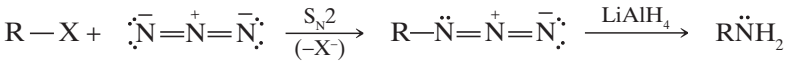


Multiple alkylations can be minimized by using a large excess of ammonia. (Why?) An example of this technique can be seen in the synthesis of alanine from 2-bromopropanoic acid:



(1 mol) **(70 mol)** **Alanine (65–70%)**

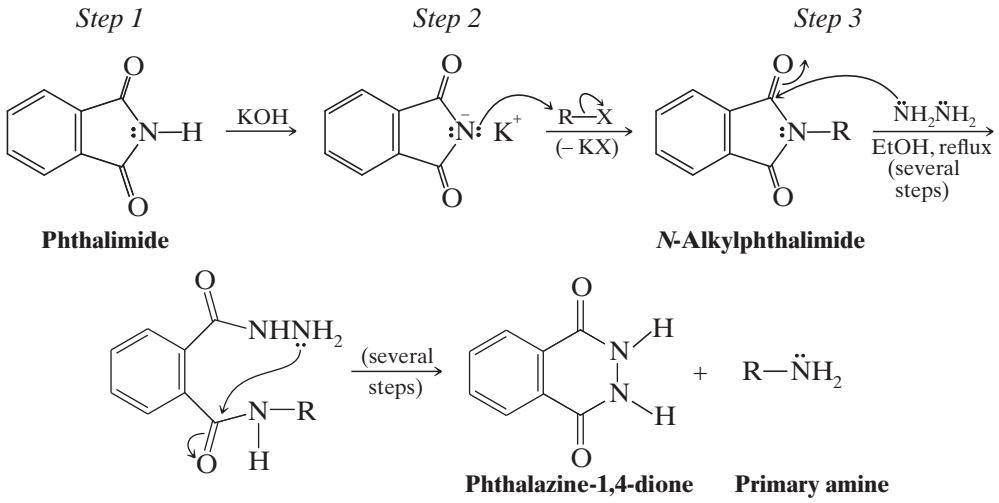
Alkylation of Azide Ion and Reduction A much better method for preparing a primary amine from an alkyl halide is first to convert the alkyl halide to an alkyl azide (R—N_3) by a nucleophilic substitution reaction, then reduce the azide to a primary amine with lithium aluminum hydride.



Azide ion (a good nucleophile) **Alkyl azide**

A word of caution: Alkyl azides are explosive, and low-molecular-weight alkyl azides should not be isolated but should be kept in solution. Sodium azide is used in automotive airbags.

The Gabriel Synthesis Potassium phthalimide (see the following reaction) can also be used to prepare primary amines by a method known as the *Gabriel synthesis*. This synthesis also avoids the complications of multiple alkylations that occur when alkyl halides are treated with ammonia:



Phthalimide **N-Alkylphthalimide** **Phthalazine-1,4-dione** **Primary amine**

Phthalimide is quite acidic ($pK_a = 9$); it can be converted to potassium phthalimide by potassium hydroxide (step 1). The phthalimide anion is a strong nucleophile and (in step 2) it reacts with an alkyl halide by an S_N2 mechanism to give an *N*-alkylphthalimide. At this point, the *N*-alkylphthalimide can be hydrolyzed with aqueous acid or base, but

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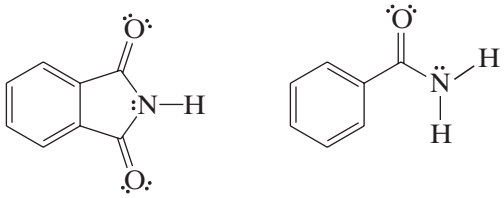
the hydrolysis is often difficult. It is often more convenient to treat the *N*-alkylphthalimide with hydrazine (NH_2NH_2) in refluxing ethanol (step 3) to give a primary amine and phthalazine-1,4-dione.

Practice Problem 18.1

(a) Write resonance structures for the phthalimide anion that account for the acidity of phthalimide. **(b)** Would you expect phthalimide to be more or less acidic than benzamide? Why? **(c)** In step 3 of our reaction several steps have been omitted. Propose reasonable mechanisms for these steps.



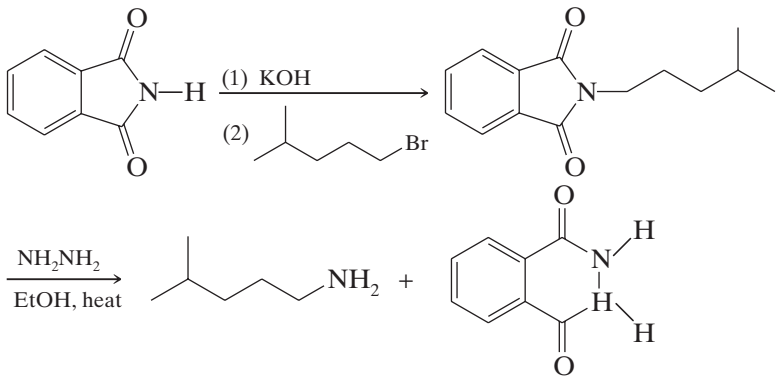
Phthalimide **Benzamide**

Syntheses of amines using the Gabriel synthesis are, as we might expect, restricted to the use of methyl, primary, and secondary alkyl halides. The use of tertiary halides leads almost exclusively to eliminations.

Solved Problem 18.1

Outline a synthesis of 4-methylpentanamine using the Gabriel synthesis.

Answer



Practice Problem 18.2

Outline a preparation of benzylamine using the Gabriel synthesis.

Alkylation of Tertiary Amines Multiple alkylations are not a problem when tertiary amines are alkylated with methyl or primary halides. Reactions such as the following take place in good yield:

$$R_3N: + RCH_2{-}Br \xrightarrow{S_N2} R_3\overset{+}{N}{-}CH_2R + Br^-$$

18.4B Preparation of Aromatic Amines through Reduction of Nitro Compounds

The most widely used method for preparing aromatic amines involves nitration of the ring and subsequent reduction of the nitro group to an amino group:

$$Ar{-}\mathbf{H} \xrightarrow[H_2SO_4]{HNO_3} Ar{-}\mathbf{NO_2} \xrightarrow{[H]} Ar{-}NH_2$$

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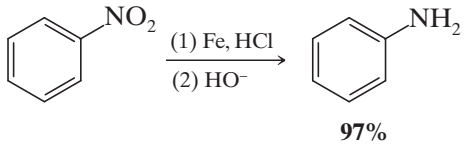
We studied ring nitration in Chapter 14 and saw there that it is applicable to a wide variety of aromatic compounds. Reduction of the nitro group can also be carried out in a number of ways. The most frequently used methods employ catalytic hydrogenation, or treatment of the nitro compound with acid and iron. Zinc, tin, or a metal salt such as $SnCl_2$ can also be used. Overall, this is a $6e^-$ reduction.

General Reaction

$$Ar{-}NO_2 \xrightarrow[\text{or (1) Fe, HCl (2) HO}^-]{\text{H}_2\text{, catalyst}} Ar{-}NH_2$$

Specific Example



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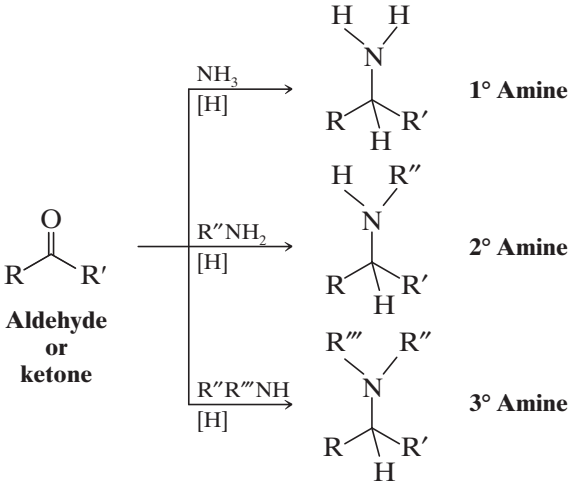
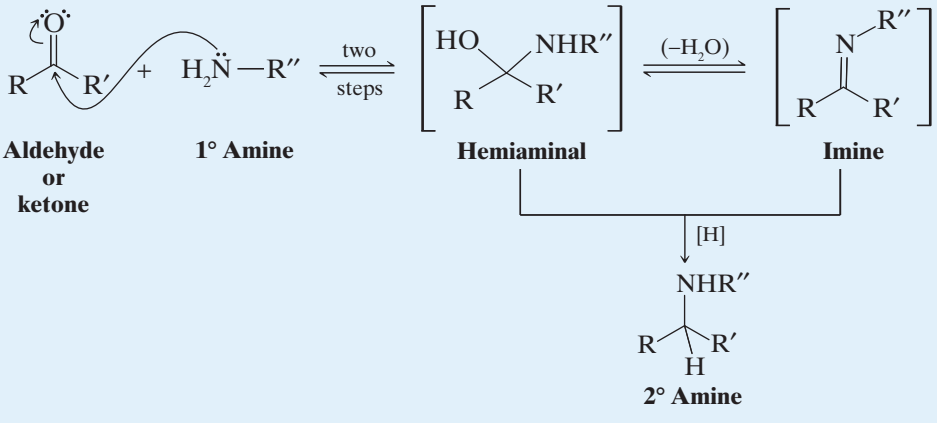
18.4C Preparation of Primary, Secondary, and Tertiary Amines through Reductive Amination

Aldehydes and ketones can be converted to amines through catalytic or chemical reduction in the presence of ammonia or an amine. Primary, secondary, and tertiary amines can be prepared this way:



This process, called **reductive amination** of the aldehyde or ketone (or *reductive alkylation* of the amine), appears to proceed through the following general mechanism (illustrated with a 1° amine).

A MECHANISM FOR THE REACTION — Reductive Amination



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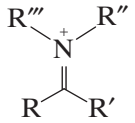
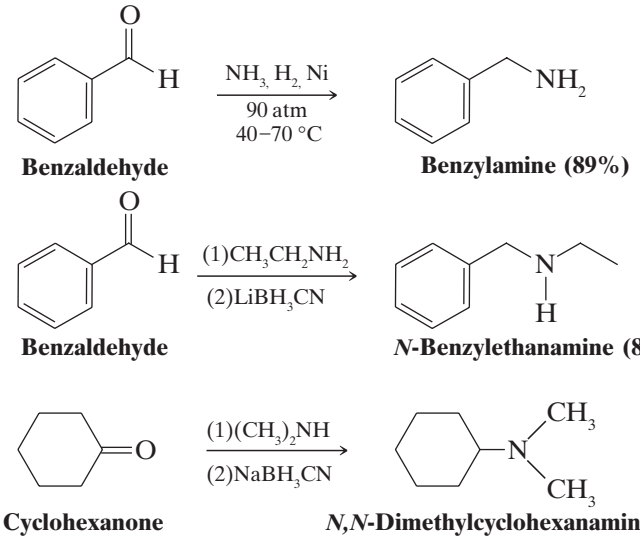
When ammonia or a primary amine is used, there are two possible pathways to the product: via an amino alcohol that is similar to a hemiacetal and is called a *hemiaminal* or via an imine (Section 15.8A). When secondary amines are used, an imine cannot form, and, therefore, the pathway is through the hemiaminal or through an iminium ion:



Iminium ion

The reducing agents employed include hydrogen and a catalyst (such as nickel) or $NaBH_3CN$ or $LiBH_3CN$ (sodium or lithium cyanoborohydride). The latter two reducing agents are similar to $NaBH_4$ and are especially effective in reductive aminations. Three specific examples of reductive amination follow:



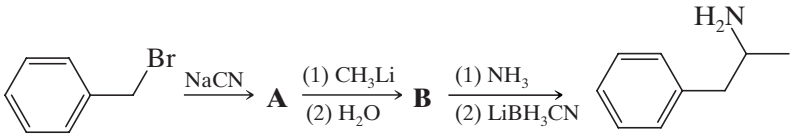
Benzaldehyde — **Benzylamine (89%)**

Benzaldehyde — ***N*-Benzylethanamine (89%)**

Cyclohexanone — ***N,N*-Dimethylcyclohexanamine (52–54%)**

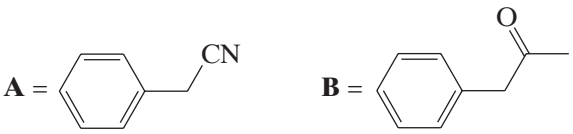
Solved Problem 18.2

Outlined below is a synthesis of the stimulant amphetamine. Provide the intermediates **A** and **B**.



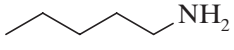
Amphetamine

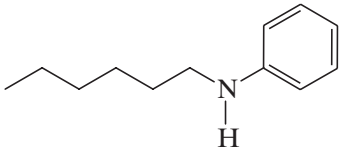
Answer

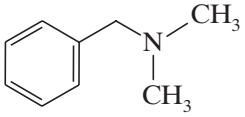


Practice Problem 18.3

Show how you might prepare each of the following amines through reductive amination:

(a) 

(b) 

(c) 

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Solved Problem 18.3

Reductive amination of a ketone is almost always a better method for the synthesis of an amine of the type



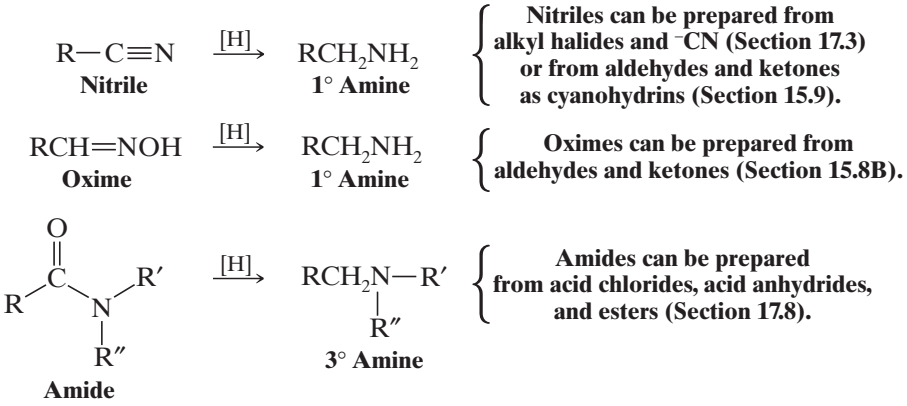
than treatment of an alkyl halide with ammonia. Explain why this is true.

Answer

Consider the structure of the required alkyl halide. Reaction of a secondary halide with ammonia would inevitably be accompanied by considerable elimination, thereby decreasing the yield of the secondary amine. Multiple *N*-alkylations may also occur.

18.4D Preparation of Primary, Secondary, or Tertiary Amines through Reduction of Nitriles, Oxides, and Amides

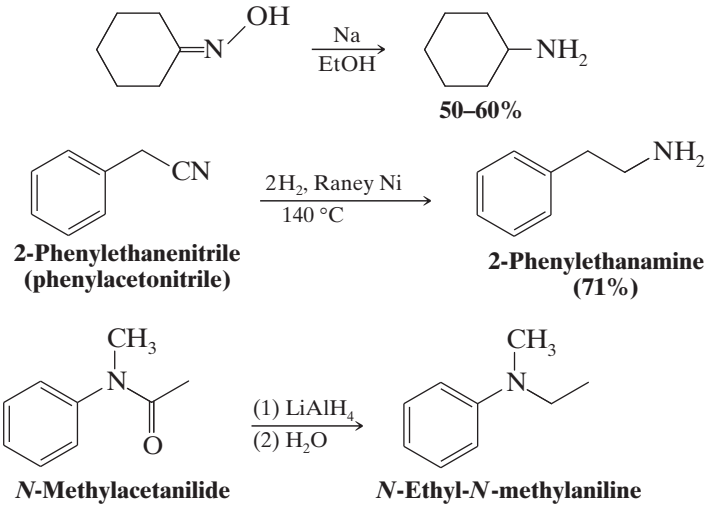
Nitriles, oximes, and amides can be reduced to amines. Reduction of a nitrile or an oxime yields a primary amine; reduction of an amide can yield a primary, secondary, or tertiary amine:



(In the last example, if R′ = H and R″ = H, the product is a 1° amine; if only R′ = H, the product is a 2° amine.)

All of these reductions can be carried out with hydrogen and a catalyst or with $LiAlH_4$. Oximes are also conveniently reduced with sodium in ethanol.

Specific examples follow:



Reduction of an amide is the last step in a useful procedure for **monoalkylation of an amine**. The process begins with *acylation* of the amine using an acyl chloride or acid anhydride; then the amide is reduced with lithium aluminum hydride. For example,

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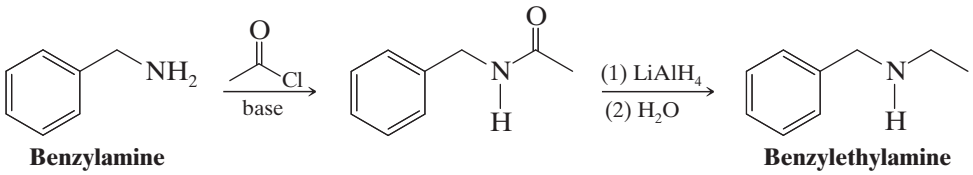


Benzylamine **Benzylethylamine**

Solved Problem 18.4

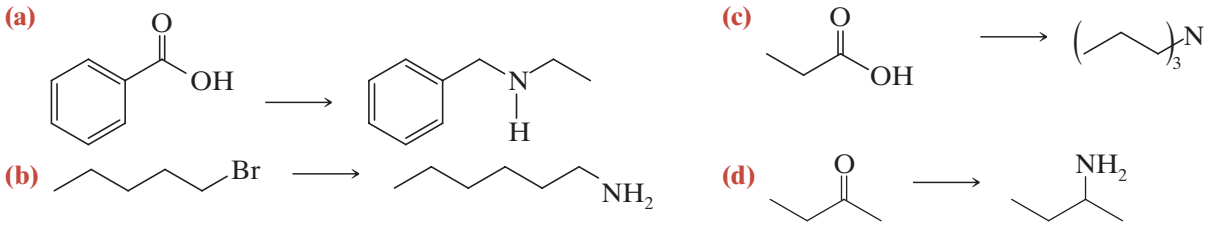
Show how you might synthesize 2-propanamine from a three-carbon starting material that is a ketone, aldehyde, nitrile, or amide.

Answer

We begin by recognizing that 2-propanamine has a primary amine group bonded to a secondary carbon. Neither a three-carbon nitrile nor a three-carbon amide can lead to this structural unit from a C_3 starting material. An oxime can lead to the proper structure, but we must start with a three-carbon ketone rather than an aldehyde. Therefore, we choose propanone as our starting material, convert it to an oxime, and then reduce the oxime to an amine.

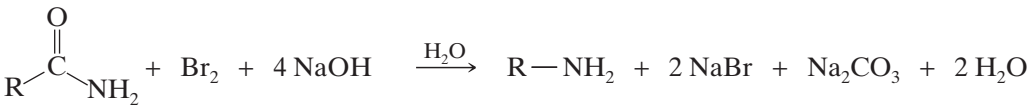
Practice Problem 18.4

Show how you might utilize the reduction of an amide, oxime, or nitrile to carry out each of the following transformations:



18.4E Preparation of Primary Amines through the Hofmann and Curtius Rearrangements

Hofmann Rearrangement Amides with no substituent on the nitrogen react with solutions of bromine or chlorine in sodium hydroxide to yield amines through loss of their carbonyl carbon by a reaction known as the *Hofmann rearrangement* or *Hofmann degradation*:



From this equation we can see that the carbonyl carbon atom of the amide is lost (as CO_3^{2-}) and that the R group of the amide becomes attached to the nitrogen of the amine. Primary amines made this way are not contaminated by 2° or 3° amines.

The mechanism for this interesting reaction is shown in the following scheme. In the first two steps the amide undergoes a base-promoted bromination, in a manner analogous to the base-promoted halogenation of a ketone that we studied in Section 16.3B. (The electron-withdrawing acyl group of the amide makes the amido hydrogens much more acidic than those of an amine.) The *N*-bromo amide then reacts with hydroxide ion to produce an anion, which spontaneously rearranges with the loss of a bromide ion to produce an isocyanate (Section 17.9A). In the rearrangement the R— group migrates with its electrons from the acyl carbon to the nitrogen atom at the same time the bromide ion departs. The isocyanate that forms in the mixture is quickly hydrolyzed by the aqueous base to a carbamate ion, which undergoes spontaneous decarboxylation resulting in the formation of the amine.

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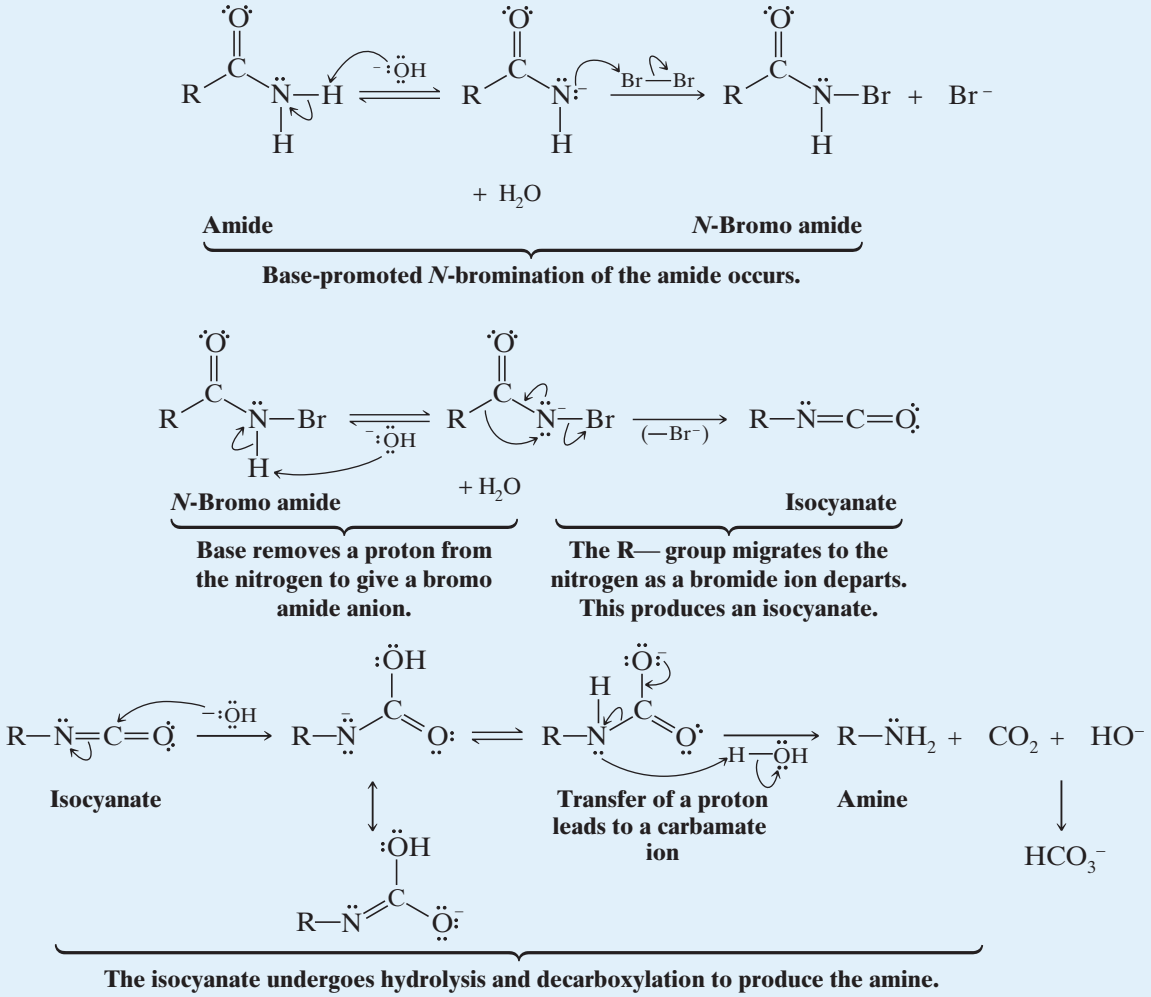
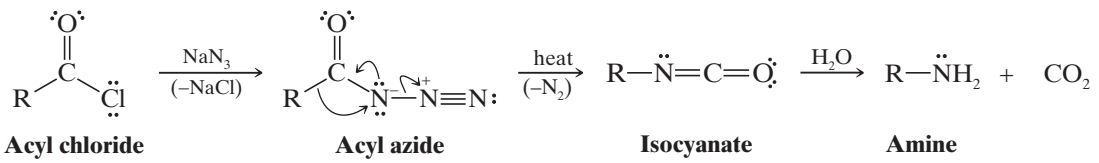
A MECHANISM FOR THE REACTION — The Hofmann Rearrangement



An examination of the first two steps of this mechanism shows that, initially, two hydrogen atoms must be present on the nitrogen of the amide for the reaction to occur. Consequently, the Hofmann rearrangement is limited to amides of the type $RCONH_2$.

Studies of the Hofmann rearrangement of optically active amides in which the chirality center is directly attached to the carbonyl group have shown that these reactions occur with *retention of configuration*. Thus, the R group migrates to nitrogen with its electrons, *but without inversion*.

Curtius Rearrangement The *Curtius rearrangement* is a rearrangement that occurs with acyl azides and yields a primary amine with loss of the acyl carbon. It resembles the Hofmann rearrangement in that an R— group migrates from the acyl carbon to the nitrogen atom as the leaving group departs. In this instance the leaving group is N_2 (the best of all possible leaving groups since it is highly stable, is virtually nonbasic, and being a gas, removes itself from the medium). Acyl azides are easily prepared by allowing acyl chlorides to react with sodium azide. Heating the acyl azide brings about the rearrangement; afterward, adding water causes hydrolysis and decarboxylation of the isocyanate:



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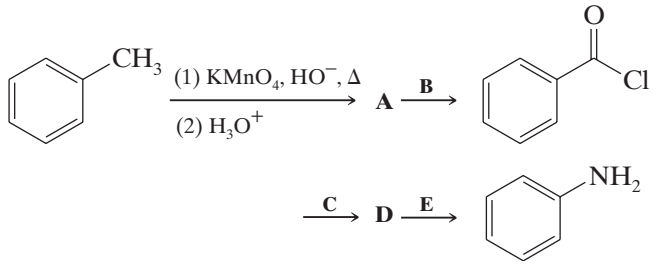
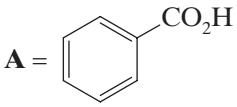
Solved Problem 18.5

The reaction sequence below shows how a methyl group on a benzene ring can be replaced by an amino group. Supply the missing reagents and intermediates.

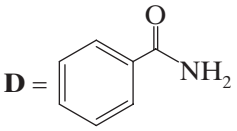


Answer

An acid chloride results from treatment of **A** with **B**. Therefore, **A** is likely to be a carboxylic acid, a conclusion that is consistent with the oxidizing conditions that led to formation of **A** from methylbenzene (toluene). **B** must be a reagent that can lead to an acid chloride. Thionyl chloride or PCl_5 would suffice. Overall, **C**, **D**, and E involve introduction of the nitrogen atom and loss of the carbonyl carbon. This sequence is consistent with preparation of an amide followed by a Hofmann rearrangement.



B = SO_2Cl **C** = NH_3

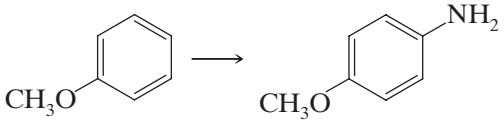


E = Br_2/HO^-

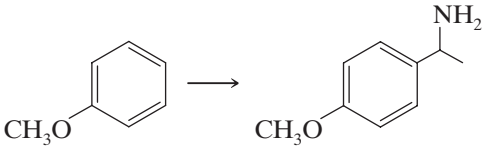
Practice Problem 18.5

Using a different method for each part, but taking care in each case to select a *good* method, show how each of the following transformations might be accomplished:

(a)



(b)



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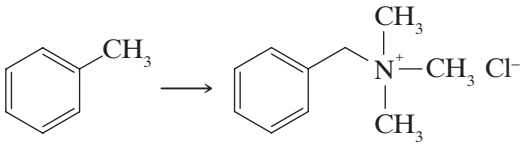
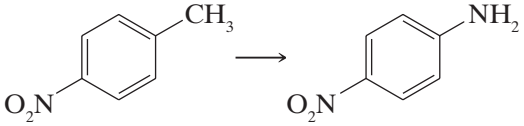
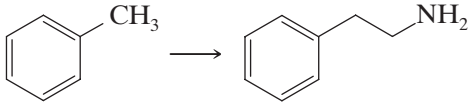


(d)



(e)

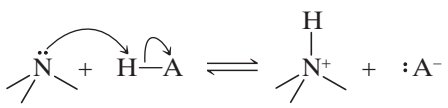


18.5 | REACTIONS OF AMINES

We have encountered a number of important reactions of amines in earlier sections. In Section 18.3 we saw reactions in which primary, secondary, and tertiary amines act *as bases*. In Section 18.4 we saw their reactions as *nucleophiles* in *alkylation reactions*, and in Chapter 17 as *nucleophiles* in *acylation reactions*. In Chapter 14 we saw that an amino group on an aromatic ring acts as a powerful *activating group* and as an *ortho–para director*.

The feature of amines that underlies all of these reactions and that forms a basis for our understanding of most of the chemistry of amines is the ability of nitrogen to share an electron pair:

Acid–Base Reactions



An amine acting as a base

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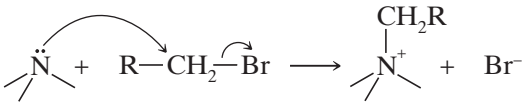
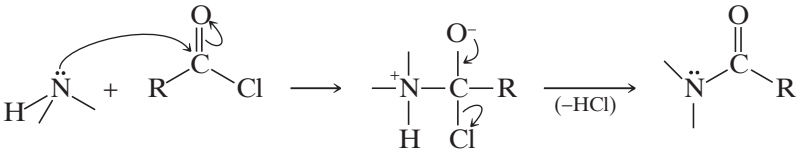
Alkylation



An amine acting as a nucleophile in an alkylation reaction

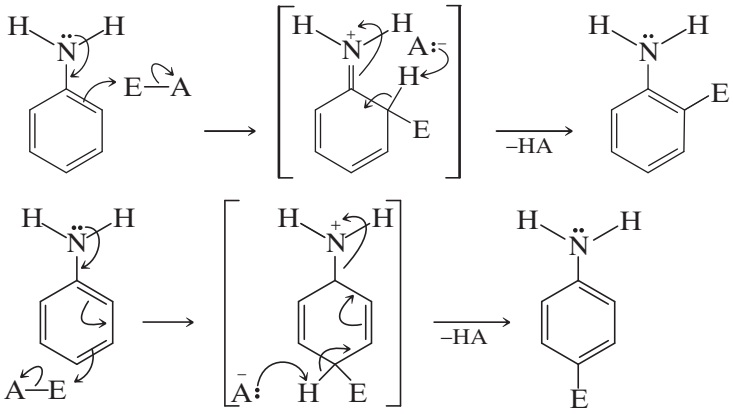
Acylation



A primary or secondary amine acting as a nucleophile in an acylation reaction

In the preceding examples the amine acts as a nucleophile by donating its electron pair to an electrophilic reagent. In the following example, resonance contributions involving the nitrogen electron pair make *carbon* atoms nucleophilic:

Electrophilic Aromatic Substitution



The amino group acting as an activating group and as an ortho–para director in electrophilic aromatic substitution

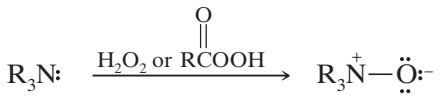
Practice Problem 18.6

Review the chemistry of amines given in earlier sections and provide a specific example for each of the previously illustrated reactions.

18.5A Oxidation of Amines

Primary and secondary aliphatic amines are subject to oxidation, although in most instances useful products are not obtained. Complicated side reactions often occur, causing the formation of complex mixtures.

Tertiary amines can be oxidized cleanly to tertiary amine oxides. This transformation can be brought about by using hydrogen peroxide or a peroxy acid:



A tertiary amine oxide

Tertiary amine oxides undergo a useful elimination reaction to be discussed in Section 18.11B.

Arylamines are very easily oxidized by a variety of reagents, including the oxygen in air. Oxidation is not confined to the amino group but also occurs in the ring. (The amino group through its electron-donating ability makes the ring electron rich and hence especially susceptible to oxidation.) The oxidation of other functional groups on an aromatic ring cannot usually be accomplished when an amino group is present on the ring, because oxidation of the ring takes place first.

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18.6 | REACTIONS OF AMINES WITH NITROUS ACID

Nitrous acid (HO—N=O) is a weak, unstable acid. It is always prepared *in situ*, usually by treating sodium nitrite ($NaNO_2$) with an aqueous solution of a strong acid:

$$HCl_{(aq)} + NaNO_{2(aq)} \longrightarrow HONO_{(aq)} + NaCl_{(aq)}$$
$$H_2SO_4 + 2\,NaNO_{2(aq)} \longrightarrow 2\,HONO_{(aq)} + Na_2SO_{4(aq)}$$

Nitrous acid reacts with all classes of amines. The products that we obtain from these reactions depend on whether the amine is primary, secondary, or tertiary and whether the amine is aliphatic or aromatic.

18.6A Reactions of Primary Aliphatic Amines with Nitrous Acid

Primary aliphatic amines react with nitrous acid through a reaction called *diazotization* to yield highly unstable aliphatic **diazonium salts**. Even at low temperatures, *aliphatic* diazonium salts decompose spontaneously by losing nitrogen to form carbocations. The carbocations go on to produce mixtures of alkenes, alcohols, and alkyl halides by removal of a proton, reaction with H_2O, and reaction with X^-:

General Reaction

$$R{-}NH_2 + NaNO_2 + 2\,HX \xrightarrow[H_2O]{(HONO)} \left[R{-}\overset{+}{N}{\equiv}N{:}\ X^-\right] + NaX + 2\,H_2O$$

1° Aliphatic amine — **Aliphatic diazonium salt (highly unstable)**

$$\left[R{-}\overset{+}{N}{\equiv}N{:}\ X^-\right] \xrightarrow{-N_2\ (\text{i.e.,}\ :N{\equiv}N:)} R^+ + X^- \longrightarrow \text{Alkenes, alcohols, alkyl halides}$$

- Diazotizations of primary aliphatic amines are of little synthetic importance because they yield such a complex mixture of products.

Diazotizations of primary aliphatic amines are used in some analytical procedures, however, because the evolution of nitrogen is quantitative. They can also be used to generate and thus study the behavior of carbocations in water, acetic acid, and other solvents.

18.6B Reactions of Primary Arylamines with Nitrous Acid

The most important reaction of amines with nitrous acid, by far, is the reaction of primary arylamines. We shall see why in Section 18.7.

- Primary arylamines react with nitrous acid to give arenediazonium salts.

Even though arenediazonium salts are unstable, they are still far more stable than aliphatic **diazonium salts**; they do not decompose at an appreciable rate in solution when the temperature of the reaction mixture is kept below 5 °C:

$$Ar{-}NH_2 + NaNO_2 + 2\,HX \longrightarrow Ar{-}\overset{+}{N}{\equiv}N{:}\ X^- + NaX + 2\,H_2O$$

Primary arylamine — **Arenediazonium salt (stable if kept below 5 °C)**

Diazotization of a primary amine takes place through a series of steps. In the presence of strong acid, nitrous acid dissociates to produce ^+NO ions. These ions then react with the nitrogen of the amine to form an unstable *N*-nitrosoaminium ion as an intermediate. This intermediate then loses a proton to form an *N*-nitrosoamine, which, in turn, tautomerizes to a diazohydroxide in a reaction that is similar to keto–enol tautomerization. Then, in the presence of acid, the diazohydroxide loses water to form the diazonium ion.

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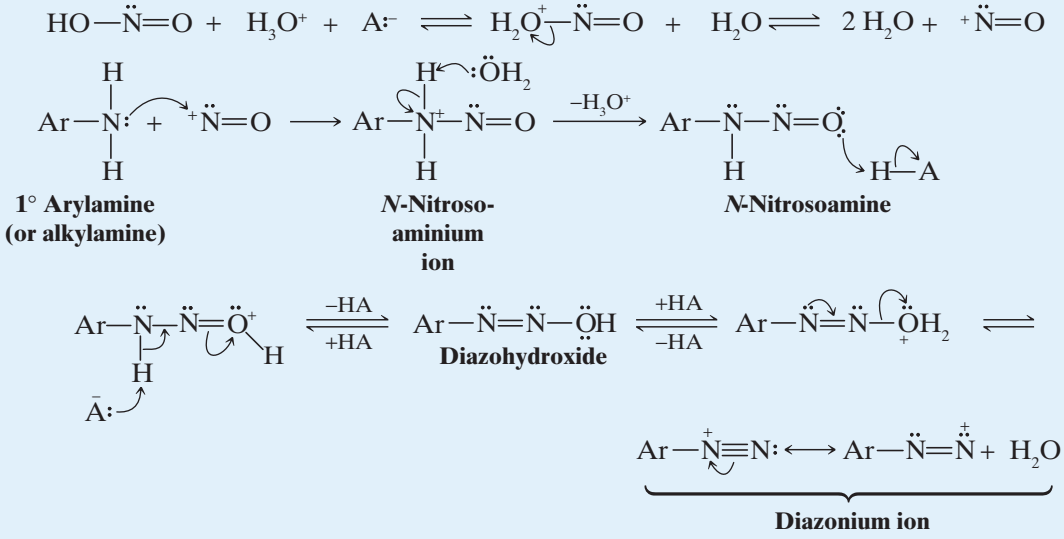
A MECHANISM FOR THE REACTION — Diazotization



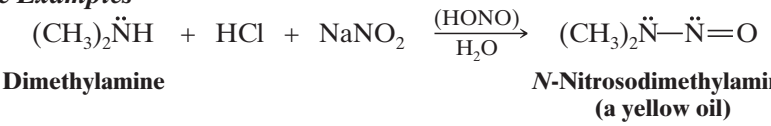
- Diazotization reactions of primary arylamines are of considerable synthetic importance because the diazonium group, —$\overset{+}{N}$≡N: can be replaced by a variety of other functional groups.

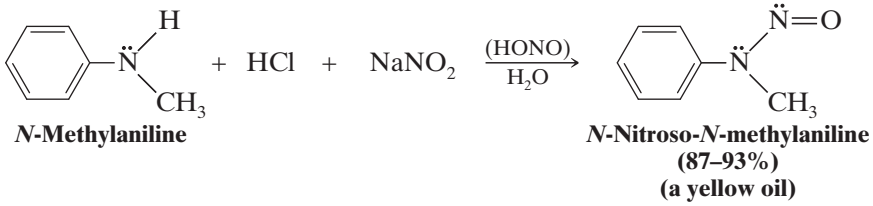
We shall examine these reactions in Section 18.7.

18.6C Reactions of Secondary Amines with Nitrous Acid

Secondary amines—both aryl and alkyl—react with nitrous acid to yield *N*-nitrosoamines. ***N*-Nitrosoamines** usually separate from the reaction mixture as oily yellow liquids:

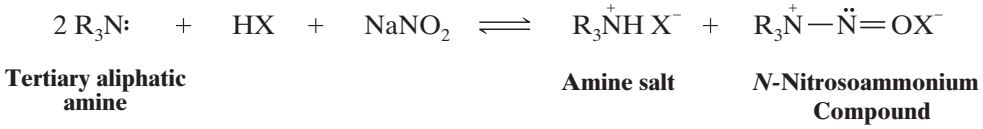
Specific Examples





18.6D Reactions of Tertiary Amines with Nitrous Acid

When a tertiary aliphatic amine is mixed with nitrous acid, an equilibrium is established among the tertiary amine, its salt, and an *N*-nitrosoammonium compound:



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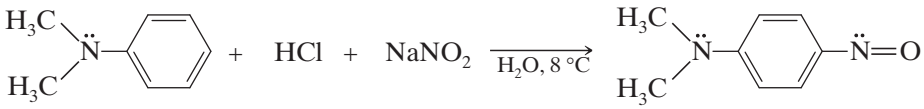
Although *N*-nitrosoammonium compounds are stable at low temperatures, at higher temperatures and in aqueous acid they decompose to produce aldehydes or ketones. These reactions are of little synthetic importance, however.

Tertiary arylamines react with nitrous acid to form *C*-nitroso aromatic compounds. Nitrosation takes place almost exclusively at the para position if it is open and, if not, at the ortho position. The reaction (see Practice Problem 18.7) is another example of electrophilic aromatic substitution.

Specific Example



p-Nitroso-*N*,*N*-dimethylaniline (80–90%)

Practice Problem 18.7

Para-nitrosation of *N*,*N*-dimethylaniline (*C*-nitrosation) is believed to take place through an electrophilic attack by $\overset{+}{N}O$ ions. **(a)** Show how $\overset{+}{N}O$ ions might be formed in an aqueous solution of $NaNO_2$ and HCl. **(b)** Write a mechanism for *p*-nitrosation of *N*,*N*-dimethylaniline. **(c)** Tertiary aromatic amines and phenols undergo *C*-nitrosation reactions, whereas most other benzene derivatives do not. How can you account for this difference?

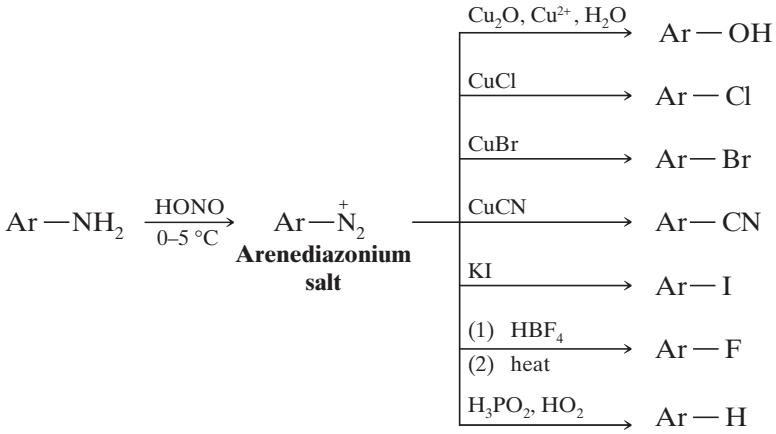
18.7 | REPLACEMENT REACTIONS OF ARENEDIAZONIUM SALTS

- Arenediazonium salts are highly useful intermediates in the synthesis of aromatic compounds, because the diazonium group can be replaced by any one of a number of other atoms or groups, including —F, —Cl, —Br, —I, —CN, —OH, and —H.

Diazonium salts are almost always prepared by diazotizing primary aromatic amines. Primary arylamines can be synthesized through reduction of nitro compounds that are readily available through direct nitration reactions.

18.7A Syntheses Using Diazonium Salts

Most arenediazonium salts are unstable at temperatures above 5–10 °C, and many explode when dry. Fortunately, however, most of the replacement reactions of diazonium salts do not require their isolation. We simply add another reagent (CuCl, CuBr, KI, etc.) to the mixture, gently warm the solution, and the replacement (accompanied by the evolution of nitrogen) takes place:



Only in the replacement of the diazonium group by —F need we isolate a diazonium salt. We do this by adding HBF_4 to the mixture, causing the sparingly soluble and reasonably stable arenediazonium fluoroborate, $ArN_2^+ BF_4^-$, to precipitate.

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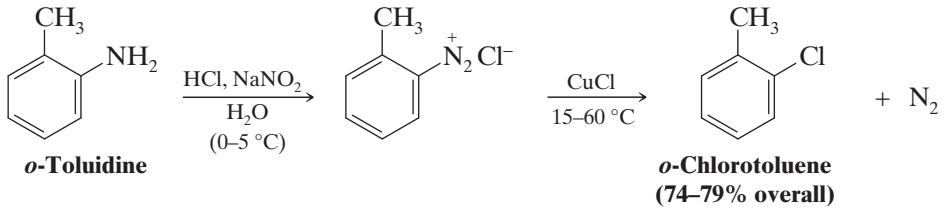
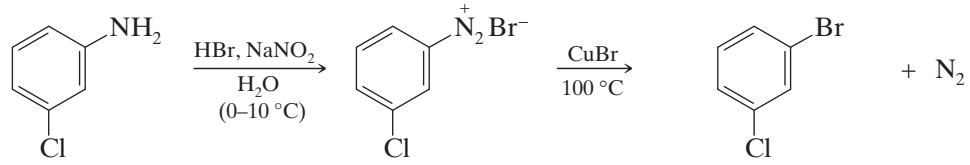
18.7B The Sandmeyer Reaction: Replacement of the Diazonium Group by —Cl, —Br, or —CN

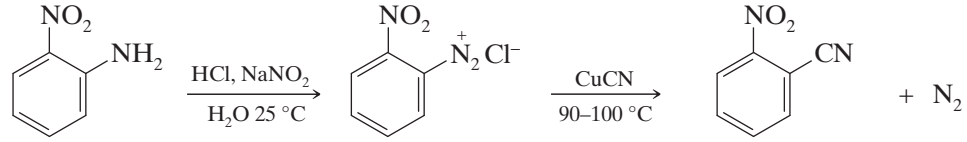
Arenediazonium salts react with cuprous chloride, cuprous bromide, and cuprous cyanide to give products in which the diazonium group has been replaced by —Cl, —Br, and —CN, respectively. These reactions are known generally as *Sandmeyer reactions*. Several specific examples follow. The mechanisms of these replacement reactions are not fully understood; the reactions appear to be radical in nature, not ionic.



***o*-Toluidine** → ***o*-Chlorotoluene (74–79% overall)**



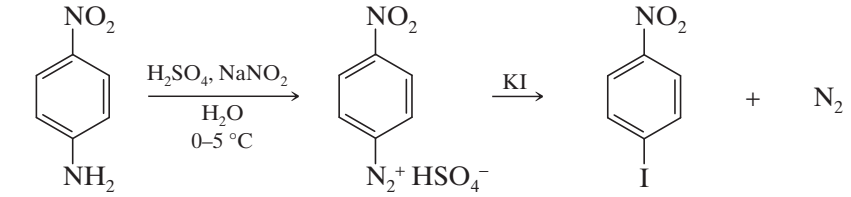
***m*-Chloroaniline** → ***m*-Bromochlorobenzene (70% overall)**



***o*-Nitroaniline** → ***o*-Nitrobenzonitrile (65% overall)**

18.7C Replacement by —I

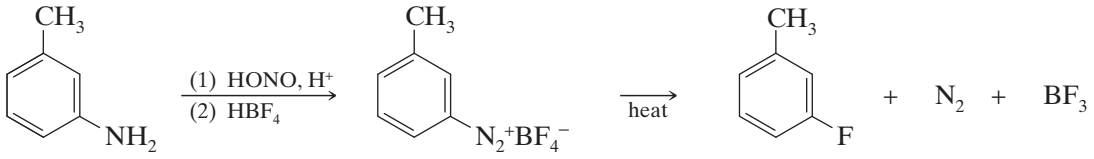
Arenediazonium salts react with potassium iodide to give products in which the diazonium group has been replaced by —I. An example is the synthesis of *p*-iodonitrobenzene:



***p*-Nitroaniline** → ***p*-Iodonitrobenzene (81% overall)**

18.7D Replacement by —F

The diazonium group can be replaced by fluorine by treating the diazonium salt with fluoroboric acid (HBF_4). The diazonium fluoroborate that precipitates is isolated, dried, and heated until decomposition occurs. An aryl fluoride is produced:



***m*-Toluidine** → ***m*-Toluenediazonium fluoroborate (79%)** → ***m*-Fluorotoluene (69%)**

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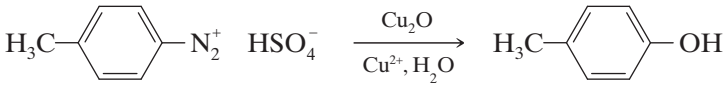
18.7E Replacement by —OH

The diazonium group can be replaced by a hydroxyl group by adding cuprous oxide to a dilute solution of the diazonium salt containing a large excess of cupric nitrate:



***p*-Toluenediazonium hydrogen sulfate** → ***p*-Cresol (93%)**

This variation of the Sandmeyer reaction (developed by T. Cohen, University of Pittsburgh) is a much simpler and safer procedure than an older method for phenol preparation, which required heating the diazonium salt with concentrated aqueous acid.

Practice Problem 18.8

In the preceding examples of diazonium reactions, we have illustrated syntheses beginning with the compounds (a)–(d) here. Show how you might prepare each of the following compounds from benzene:

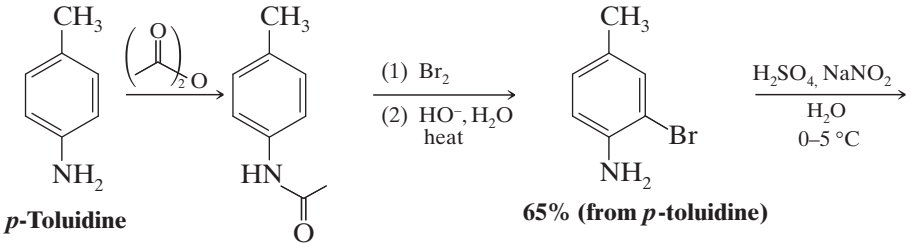
(a) *m*-Chloroaniline **(b)** *m*-Bromoaniline **(c)** *o*-Nitroaniline **(d)** *p*-Nitroaniline

18.7F Replacement by Hydrogen: Deamination by Diazotization

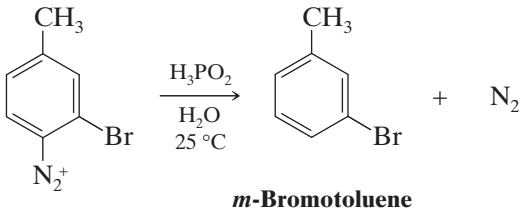
Arenediazonium salts react with hypophosphorous acid (H_3PO_2) to yield products in which the diazonium group has been replaced by —H.

Since we usually begin a synthesis using diazonium salts by nitrating an aromatic compound, that is, replacing —H by $-NO_2$ and then by $-NH_2$, it may seem strange that we would ever want to replace a diazonium group by —H. However, replacement of the diazonium group by —H can be a useful reaction. We can introduce an amino group into an aromatic ring to influence the orientation of a subsequent reaction. Later we can remove the amino group (i.e., carry out a *deamination*) by diazotizing it and treating the diazonium salt with H_3PO_2.

We can see an example of the usefulness of a deamination reaction in the following synthesis of *m*-bromotoluene.



***p*-Toluidine** → **65% (from *p*-toluidine)**



***m*-Bromotoluene (85% from 2-bromo-4-methylaniline)**

We cannot prepare *m*-bromotoluene by direct bromination of toluene or by a Friedel–Crafts alkylation of bromobenzene because both reactions give *o*- and *p*-bromotoluene. (Both CH_3— and Br— are ortho–para directors.) However, if we begin with *p*-toluidine (prepared by nitrating toluene, separating the para isomer, and reducing the nitro group), we can carry out the sequence of reactions shown and obtain *m*-bromotoluene in good yield. The first step, synthesis of the *N*-acetyl derivative of *p*-toluidine, is done to reduce the activating effect of the amino group. (Otherwise both ortho positions would be brominated.) Later, the acetyl group is removed by hydrolysis.

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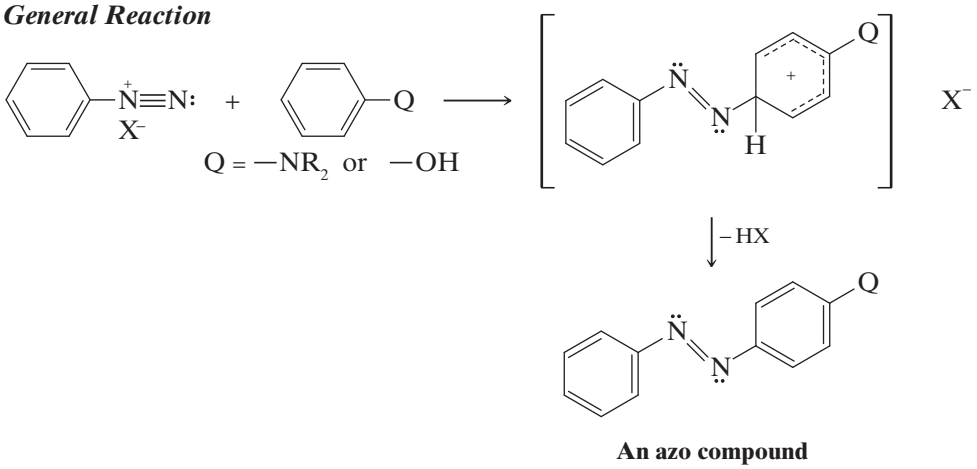
18.8 | COUPLING REACTIONS OF ARENEDIAZONIUM SALTS

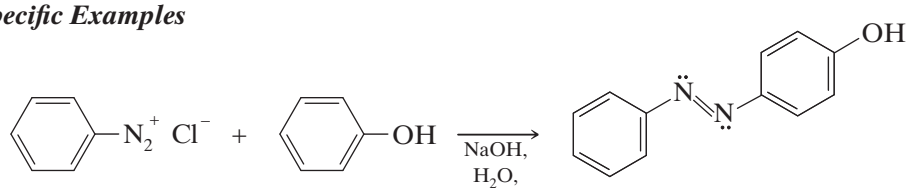
Arenediazonium ions are weak electrophiles; they react with highly reactive aromatic compounds—with phenols and tertiary arylamines—to yield *azo* compounds. This electrophilic aromatic substitution is often called a *diazo coupling reaction*.

General Reaction

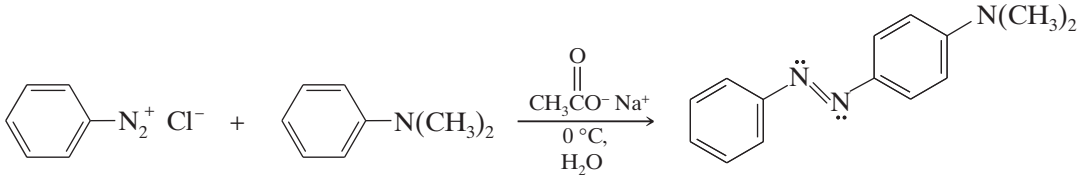


An azo compound

Specific Examples

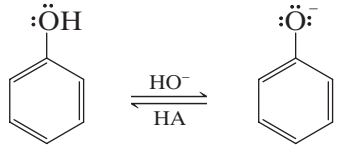


Benzenediazonium chloride + **Phenol** → ***p*-(Phenylazo)phenol (orange solid)**

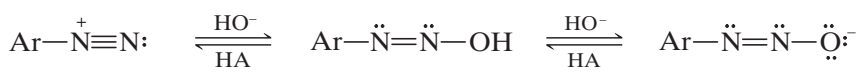


Benzenediazonium chloride + ***N,N*-Dimethylaniline** → ***N,N*-Dimethyl-*p*-(phenylazo)aniline (yellow solid)**

Couplings between arenediazonium cations and phenols take place most rapidly in *slightly* alkaline solution. Under these conditions an appreciable amount of the phenol is present as a phenoxide ion, ArO^-, and phenoxide ions are even more reactive toward electrophilic substitution than are phenols themselves. (Why?) If the solution is too alkaline (pH > 10), however, the arenediazonium salt itself reacts with hydroxide ion to form a relatively unreactive diazohydroxide or diazotate ion:



Phenol (couples slowly) ⇌ **Phenoxide ion (couples rapidly)**



Arenediazonium ion (couples) ⇌ **Diazohydroxide (does not couple)** ⇌ **Diazotate ion (does not couple)**

Couplings between arenediazonium cations and amines take place most rapidly in slightly acidic solutions (pH 5–7). Under these conditions the concentration of the arenediazonium cation is at a maximum; at the same time an excessive amount of the amine has not been converted to an unreactive aminium salt:

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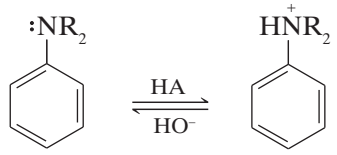
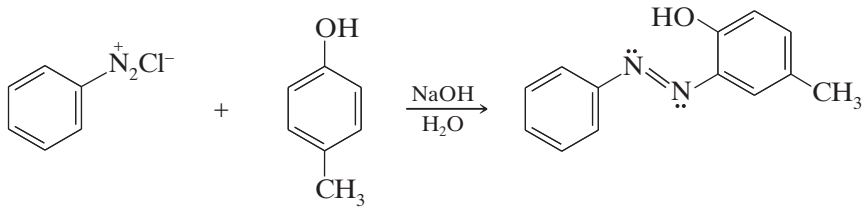


Amine (couples) **Aminium salt (does not couple)**

If the pH of the solution is lower than 5, the rate of amine coupling is low.

With phenols and aniline derivatives, coupling takes place almost exclusively at the para position if it is open. If it is not, coupling takes place at the ortho position.

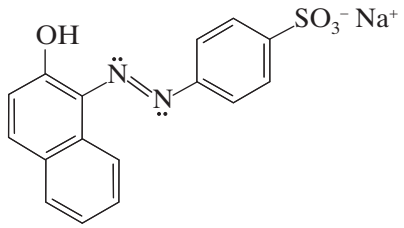


4-Methylphenol (*p*-cresol) **4-Methyl-2-(phenylazo)phenol**

Azo compounds are usually intensely colored because the azo (diazenediyl) linkage, —N═N—, brings the two aromatic rings into conjugation. This gives an extended system of delocalized π electrons and allows absorption of light in the visible region. Azo compounds, because of their intense colors and because they can be synthesized from relatively inexpensive compounds, are used extensively as *dyes*.

Azo dyes almost always contain one or more $-SO_3^-Na^+$ groups to confer water solubility on the dye and assist in binding the dye to the surfaces of polar fibers (wool, cotton, or nylon). Many dyes are made by coupling reactions of naphthylamines and naphthols.

Orange II, a dye introduced in 1876, is made from 2-naphthol:



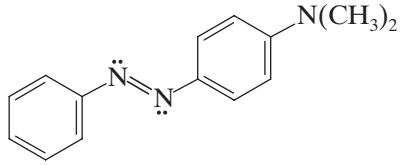
Orange II

Practice Problem 18.9

Outline a synthesis of orange II from 2-naphthol and *p*-aminobenzenesulfonic acid.

Practice Problem 18.10

Butter yellow is a dye once used to color margarine. It has since been shown to be carcinogenic, and its use in food is no longer permitted. Outline a synthesis of butter yellow from benzene and *N*,*N*-dimethylaniline.



Butter yellow

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Practice Problem 18.11

Azo compounds can be reduced to amines by a variety of reagents including stannous chloride ($SnCl_2$):

$$Ar{-}N{=}N{-}Ar' \xrightarrow{SnCl_2} ArNH_2 + Ar'NH_2$$

This reduction can be useful in synthesis as the following example shows:

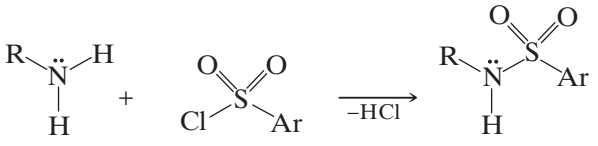
$$\text{4-Ethoxyaniline} \xrightarrow[\text{(2) Phenol, } HO^-]{\text{(1) HONO, } H_3O^+} \mathbf{A}\ (C_{14}H_{14}N_2O_2) \xrightarrow{NaOH,\ CH_3CH_2Br} \mathbf{B}\ (C_{16}H_{18}N_2O_2) \xrightarrow{SnCl_2}$$

$$\text{two molar equivalents of } \mathbf{C}\ (C_8H_{11}NO) \xrightarrow{\text{acetic anhydride}} \text{phenacetin } (C_{10}H_{13}NO_2)$$

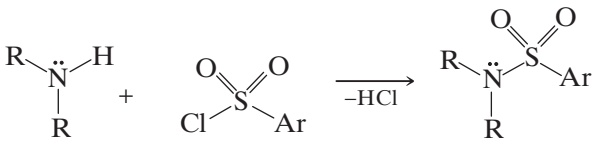
Give a structure for phenacetin and for the intermediates **A**, **B**, and **C**.

18.9 | REACTIONS OF AMINES WITH SULFONYL CHLORIDES

Primary and secondary amines react with sulfonyl chlorides to form **sulfonamides**:

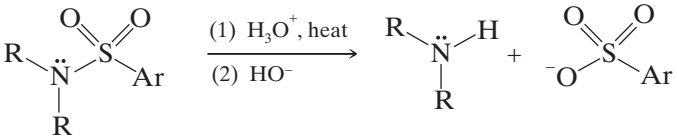


1° Amine | **Sulfonyl chloride** | ***N*-Substituted sulfonamide**



2° Amine | ***N*,*N*-Disubstituted sulfonamide**

When heated with aqueous acid, sulfonamides are hydrolyzed to amines:



This hydrolysis is much slower, however, than hydrolysis of carboxamides.

18.9A The Hinsberg Test

- Sulfonamide formation is the basis for a chemical test, called the Hinsberg test, that can be used to demonstrate whether an amine is primary, secondary, or tertiary.

A Hinsberg test involves two steps. First, a mixture containing a small amount of the amine and benzenesulfonyl chloride is shaken with *excess* potassium hydroxide. Next, after allowing time for a reaction to take place, the mixture is acidified. Each type of amine—primary, secondary, or tertiary—gives a different set of *visible* results after each of these two stages of the test.

Primary amines react with benzenesulfonyl chloride to form *N*-substituted benzenesulf-onamides. These, in turn, undergo acid–base reactions with the excess potassium hydroxide to form water-soluble potassium salts. (These reactions take place because the hydrogen attached to nitrogen is made acidic by the strongly electron-withdrawing $-SO_2-$ group.) At this stage our test tube contains a clear solution. Acidification of this solution will, in the next stage, cause the water-insoluble *N*-substituted sulfonamide to precipitate:

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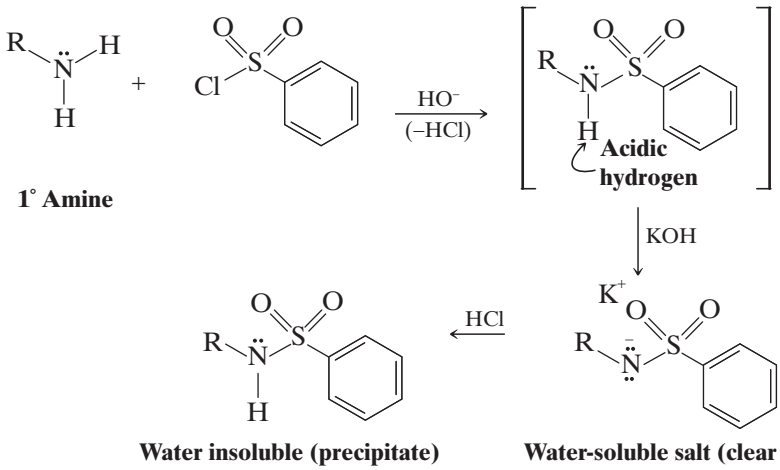
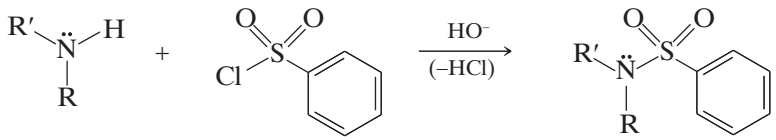


1° Amine

Water insoluble (precipitate) **Water-soluble salt (clear solution)**

Secondary amines react with benzenesulfonyl chloride in aqueous potassium hydroxide to form insoluble *N*,*N*-disubstituted sulfonamides that precipitate after the first stage. *N*,*N*-Disubstituted sulfonamides do not dissolve in aqueous potassium hydroxide because they do not have an acidic hydrogen. Acidification of the mixture obtained from a secondary amine produces no visible result; the nonbasic *N*,*N*-disubstituted sulfonamide remains as a precipitate and no new precipitate forms:

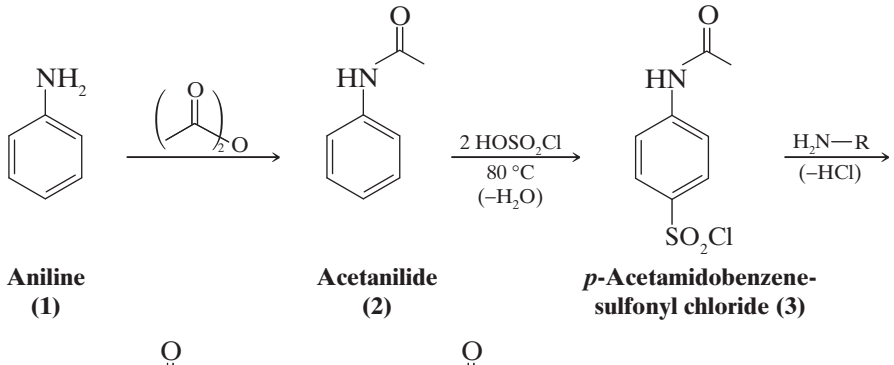


Water insoluble (precipitate)

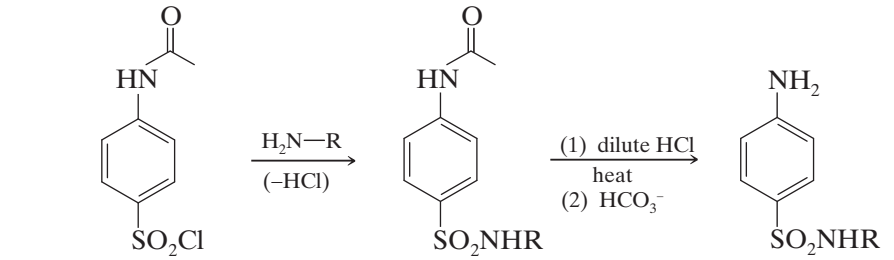
If the amine is a tertiary amine and if it is water insoluble, no apparent change will take place in the mixture as we shake it with benzenesulfonyl chloride and aqueous KOH. When we acidify the mixture, the tertiary amine dissolves because it forms a water-soluble salt.

18.10 | SYNTHESIS OF SULFA DRUGS

Sulfanilamides (**sulfa drugs**) can be synthesized from aniline through the following sequence of reactions:



Aniline (1) **Acetanilide (2)** ***p*-Acetamidobenzene-sulfonyl chloride (3)**



***p*-Acetamidobenzene-sulfonyl chloride (3)** **(4)** **A sulfanilamide (5)**

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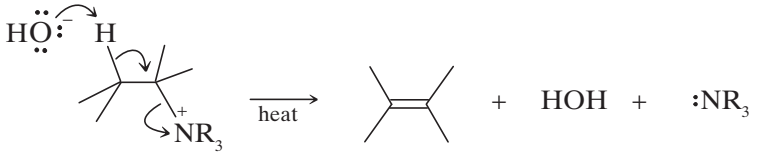
Acetylation of aniline produces acetanilide **(2)** and protects the amino group from the reagent to be used next. Treatment of **2** with chlorosulfonic acid brings about an electrophilic aromatic substitution reaction and yields *p*-acetamidobenzenesulfonyl chloride **(3)**. Addition of ammonia or a primary amine gives the diamide, **4** (an amide of both a carboxylic acid and a sulfonic acid). Finally, refluxing **4** with dilute hydrochloric acid selectively hydrolyzes the carboxamide linkage and produces a sulfanilamide. (Hydrolysis of carboxamides is much more rapid than that of sulfonamides.)

18.11 | ELIMINATIONS INVOLVING AMMONIUM COMPOUNDS

18.11A The Hofmann Elimination

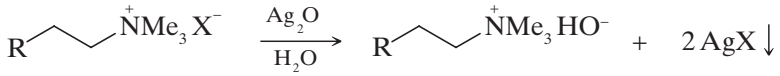
All of the eliminations that we have described so far have involved electrically neutral substrates. However, eliminations are known in which the substrate bears a positive charge. One of the most important of these is the E2-type elimination that takes place when a quaternary ammonium hydroxide is heated. The products are an alkene, water, and a tertiary amine:



A quaternary ammonium hydroxide — **An alkene** — **A tertiary amine**

This reaction was discovered in 1851 by August W. von Hofmann and has since come to bear his name.

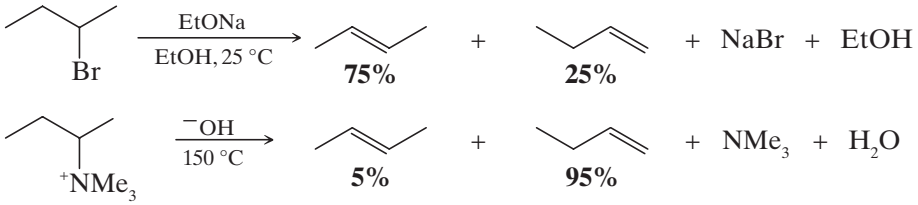
Quaternary ammonium hydroxides can be prepared from quaternary ammonium halides in aqueous solution through the use of silver oxide or an ion exchange resin:



A quaternary ammonium halide — **A quaternary ammonium hydroxide**

Silver halide precipitates from the solution and can be removed by filtration. The quaternary ammonium hydroxide can then be obtained by evaporation of the water.

Although most eliminations involving neutral substrates tend to follow the *Zaitsev rule* (Section 7.6B), eliminations with charged substrates tend to follow what is called the **Hofmann rule** and *yield mainly the least substituted alkene*. We can see an example of this behavior if we compare the following reactions:



The precise mechanistic reasons for these differences are complex and are not yet fully understood. One possible explanation is that the transition states of elimination reactions with charged substrates have considerable carbanionic character. Therefore, these transition states show little resemblance to the final alkene product and are not stabilized appreciably by a developing double bond:



Carbanion-like transition state (gives Hofmann orientation) — **Alkene-like transition state (gives Zaitsev orientation)**

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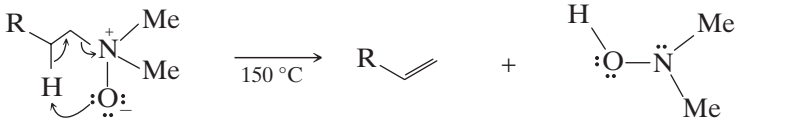
With a charged substrate, the base attacks the most acidic hydrogen instead. A primary hydrogen atom is more acidic because its carbon atom bears only one electron-releasing group.

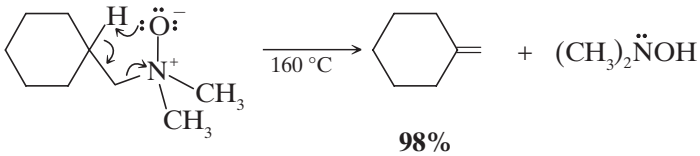
18.12 | THE COPE ELIMINATION

Tertiary amine oxides undergo the elimination of a dialkylhydroxylamine when they are heated. The reaction is called the Cope elimination, it is a syn elimination and proceeds through a cyclic transition state.



A tertiary amine oxide **An alkene** ***N,N*-Dimethylhydroxylamine**

Tertiary amine oxides are easily prepared by treating tertiary amines with hydrogen peroxide (Section 18.5A). The Cope elimination is useful synthetically. Consider the following synthesis of methylenecyclohexane:

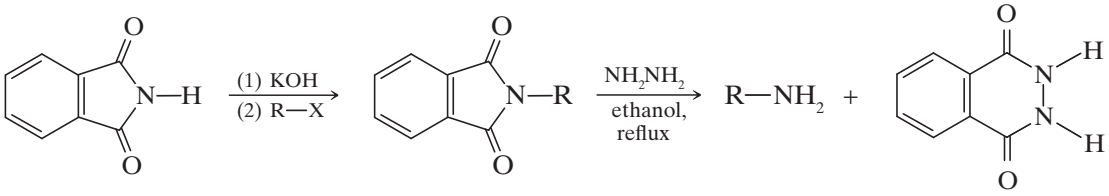


98%

18.13 | SUMMARY OF PREPARATIONS AND REACTIONS OF AMINES

Preparation of Amines

1. Gabriel synthesis (discussed in Section 18.4A):



2. By reduction of alkyl azides (discussed in Section 18.4A):

$$R{-}Br \xrightarrow[\text{ethanol}]{NaN_3} R{-}N{=}\overset{+}{N}{=}N^- \xrightarrow[\text{or } LiAlH_4]{\text{Na/alcohol}} R{-}NH_2$$

3. By amination of alkyl halides (discussed in Section 18.4A):

$$R{-}Br + NH_3 \longrightarrow RNH_3^+\,Br^- + R_2NH_2^+\,Br^- + R_3NH^+\,Br^- + R_4N^+\,Br^-$$

$$\downarrow HO^-$$

$$RNH_2 + R_2NH + R_3N + R_4N^+\,OH^-$$

(A mixture of products results.)

(R = a 1° alkyl group)

4. By reduction of nitroarenes (discussed in Section 18.4B):

$$Ar{-}NO_2 \xrightarrow[\text{or}\ (1)\ Fe/HCl\ (2)\ NaOH]{H_2,\ \text{catalyst}} Ar{-}NH_2$$

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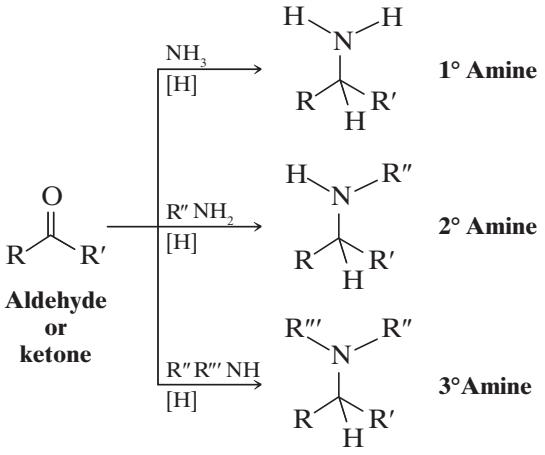
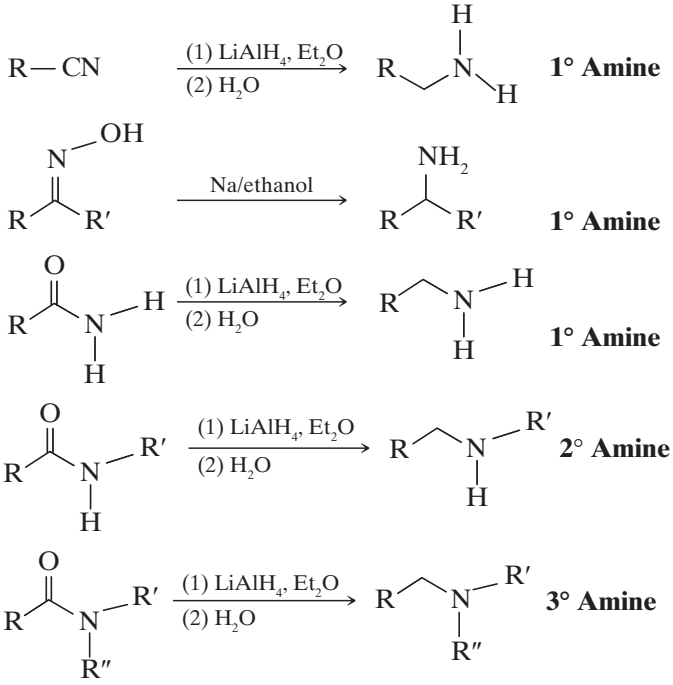
5. By reductive amination (discussed in Section 18.4C):

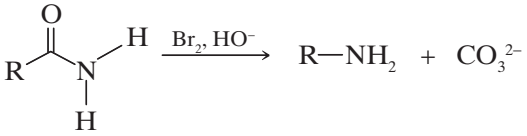


6. By reduction of nitriles, oximes, and amides (discussed in Section 18.4D):

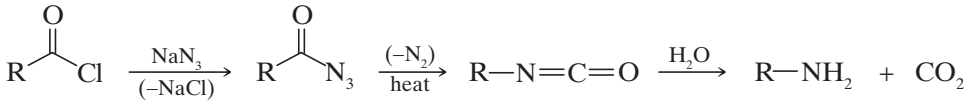


7. Through the Hofmann and Curtius rearrangements (discussed in Section 18.4E):

Hofmann Rearrangement



Curtius Rearrangement



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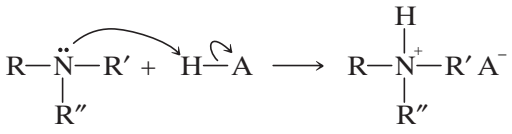
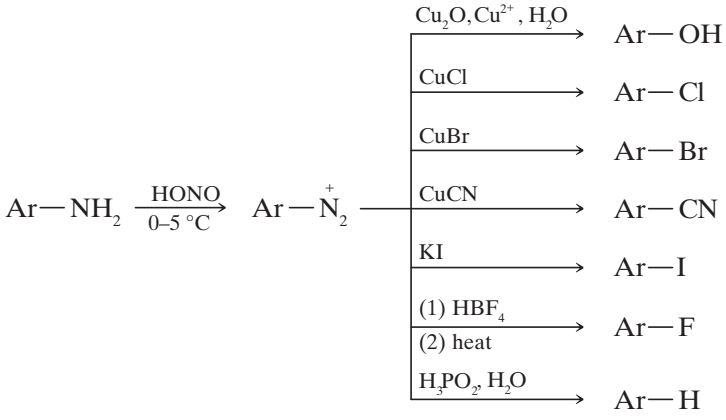
Reactions of Amines

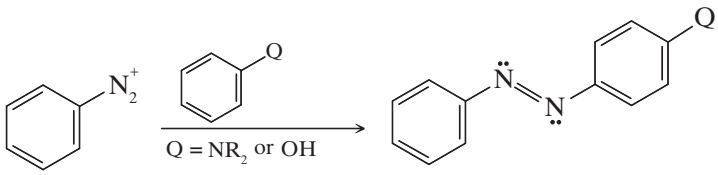
1. As bases (discussed in Section 18.3):



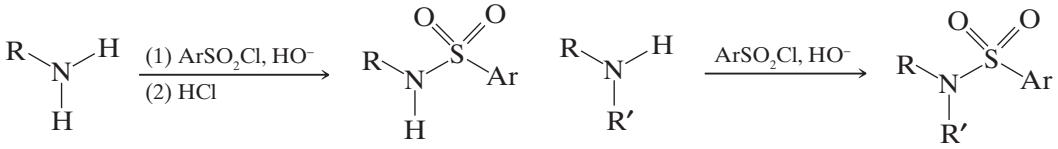
(R, R′, and/or R″ may be alkyl, H, or Ar)

2. Diazotization of 1° arylamines and replacement of, or coupling with, the diazonium group (discussed in Sections 18.7 and 18.8):

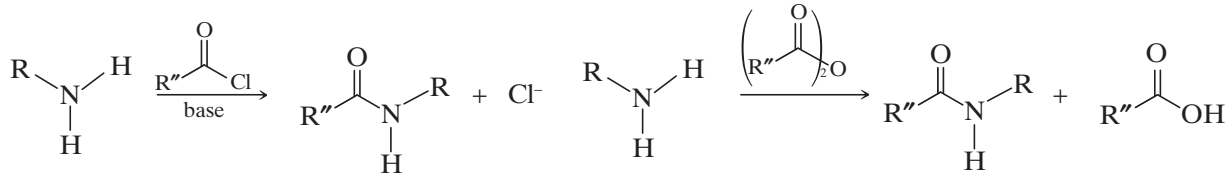


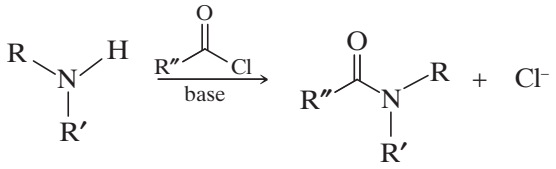


3. Conversion to sulfonamides (discussed in Section 18.9):



4. Conversion to amides (discussed in Section 17.8):





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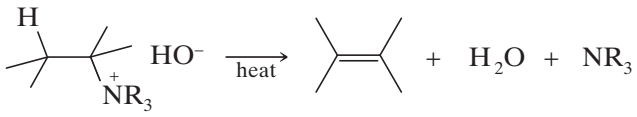
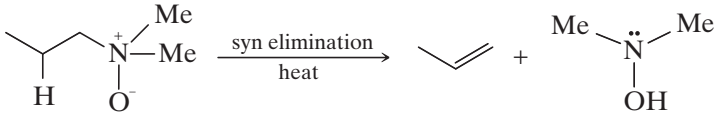
5. Hofmann and Cope eliminations (discussed in Sections 18.11 and 18.12):

Hofmann Elimination



Cope Elimination

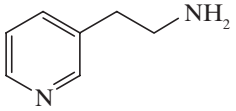


REVIEW PROBLEMS

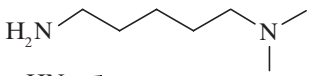
Amine Synthesis and Reactivity

18.12 Which is the most basic nitrogen in each compound. Explain your choices.

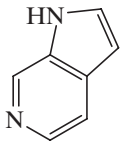
(a)



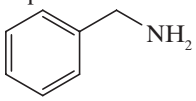
(b)



(c)

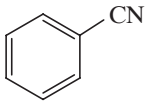


18.13 Show how you might prepare benzylamine from each of the following compounds:



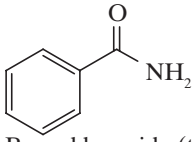
Benzylamine

(a)



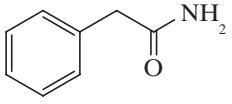
Benzonitrile

(b)



Benzamide

(c) Benzyl bromide (two ways)
(d) Benzyl tosylate
(e) Benzaldehyde
(f) Phenylnitromethane
(g)

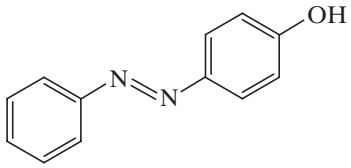


Phenylacetamide

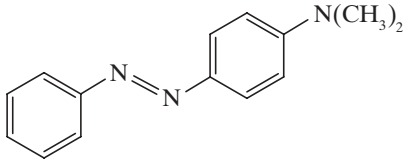
18.14 Show how you might prepare aniline from each of the following compounds:
(a) Benzene **(b)** Bromobenzene **(c)** Benzamide

18.15 Show how you might synthesize each of the following compounds from 1-butanol:
(a) Butylamine (free of 2° and 3° amines)
(b) Pentylamine
(c) Propylamine
(d) Butylmethylamine

18.16 Show how you might convert aniline into each of the following compounds. (You need not repeat steps carried out in earlier parts of this problem.)
(a) Acetanilide
(b) *N*-Phenylphthalimide
(c) *p*-Nitroaniline
(d) Sulfanilamide
(e) *N*,*N*-Dimethylaniline
(f) Fluorobenzene
(g) Chlorobenzene
(h) Bromobenzene
(i) Iodobenzene
(j) Benzonitrile
(k) Benzoic acid
(l) Phenol
(m) Benzene
(n)

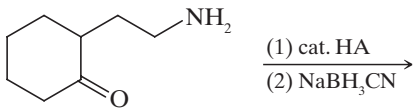


(o)

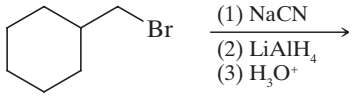


18.17 Provide the major organic product from each of the following reactions.

(a)



(b)



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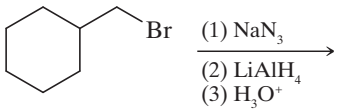
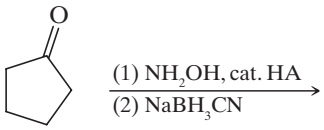
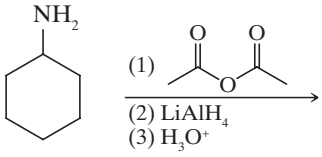
(c)



(d)



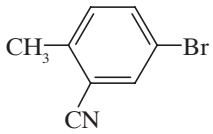
(e)



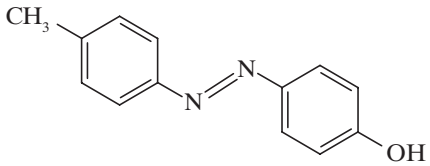
18.18 Starting with benzene or toluene, outline a synthesis of each of the following compounds using diazonium salts as intermediates. (You need not repeat syntheses carried out in earlier parts of this problem.)

(a) *p*-Fluorotoluene
(b) *o*-Iodotoluene
(c) *p*-Cresol
(d) *m*-Dichlorobenzene
(e) *m*-$C_6H_4(CN)_2$
(f) *m*-Bromobenzonitrile
(g) 1,3-Dibromo-5-nitrobenzene
(h) 3,5-Dibromoaniline
(i) 3,4,5-Tribromophenol
(j) 3,4,5-Tribromobenzonitrile
(k) 2,6-Dibromobenzoic acid
(l) 1,3-Dibromo-2-iodobenzene

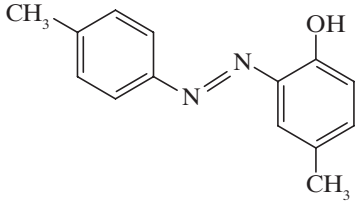
(m)



(n)



(o)

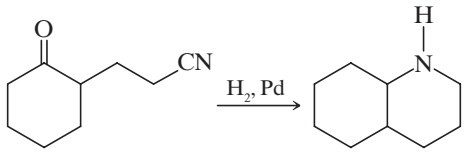


18.19 Write equations for simple chemical tests that would distinguish between

(a) Benzylamine and benzamide
(b) Allylamine and propylamine
(c) *p*-Toluidine and *N*-methylaniline
(d) Cyclohexylamine and piperidine
(e) Pyridine and benzene
(f) Cyclohexylamine and aniline
(g) Triethylamine and diethylamine
(h) Tripropylaminium chloride and tetrapropylammonium chloride
(i) Tetrapropylammonium chloride and tetrapropylammonium hydroxide

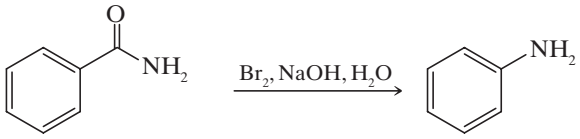
Mechanisms

18.20 Using reactions that we have studied in this chapter, propose a mechanism that accounts for the following reaction:

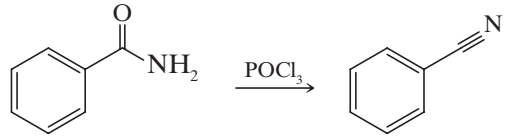


18.21 Provide a detailed mechanism for each of the following reactions.

(a)



(b)



18.22 Suggest an experiment to test the proposition that the Hofmann reaction is an intramolecular rearrangement—that is, one in which the migrating R group never fully separates from the amide molecule.

ADDITIONAL OBJECTIVE QUESTIONS

Single Correct Choice Type

1. Acetamide is treated separately with the following reagents. Which of these would give methyl amine?

(a) PCl_5 **(b)** $NaOH + Br_2$
(c) Soda lime **(d)** Hot conc. H_2SO_4

2. Best method for preparing primary amines from alkyl halides without changing the number of carbon atoms in the chain is

(a) Hoffman Bromamide reaction.
(b) Gabriel phthalimide synthesis.
(c) Sandmeyer reaction.
(d) reaction with NH_3

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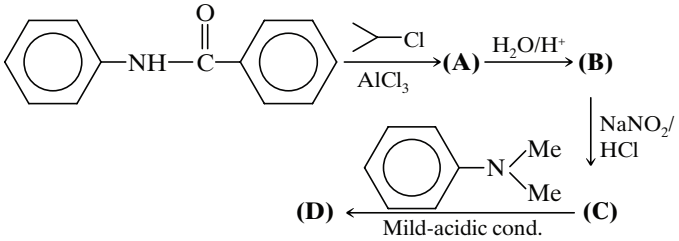
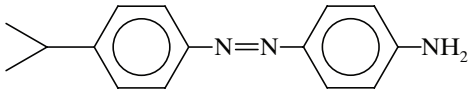
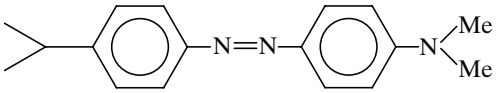
3. The Gabriel synthesis is a method to generate primary
- **(a)** nitriles.
- **(b)** acids.
- **(c)** alkylamines.
- **(d)** aldehydes.

4. Product (D) in the below reaction is



(a)


(b)


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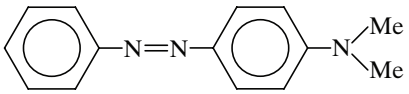
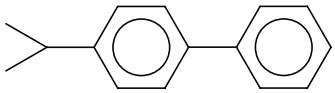
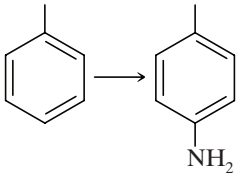


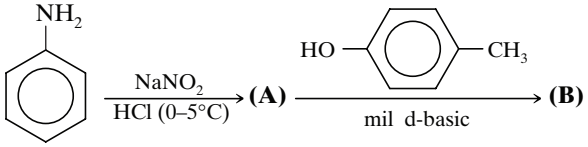
(d)


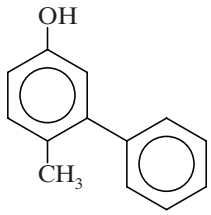
5. Which method below will perform the indicated transformation?



- **(a)** NH_3, heat
- **(b)** HNO_3, H_2SO_4
- **(c)** (i) Br_2, $FeBr_3$; (ii) $NaNH_2$, NH_3, heat
- **(d)** (i) HNO_3, H_2SO_4; (ii) $NaNH_2$, NH_3, heat

6. Product (B) in the below reaction is



(a)


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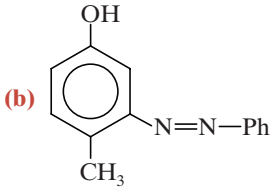

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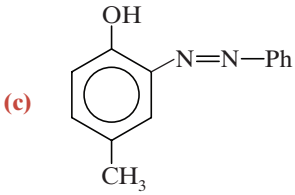
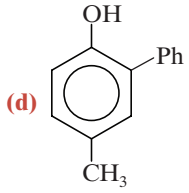
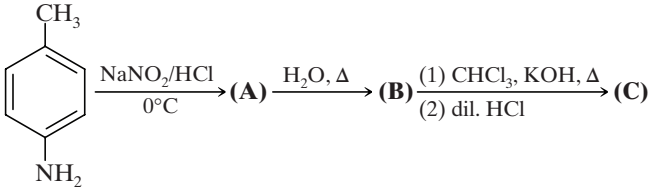
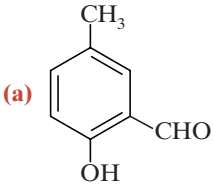


(d)


7. An organic compound A upon reacting with NH_3 gives B. On heating, B gives C. C in presence of KOH reacts with Br_2 to give $CH_3CH_2NH_2$. A is
- **(a)** CH_3CH_2COOH
- **(b)** CH_3COOH
- **(c)** $CH_3CH_2CH_2COOH$
- **(d)** $CH_3-\underset{\displaystyle CH_3}{\overset{}{CH}}-COOH$

8. Identify (C) in the following reaction sequence



(a)


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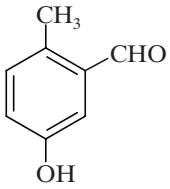
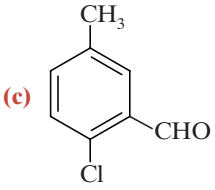
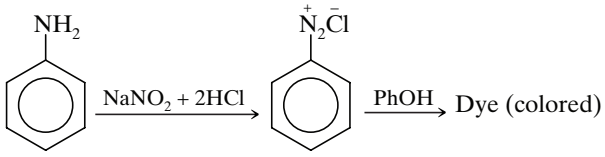


(c)


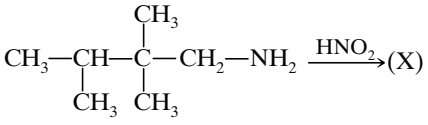
(d) None of these

9. In the following reaction, what is the color of the dye formed?



(a) Red **(b)** Orange **(c)** Yellow **(d)** Blue

10. The major product (X) in the following reaction is



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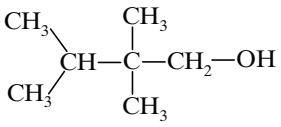

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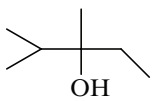

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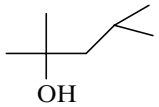

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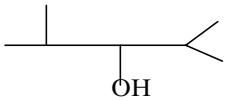

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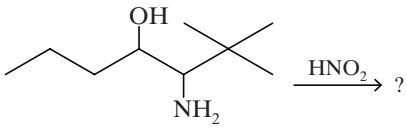
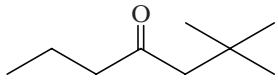
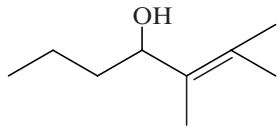
11. Which one of the following methods is neither meant for the synthesis nor for separation of amines?

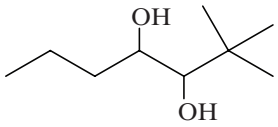
(a) Hinsberg method **(b)** Hofmann method
(c) Wurtz reaction **(d)** Curtius reaction

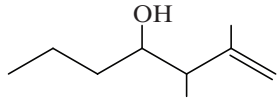
12. Predict the major product in the following reaction.



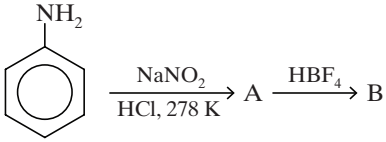
(a) 

(b) 

(c) 

(d) 

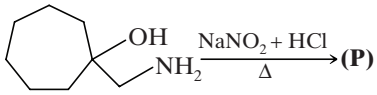
13. In the following chemical reactions,

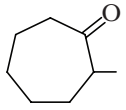


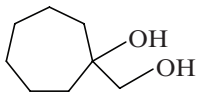
the compounds A and B respectively are

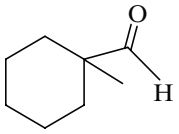
(a) benzene diazonium chloride and fluorobenzene.
(b) nitrobenzene and chlorobenzene.
(c) nitrobenzene and fluorobenzene.
(d) phenol and benzene.

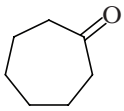
14. The major product (P) is



(a) 

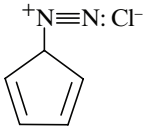
(b) 

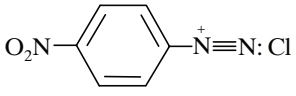
(c) 

(d) 

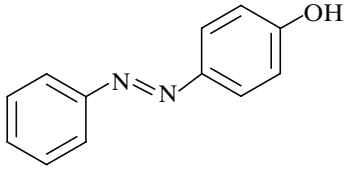
15. Which of the following diazonium salts cannot be isolated?

(a) $CH_3-\underset{\underset{{}^{+}N\equiv N:Cl^-}{|}}{CH}-CH_2-CH_3$ **(b)** $Ph-\overset{+}{N}\equiv N:Cl^-$

(c) 

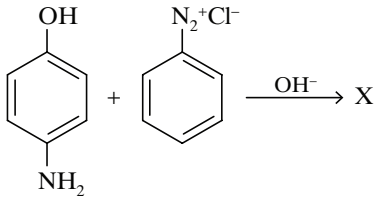
(d) 

16. What is the most significant use of diazo compounds?

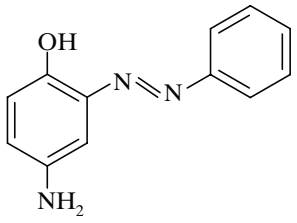


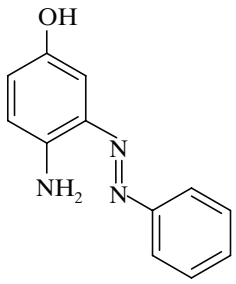
(a) Antibiotics **(b)** Antiseptics
(c) Antioxidants **(d)** Dyes

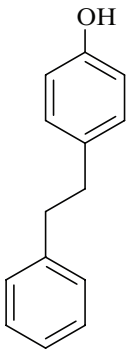
17. Consider the reaction



Here X is

(a) 

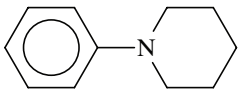
(b) 

(c) 

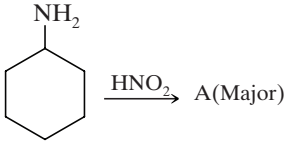
(d) None

18. Which amine yields *N*-nitroso amine after treatment with nitrous acid?

(a) $H_3C-C_6H_4-NH_2$ **(b)** $C_6H_5-CH_2-NH_2$

(c) $C_6H_5-NH-CH_3$ **(d)** 

19. The product (A) in the following reaction is



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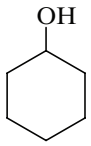
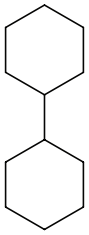
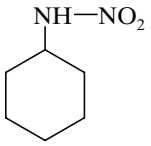
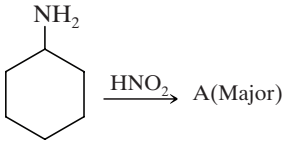
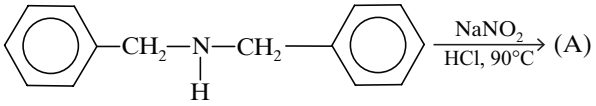
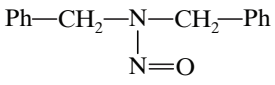
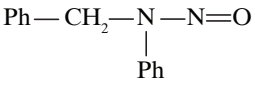
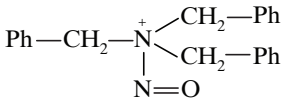
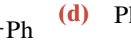
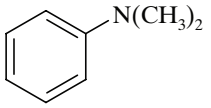
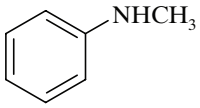
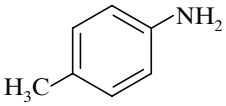
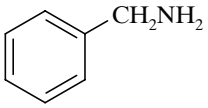
(a) 
(b) 
(c) 
(d) 

20. In the following reaction, product (A) is

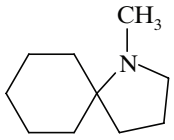
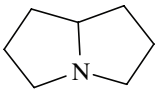
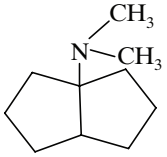
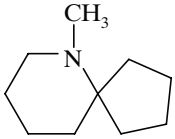


(a) 
(b) 
(c) 
(d) 

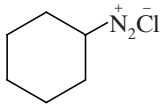
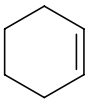
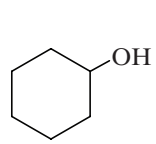
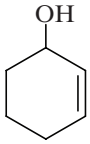
21. Amongst the compounds given, the one that would form a brilliant colored dye on treatment with $NaNO_2$ in dil. HCl followed by addition to an alkaline solution of β-naphthol is

(a) 
(b) 
(c) 
(d) 

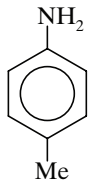
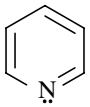
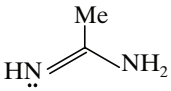
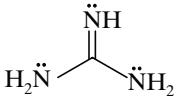
22. The nitrogen atom in the following cyclic compounds can be removed as trimethylamine by successive Hoffmann eliminations (involving exhaustive methylation followed by heating with AgOH). The amine which will require a greater number of Hofmann eliminations is

(a) 
(b) 
(c) 
(d) 

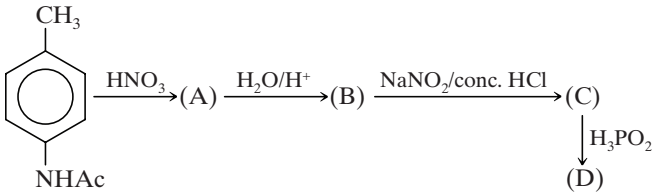
23. What will be the final product of the reaction of cyclohexanamine with sodium nitrite in dil. HCl?

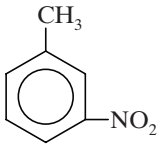
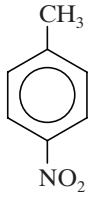
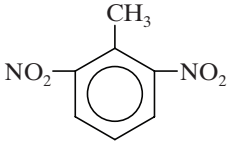
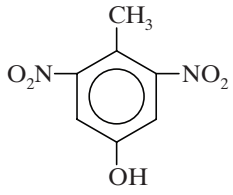
(a) 
(b) 
(c) 
(d) 

24. Which of the following compound is the strongest base?

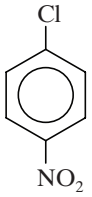
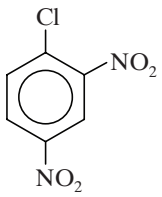
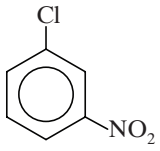
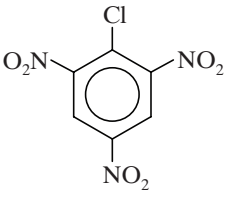
(a) 
(b) 
(c) 
(d) 

25. In the given reaction, (D) is

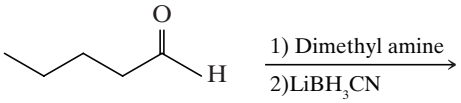


(a) 
(b) 
(c) 
(d) 

26. Which of the following is least reactive toward S_NAr?

(a) 
(b) 
(c) 
(d) 

27. What is the product of the following reaction?



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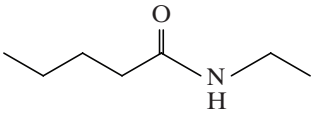
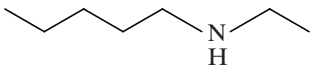
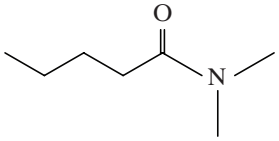
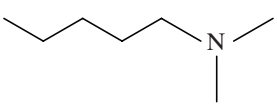
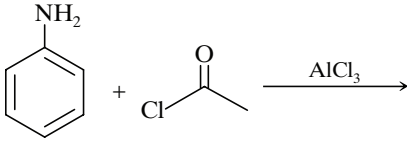
(a) 

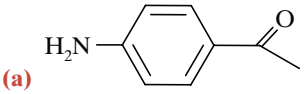
(b) 

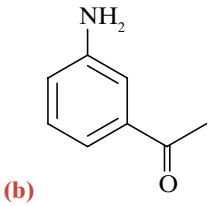
(c) 

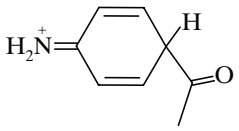
(d) 

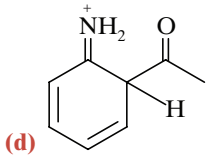
28. Consider carefully the mechanism of the reaction shown below. Which of the following intermediates or products will not be formed during the course of the reaction?



(a) 

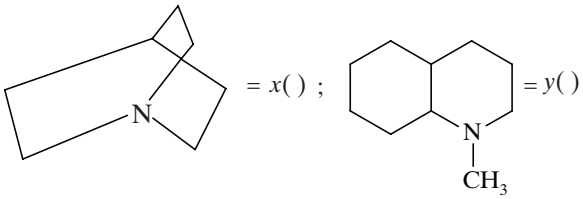
(b) 

(c) 

(d) 

Integer Type

1. In the following figure, x and y represent the number of times of Hofmann exhaustive methylation takes place to remove nitrogen from the compound. The sum of $x + y$ is _____.



ANSWER KEY

Single Correct Choice Type

1. (b)	**2.** (c)	**3.** (c)	**4.** (b)	**5.** (c)
6. (c)	**7.** (a)	**8.** (a)	**9.** (b)	**10.** (c)
11. (c)	**12.** (a)	**13.** (a)	**14.** (d)	**15.** (a)
16. (d)	**17.** (a)	**18.** (c)	**19.** (a)	**20.** (a)
21. (c)	**22.** (b)	**23.** (a)	**24.** (d)	**25.** (a)
26. (c)	**27.** (d)	**28.** (b)		

Integer Type

1. (5)

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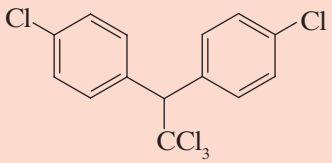
19

Phenols and Aryl Halides

Nucleophilic Aromatic Substitution



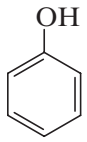
DDT
[1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane]

Contents

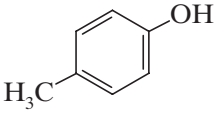
19.1 | Structure and Nomenclature of Phenols
19.2 | Naturally Occurring Phenols
19.3 | Physical Properties of Phenols
19.4 | Synthesis of Phenols
19.5 | Reactions of Phenols as Acids
19.6 | Other Reactions of the O—H Group of Phenols
19.7 | Cleavage of Alkyl Aryl Ethers
19.8 | Reactions of the Benzene Ring of Phenols
19.9 | The Claisen Rearrangement
19.10 | Quinones
19.11 | Aryl Halides and Nucleophilic Aromatic Substitution

19.1 | STRUCTURE AND NOMENCLATURE OF PHENOLS

Compounds that have a hydroxyl group directly attached to a benzene ring are called **phenols**. Thus, **phenol** is the specific name for hydroxybenzene, and it is the general name for the family of compounds derived from hydroxybenzene:

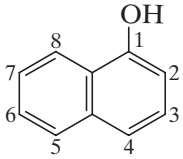


Phenol

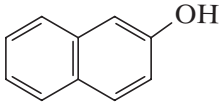


4-Methylphenol (a phenol)

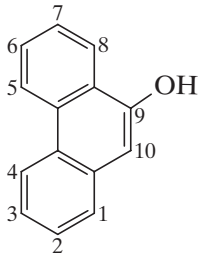
Compounds that have a hydroxyl group attached to a polycyclic benzenoid ring are chemically similar to phenols, but they are called **naphthols** and **phenanthrols**. For example:



1-Naphthol (α-naphthol)



2-Naphthol (β-naphthol)



9-Phenanthrol

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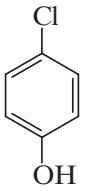
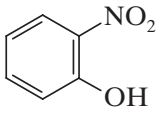
19.1A Nomenclature of Phenols

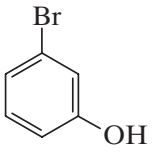
We studied the nomenclature of some phenols in Chapter 13. In many compounds *phenol* is the base name:



4-Chlorophenol (*p*-chlorophenol)

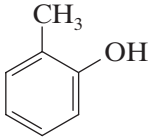


2-Nitrophenol (*o*-nitrophenol)

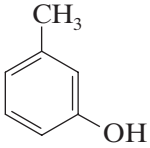


3-Bromophenol (*m*-bromophenol)

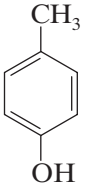
The methylphenols are commonly called *cresols*:



2-Methylphenol (*o*-cresol)

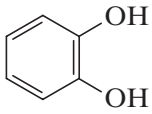


3-Methylphenol (*m*-cresol)

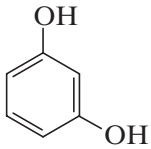


4-Methylphenol (*p*-cresol)

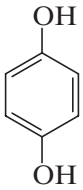
The benzenediols also have common names:



1,2-Benzenediol (catechol)



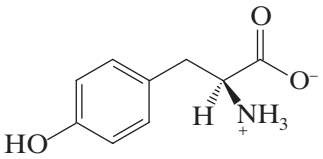
1,3-Benzenediol (resorcinol)



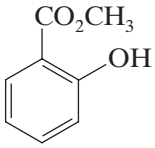
1,4-Benzenediol (hydroquinone)

19.2 | NATURALLY OCCURRING PHENOLS

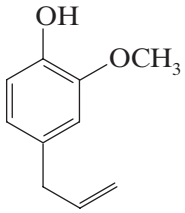
Phenols and related compounds occur widely in nature. Tyrosine is an amino acid that occurs in proteins. Methyl salicylate is found in oil of wintergreen, eugenol is found in oil of cloves, and thymol is found in thyme.



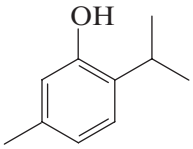
L-Tyrosine



Methyl salicylate (oil of wintergreen)



Eugenol (oil of cloves)



Thymol (thyme)

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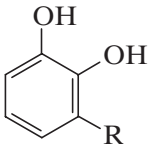
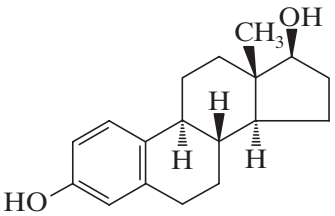
The urushiols are blistering agents (vesicants) found in poison ivy.



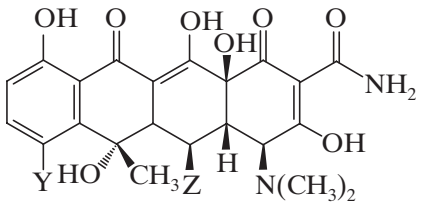
Urushiols

R = $-(CH_2)_{14}CH_3$,
$-(CH_2)_7CH{=}CH(CH_2)_5CH_3$, or
$-(CH_2)_7CH{=}CHCH_2CH{=}CH(CH_2)_2CH_3$, or
$-(CH_2)_7CH{=}CHCH_2CH{=}CHCH{=}CHCH_3$ or
$-(CH_2)_7CH{=}CHCH_2CH{=}CHCH_2CH{=}CH_2$

Estradiol is a female sex hormone, and the tetracyclines are important antibiotics.



Estradiol



Tetracyclines
(Y = Cl, Z = H; Aureomycin)
(Y = H, Z = OH; Terramycin)

19.3 | PHYSICAL PROPERTIES OF PHENOLS

The presence of hydroxyl groups in phenols means that phenols are like alcohols (Section 10.2) in some respects. For example, they are able to form strong intermolecular hydrogen bonds, and therefore have higher boiling points than hydrocarbons of the same molecular weight. Phenol (bp 182 °C) has a boiling point more than 70 °C higher than toluene (bp 110.6 °C), even though the two compounds have almost the same molecular weight. Phenols are also modestly soluble in water because of their ability to form strong hydrogen bonds with water molecules.

19.4 | SYNTHESIS OF PHENOLS

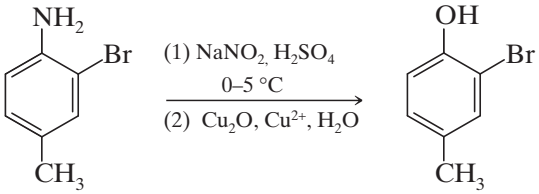
19.4A Laboratory Synthesis

The most important laboratory synthesis of phenols is by hydrolysis of arenediazonium salts (Section 18.7E). This method is highly versatile, and the conditions required for the diazotization step and the hydrolysis step are mild. This means that other groups present on the ring are unlikely to be affected.

General Reaction

$$Ar{-}NH_2 \xrightarrow{HONO} Ar{-}\overset{+}{N}_2 \xrightarrow[H_2O]{Cu_2O,\ Cu^{2+}} Ar{-}OH$$

Specific Example



2-Bromo-4-methylphenol (80–92%)

19.4B Industrial Syntheses

Phenol is a highly important industrial chemical; it serves as the raw material for a large number of commercial products ranging from aspirin to a variety of plastics. Worldwide production of phenol (which in industry is sometimes called carbolic acid) is more than 3 million tons per year. Several methods have been used to synthesize phenol commercially.

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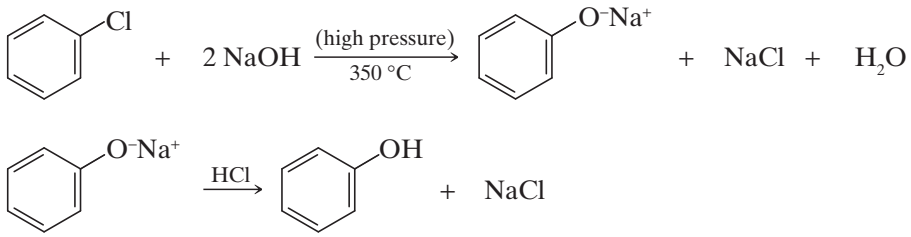
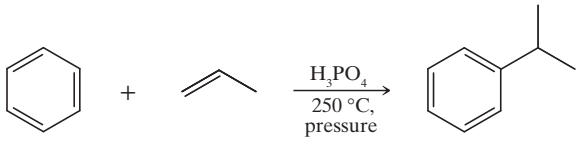
1. **Hydrolysis of Chlorobenzene (Dow Process).** In this process chlorobenzene is heated at 350 °C (under high pressure) with aqueous sodium hydroxide. The reaction produces sodium phenoxide, which, on acidification, yields phenol. The mechanism for the reaction probably involves the formation of benzyne (Section 19.11B).



2. **From Cumene Hydroperoxide.** This process illustrates industrial chemistry at its best. Overall, it is a method for converting two relatively inexpensive organic compounds—benzene and propene—into two more valuable ones—phenol and acetone. The only other substance consumed in the process is oxygen from air. Most of the worldwide production of phenol is now based on this method. The synthesis begins with the Friedel–Crafts alkylation of benzene with propene to produce cumene (isopropylbenzene):

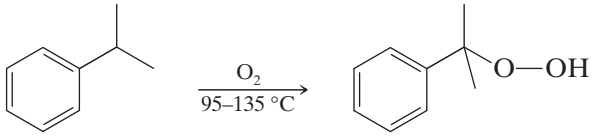
Reaction 1



Cumene

Then cumene is oxidized to cumene hydroperoxide:

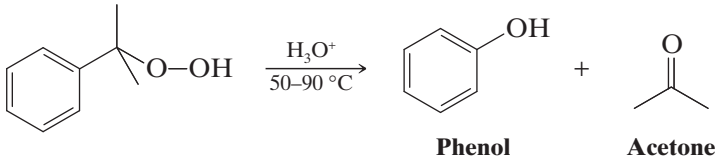
Reaction 2



Cumene hydroperoxide

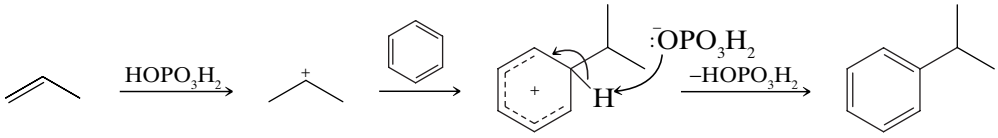
Finally, when treated with 10% sulfuric acid, cumene hydroperoxide undergoes a hydrolytic rearrangement that yields phenol and acetone:

Reaction 3



Phenol **Acetone**

The mechanism of each of the reactions in the synthesis of phenol from benzene and propene via cumene hydroperoxide requires some comment. The first reaction is a familiar one. The isopropyl cation generated by the reaction of propene with the acid (H_3PO_4) alkylates benzene in a typical Friedel–Crafts electrophilic aromatic substitution:



The second reaction is a radical chain reaction. A radical initiator abstracts the benzylic hydrogen atom of cumene, producing a 3° benzylic radical. Then a chain reaction with oxygen, which exists as a paramagnetic diradical in the ground state, produces cumene hydroperoxide:

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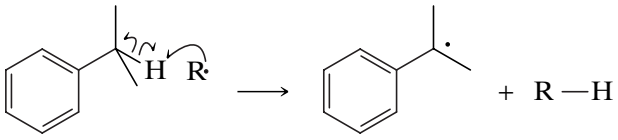
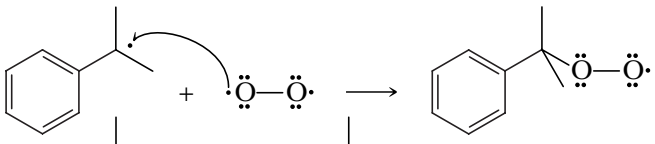
Chain Initiation

Step 1

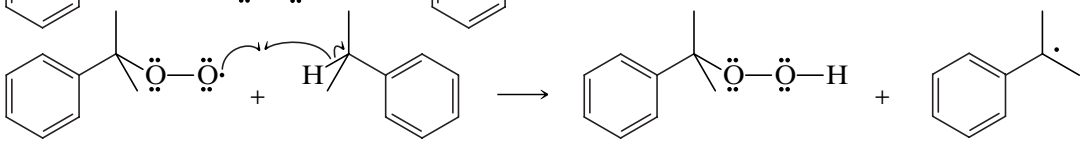


Chain Propagation

Step 2

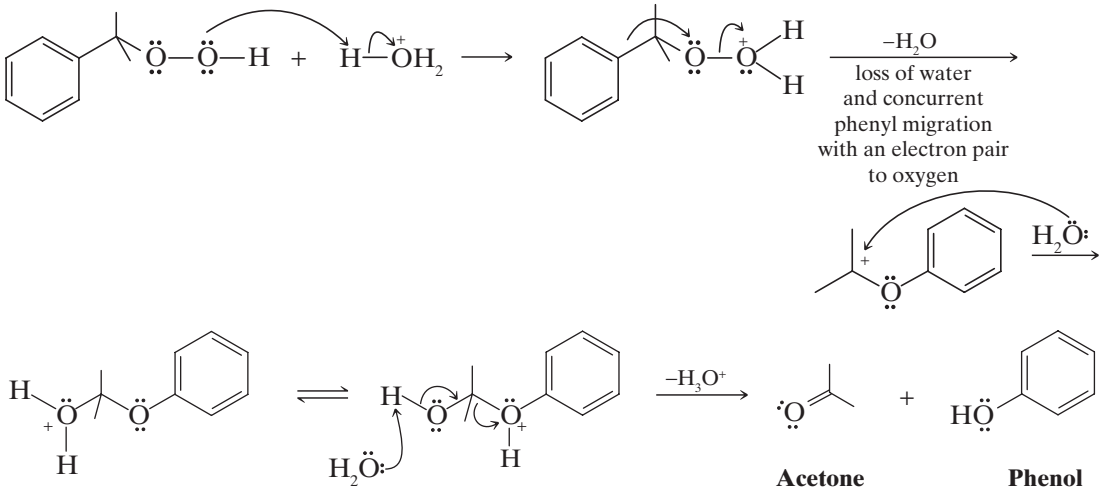


Step 3



The reaction continues with steps 2, 3, 2, 3, and so on.

The third reaction—the hydrolytic rearrangement—resembles the carbocation rearrangements that we have studied before. In this instance, however, the rearrangement involves the migration of a phenyl group to *a cationic oxygen atom*. Phenyl groups have a much greater tendency to migrate to a cationic center than do methyl groups. The following equations show all the steps of the mechanism.



The second and third steps of the mechanism may actually take place at the same time; that is, the loss of H_2O and the migration of C_6H_5— may be concerted.

19.5 | REACTIONS OF PHENOLS AS ACIDS

19.5A Strength of Phenols as Acids

Although phenols are structurally similar to alcohols, they are much stronger acids. The pK_a values of most alcohols are of the order of 18. However, as we see in Table 19.1, the pK_a values of phenols are smaller than 11.

Let us compare two *superficially* similar compounds, cyclohexanol and phenol:



Cyclohexanol $pK_a = 18$ **Phenol $pK_a = 9.89$**

Although phenol is a weak acid when compared with a carboxylic acid such as acetic acid ($pK_a = 4.76$), phenol is a much stronger acid than cyclohexanol (by a factor of eight pK_a units).

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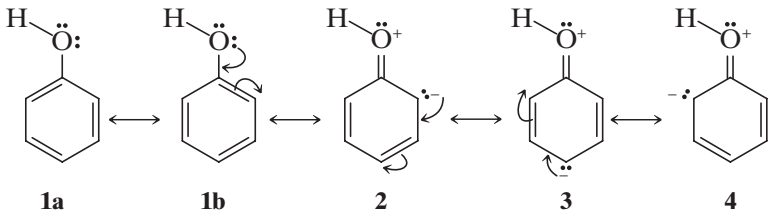
Table 19.1 Acidity Constants of Phenols

Name	pK_a (in H_2O at 25 °C)	Name	pK_a (in H_2O at 25 °C)
Phenol	9.89	3-Nitrophenol	8.28
2-Methylphenol	10.20	4-Nitrophenol	7.15
3-Methylphenol	10.01	2,4-Dinitrophenol	3.96
4-Methylphenol	10.17	2,4,6-Trinitrophenol (picric acid)	0.38
2-Chlorophenol	8.11		
3-Chlorophenol	8.80	1-Naphthol	9.31
4-Chlorophenol	9.20	2-Naphthol	9.55
2-Nitrophenol	7.17		

Experimental and theoretical results have shown that the greater acidity of phenol owes itself primarily to an electrical charge distribution in phenol that causes the —OH oxygen to be more positive; therefore, the proton is held less strongly. In effect, the benzene ring of phenol acts as if it were an electron-withdrawing group when compared with the cyclohexane ring of cyclohexanol.

We can understand this effect by noting that the carbon atom which bears the hydroxyl group in phenol is sp^2 hybridized, whereas in cyclohexane it is sp^3 hybridized. Because of their greater *s* character, sp^2-hybridized carbon atoms are more electronegative than sp^3-hybridized carbon atoms (Section 3.9A).

Another factor influencing the electron distribution may be the contributions to the overall resonance hybrid of phenol made by structures **2**–**4**. Notice that the effect of these structures is to withdraw electrons from the hydroxyl group and to make the oxygen positive:

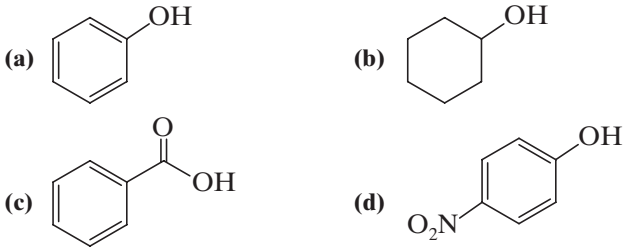


1a **1b** **2** **3** **4**

An alternative explanation for the greater acidity of phenol relative to cyclohexanol can be based on similar resonance structures for the phenoxide ion. Unlike the structures for phenol, **2**–**4**, resonance structures for the phenoxide ion do not involve charge separation. According to resonance theory, such structures should stabilize the phenoxide ion more than structures **2**–**4** stabilize phenol. (No resonance structures can be written for cyclohexanol or its anion, of course.) Greater stabilization of the phenoxide ion (the conjugate base) than of phenol (the acid) has an acid-strengthening effect.

Solved Problem 19.1

Rank the following compounds in order of increasing acidity.



Answer

Alcohols are less acidic than phenols, and phenols are less acidic than carboxylic acids. An electron-withdrawing group increases the acidity of a phenol relative to phenol itself. Thus the order of increasing acidity among these examples is cyclohexanol < phenol < 4-nitrophenol < benzoic acid.

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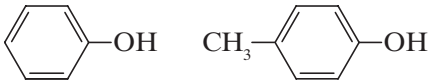
Practice Problem 19.1

If we examine Table 19.1, we find that the methylphenols (cresols) are less acidic than phenol itself. For example,



Phenol $pK_a = 9.89$ | **4-Methylphenol** $pK_a = 10.17$

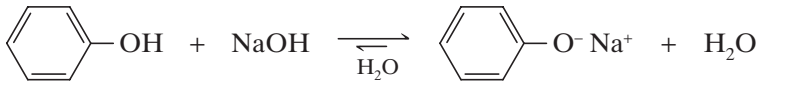
This behavior is characteristic of phenols bearing electron-releasing groups. Provide an explanation.

Practice Problem 19.2

If we examine Table 19.1, we see that phenols having electron-withdrawing groups (Cl— or O_2N—) attached to the benzene ring are more acidic than phenol itself. Account for this trend on the basis of resonance and inductive effects. Your answer should also explain the large acid-strengthening effect of nitro groups, an effect that makes 2,4,6-trinitrophenol (also called *picric acid*) so exceptionally acidic ($pK_a = 0.38$) that it is more acidic than acetic acid ($pK_a = 4.76$).

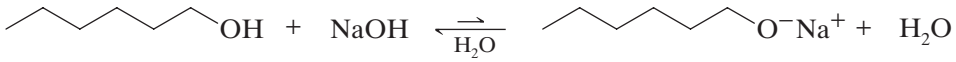
19.5B Distinguishing and Separating Phenols from Alcohols and Carboxylic Acids

Because phenols are more acidic than water, the following reaction goes essentially to completion and produces water-soluble sodium phenoxide:



Stronger acid $pK_a \cong 10$ **(slightly soluble)** | **Stronger base** | **Weaker base (soluble)** | **Weaker acid** $pK_a \cong 16$

The corresponding reaction of 1-hexanol with aqueous sodium hydroxide does not occur to a significant extent because 1-hexanol is a weaker acid than water:



Weaker acid $pK_a \cong 18$ **(very slightly soluble)** | **Weaker base** | **Stronger base** | **Stronger acid** $pK_a \cong 16$

The fact that phenols dissolve in aqueous sodium hydroxide, whereas most alcohols with six carbon atoms or more do not, gives us a convenient means for distinguishing and separating phenols from most alcohols. (Alcohols with five carbon atoms or fewer are quite soluble in water—some are infinitely so—and so they dissolve in aqueous sodium hydroxide even though they are not converted to sodium alkoxides in appreciable amounts.)

Most phenols, however, are not soluble in aqueous sodium bicarbonate ($NaHCO_3$), but carboxylic acids are soluble. Thus, aqueous $NaHCO_3$ provides a method for distinguishing and separating most phenols from carboxylic acids.

Solved Problem 19.2

Assume that each of the following mixtures was added to a flask or a separatory funnel that contained diethyl ether (as an organic solvent) and mixed well. In which layer (diethyl ether or water) would the organic compound predominate in each case, and in what form would it exist (in its neutral form or as its conjugate base)?

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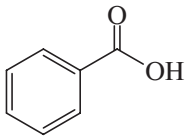
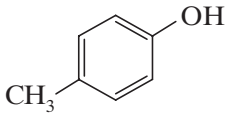
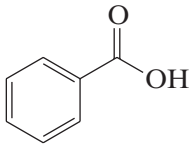
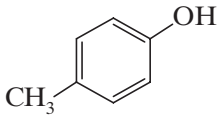
(a)  + aqueous $NaHCO_3$

(b)  + aqueous $NaHCO_3$

(c)  + aqueous NaOH

(d)  + aqueous NaOH

Answer

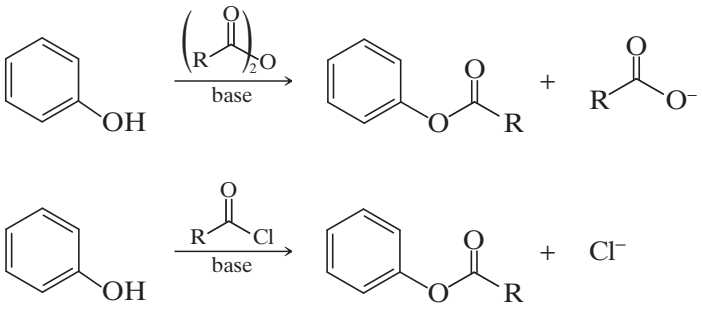
Sodium bicarbonate will remove a proton from a carboxylic acid to form a water-soluble carboxylate salt, but sodium bicarbonate will not remove a proton from a typical phenol. Sodium hydroxide will remove a proton from both a carboxylic acid and a phenol to form salts in each case. Thus, in **(a)** benzoic acid will be found in the water layer as its sodium salt, whereas in **(b)** 4-methylphenol will remain in its neutral form and be found predominantly in the ether layer. In **(c)** and **(d)** both benzoic acid and 4-methylphenol will be found in the aqueous layer as their corresponding salts.

Practice Problem 19.3

Your laboratory instructor gives you a mixture of 4-methylphenol, benzoic acid, and toluene. Assume that you have available common laboratory acids, bases, and solvents and explain how you would proceed to separate this mixture by making use of the solubility differences of its components.

19.6 | OTHER REACTIONS OF THE O—H GROUP OF PHENOLS

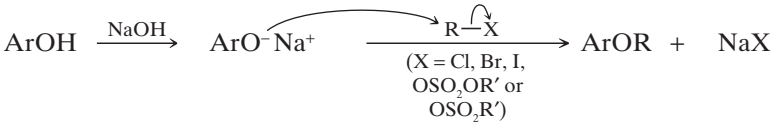
Phenols react with carboxylic acid anhydrides and acid chlorides to form esters. These reactions are quite similar to those of alcohols (Section 17.7).



19.6A Phenols in the Williamson Synthesis

Phenols can be converted to ethers through the Williamson synthesis (Section 10.10B). Because phenols are more acidic than alcohols, they can be converted to sodium phenoxides through the use of sodium hydroxide (rather than sodium hydride or metallic sodium, the reagents used to convert alcohols to alkoxide ions).

General Reaction



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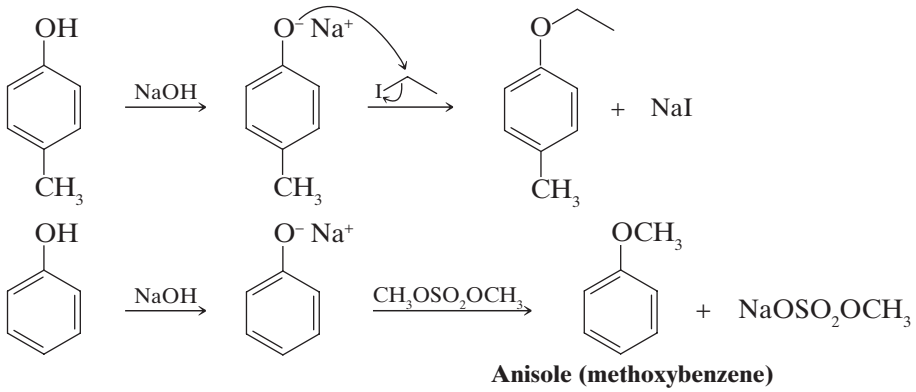
Specific Examples



Anisole (methoxybenzene)

19.7 | CLEAVAGE OF ALKYL ARYL ETHERS

We learned in Section 10.11A that when dialkyl ethers are heated with excess concentrated HBr or HI, the ethers are cleaved and alkyl halides are produced from both alkyl groups:

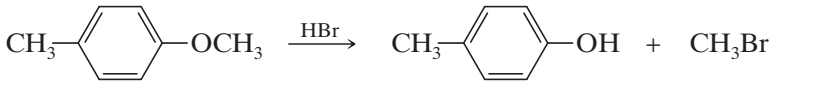
$$R{-}O{-}R' \xrightarrow[\text{heat}]{\text{concd HX}} R{-}X + R'{-}X + H_2O$$

When alkyl aryl ethers react with strong acids such as HI and HBr, the reaction produces an alkyl halide and a phenol. The phenol does not react further to produce an aryl halide because the phenol carbon–oxygen bond is very strong and because phenyl cations do not form readily.

General Reaction

$$Ar{-}O{-}R \xrightarrow[\text{heat}]{\text{concd HX}} Ar{-}OH + R{-}X$$

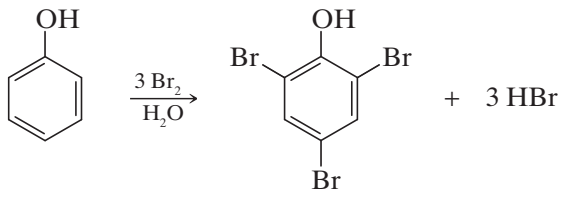
Specific Example



***p*-Methylanisole** **4-Methylphenol** **Methyl bromide**

19.8 | REACTIONS OF THE BENZENE RING OF PHENOLS

Bromination The hydroxyl group is a powerful activating group—and an ortho–para director—in **electrophilic aromatic substitutions**. Phenol itself reacts with bromine in aqueous solution to yield 2,4,6-tribromophenol in nearly quantitative yield. Note that a Lewis acid is not required for the bromination of this highly activated ring:



2,4,6-Tribromophenol (~100%)

Monobromination of phenol can be achieved by carrying out the reaction in carbon disulfide at a low temperature, conditions that reduce the electrophilic reactivity of bromine. The major product is the para isomer:

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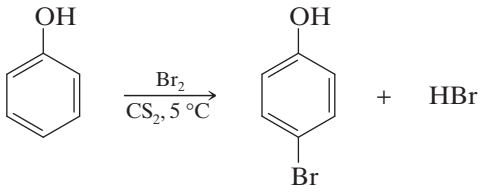
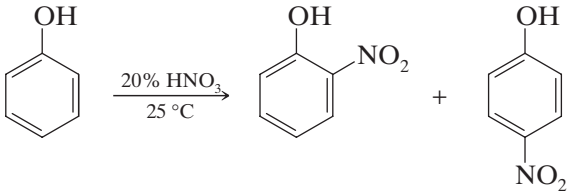


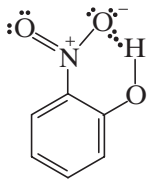
***p*-Bromophenol**
(80–84%)

Nitration Phenol reacts with dilute nitric acid to yield a mixture of *o*- and *p*-nitrophenol:

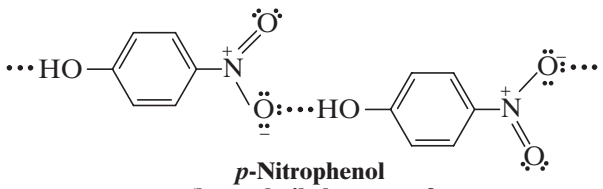


30–40% **15%**

Although the yield is relatively low (because of oxidation of the ring), the ortho and para isomers can be separated by steam distillation. *o*-Nitrophenol is the more volatile isomer because its hydrogen bonding (see the following structures) is *intramolecular*. *p*-Nitrophenol is less volatile because *intermolecular* hydrogen bonding causes association among its among its molecules. Thus, *o*-nitrophenol passes over with the steam, and *p*-nitrophenol remains in the distillation flask.

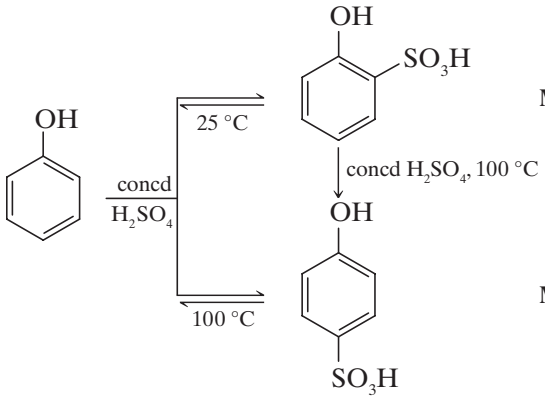


***o*-Nitrophenol**
(more volatile because of intramolecular hydrogen bonding)



***p*-Nitrophenol**
(less volatile because of intermolecular hydrogen bonding)

Sulfonation Phenol reacts with concentrated sulfuric acid to yield mainly the orthosulfonated product if the reaction is carried out at 25 °C and mainly the para-sulfonated product at 100 °C. This is another example of thermodynamic versus kinetic control of a reaction:



Major product under kinetic control

Major product under thermodynamic control

Solved Problem 19.3

Consider the sulfonation reactions of phenol shown above. **(a)** Which sulfonation product is more stable, ortho or para? **(b)** For which sulfonation product is the free energy of activation lower?

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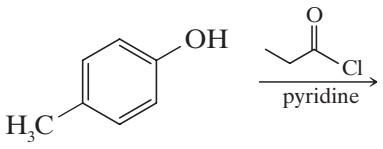
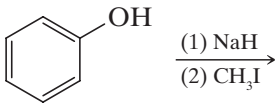
Answer

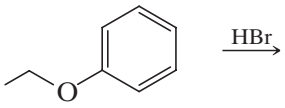
(a) The para-sulfonated phenol is more stable. We know this because at the higher temperature, where the reaction is under equilibrium control, it is the major product. **(b)** The free energy of activation is lower for ortho substitution. We know this because at the lower temperature, where the reaction is under kinetic control, it is formed faster.

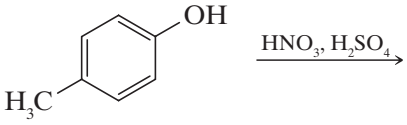
Practice Problem 19.4

Predict the products of each of the following reactions.

(a) 

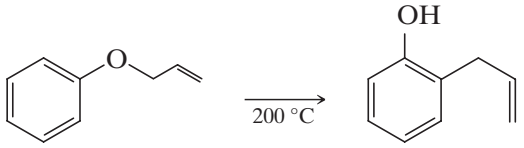
(b) 

(c) 

(d) 

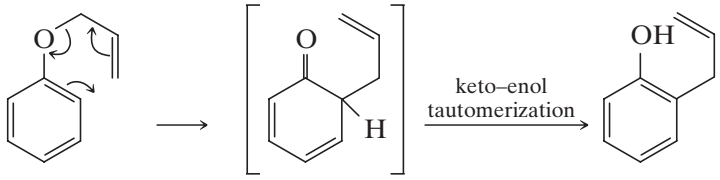
19.9 | THE CLAISEN REARRANGEMENT

Heating allyl phenyl ether to 200 °C effects an intramolecular reaction called a **Claisen rearrangement**. The product of the rearrangement is *o*-allylphenol:



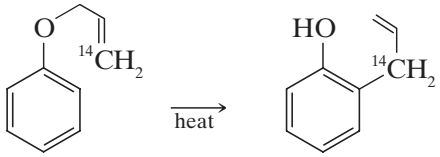
Allyl phenyl ether **o-Allylphenol**

The reaction takes place through a **concerted rearrangement** in which the bond between C3 of the allyl group and the ortho position of the benzene ring forms at the same time that the carbon–oxygen bond of the allyl phenyl ether breaks. The product of this rearrangement is an unstable intermediate that, like the unstable intermediate in the Kolbe reaction (Section 19.8), undergoes a proton shift (a keto–enol tautomerization, see Section 16.2) that leads to the *o*-allylphenol:



Unstable intermediate

That only C3 of the allyl group becomes bonded to the benzene ring was demonstrated by carrying out the rearrangement with allyl phenyl ether containing ^{14}C at C3. All of the product of this reaction had the labeled carbon atom bonded to the ring:



Only product

Practice Problem 19.5

The labeling experiment just described eliminates from consideration a mechanism in which the allyl phenyl ether dissociates to produce an allyl cation and a phenoxide ion, which then subsequently undergo a Friedel–Crafts alkylation

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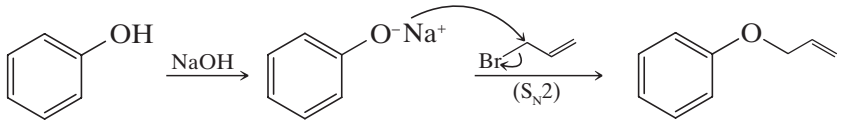
(Section 14.6) to produce the *o*-allylphenol. Explain how this alternative mechanism can be discounted by showing the product (or products) that would result from it.

Solved Problem 19.4

Show how you could synthesize allyl phenyl ether from phenol and allyl bromide.

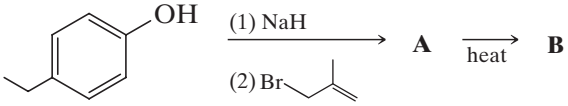
Answer

Use a Williamson ether synthesis (Section 19.6A).

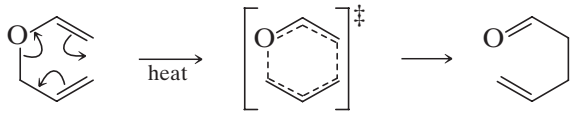


Practice Problem 19.6

What are compounds **A** and **B** in the following sequence?

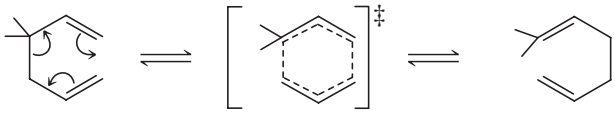


A Claisen rearrangement also takes place when allyl vinyl ethers are heated. For example,



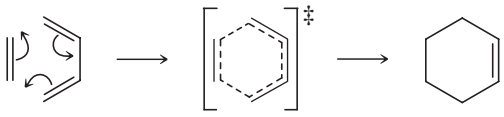
Allyl vinyl ether — **Aromatic transition state** — **4-Pentenal**

The transition state for the Claisen rearrangement involves a cycle of six electrons. Having six electrons suggests that the transition state has aromatic character (Section 13.7). Other reactions of this general type are known, and they are called **pericyclic reactions**. Another similar pericyclic reaction is the **Cope rearrangement** shown here:



3,3-Dimethyl-1,5-hexadiene — **Aromatic transition state** — **2-Methyl-2,6-heptadiene**

The Diels–Alder reaction (Section 12.5) is also a pericyclic reaction. The transition state for the Diels–Alder reaction also involves six electrons:



Aromatic transition state

19.10 | QUINONES

Oxidation of hydroquinone (1,4-benzenediol) produces a compound known as *p*-benzoquinone. The oxidation can be brought about by mild oxidizing agents, and, overall, the oxidation amounts to the removal of a pair of electrons ($2\ e^-$) and two protons from hydroquinone. (Another way of visualizing the oxidation is as the loss of a hydrogen molecule, H:H, making it a dehydrogenation.)

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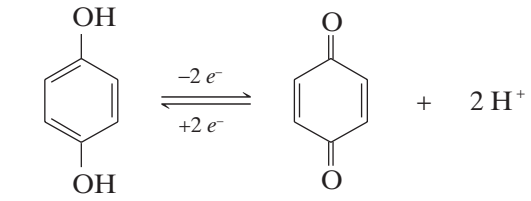


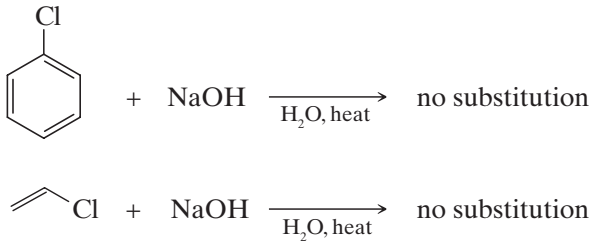
Hydroquinone **p-Benzoquinone**

This reaction is reversible; *p*-benzoquinone is easily reduced by mild reducing agents to hydroquinone.

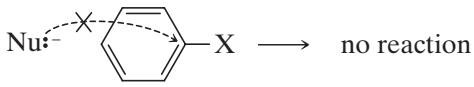
19.11 | ARYL HALIDES AND NUCLEOPHILIC AROMATIC SUBSTITUTION

- Simple aryl halides, like vinylic halides (Section 6.14A), are relatively unreactive toward nucleophilic substitution under conditions that would give rapid nucleophilic substitution with alkyl halides.

Chlorobenzene, for example, can be boiled with sodium hydroxide for days without producing a detectable amount of phenol (or sodium phenoxide).* Similarly, when vinyl chloride is heated with sodium hydroxide, no substitution occurs:

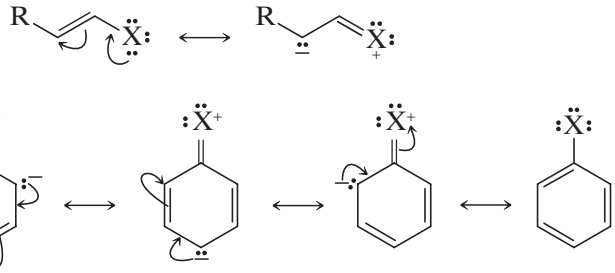


We can understand this lack of reactivity on the basis of several factors. The benzene ring of an aryl halide prevents back-side attack in an S_N2 reaction:



Phenyl cations are very unstable; thus S_N1 reactions do not occur. The carbon–halogen bonds of aryl (and vinylic) halides are shorter and stronger than those of alkyl, allylic, and benzylic halides. Stronger carbon–halogen bonds mean that bond breaking by either an S_N1 or S_N2 mechanism will require more energy.

Two effects make the carbon–halogen bonds of aryl and vinylic halides shorter and stronger: (1) The carbon of either type of halide is sp^2 hybridized, and therefore the electrons of the carbon orbital are closer to the nucleus than those of an sp^3-hybridized carbon. (2) Resonance of the type shown here strengthens the carbon–halogen bond by giving it *double-bond character*:



Having said all this, we shall find in the next two subsections that *aryl halides can be remarkably reactive toward nucleophiles* if they bear certain substituents or when we allow them to react under the proper conditions.

*The Dow process for making phenol by substitution (Section 19.4B) requires extremely high temperature and pressure to effect the reaction. These conditions are not practical in the laboratory.

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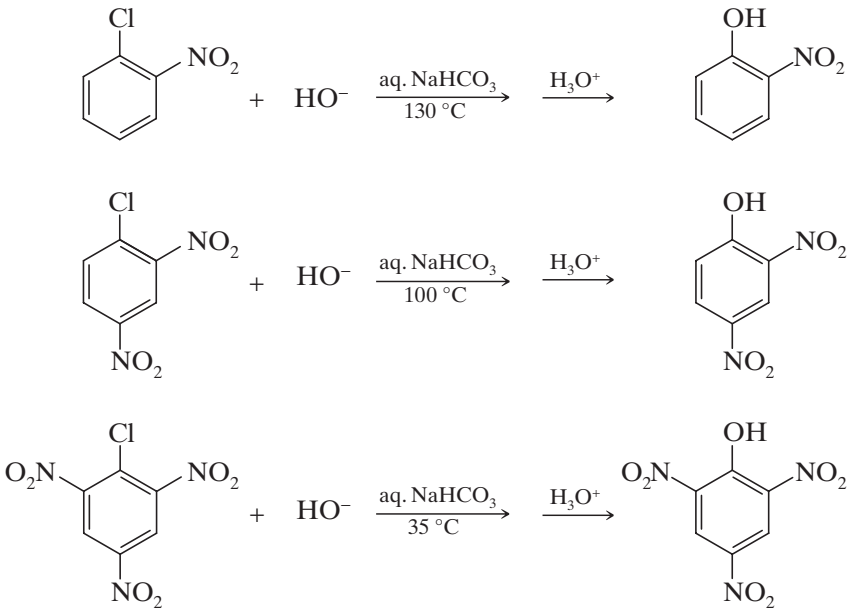
19.11A Nucleophilic Aromatic Substitution by Addition–Elimination: The S_NAr Mechanism

Nucleophilic substitution reactions of aryl halides *do* occur readily when an electronic factor makes the aryl carbon bonded to the halogen susceptible to nucleophilic attack.

- Nucleophilic aromatic substitution can occur when strong electron-withdrawing groups are ortho or para to the halogen atom:



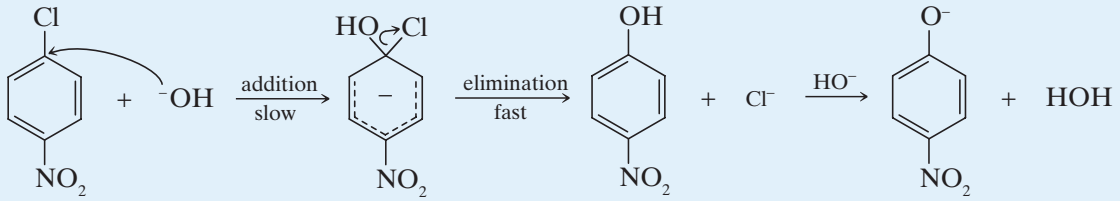
We also see in these examples that the temperature required to bring about the reaction is related to the number of ortho or para nitro groups. Of the three compounds, *o*-nitrochlorobenzene requires the highest temperature (*p*-nitrochlorobenzene reacts at 130 °C as well) and 2,4,6-trinitrochlorobenzene requires the lowest temperature.

A meta-nitro group does not produce a similar activating effect. For example, *m*-nitrochlorobenzene gives no corresponding reaction.

- The mechanism that operates in these reactions is an *addition–elimination* mechanism involving the formation of a *carbanion* with delocalized electrons, called a **Meisenheimer intermediate**. The process is called **nucleophilic aromatic substitution (S_NAr)**.

In the first step of the following example, addition of a hydroxide ion to *p*-nitrochlorobenzene produces the carbanion; then elimination of a chloride ion yields the substitution product as the aromaticity of the ring is recovered.

A MECHANISM FOR THE REACTION — The S_NAr Mechanism



Carbanion (Meisenheimer intermediate)

Structures of the contributing resonance forms are shown further below.

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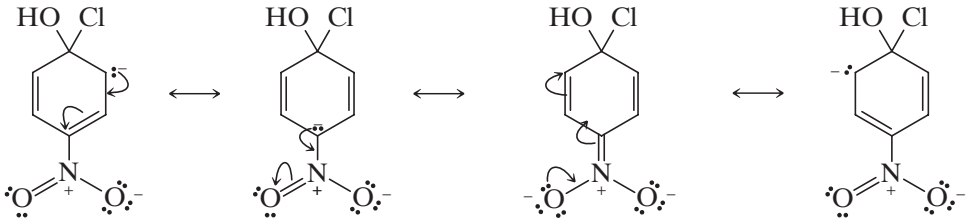
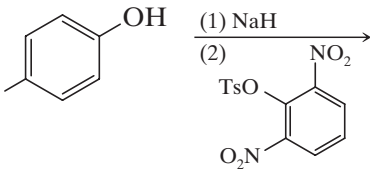
The carbanion is stabilized by *electron-withdrawing groups* in the positions ortho and para to the halogen atom. If we examine the following resonance structures for a Meisenheimer intermediate, we can see how:



Especially stable (Negative charges are both on oxygen atoms.)

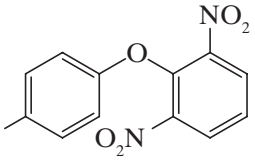
Solved Problem 19.5

What is the product of the following reaction?



Answer

NaH is a strong base that will convert 4-methylphenol to its phenoxide salt. 1-(*p*-Toluenesulfonyl)-2,6-dinitrobenzene contains both a good leaving group and two strong electron-withdrawing groups. Thus the likely reaction is a nucleophilic aromatic substitution (S_NAr), leading to the following diaryl ether.



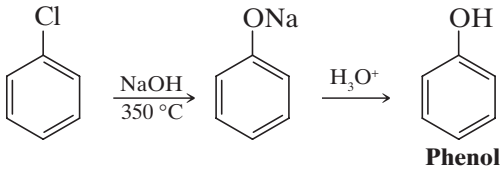
Practice Problem 19.7

1-Fluoro-2,4-dinitrobenzene is highly reactive toward nucleophilic substitution through an S_NAr mechanism. What product would be formed when 1-fluoro-2,4-dinitrobenzene reacts with each of the following reagents?

(a) EtONa **(b)** NH_3 **(c)** $C_6H_5NH_2$ **(d)** EtSNa

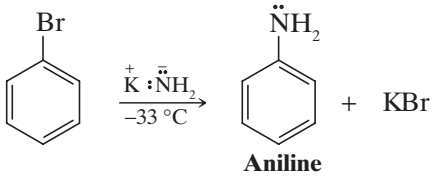
19.11B Nucleophilic Aromatic Substitution through an Elimination–Addition Mechanism: Benzyne

Although aryl halides such as chlorobenzene and bromobenzene do not react with most nucleophiles under ordinary circumstances, they do react under highly forcing conditions. Chlorobenzene can be converted to phenol by heating it with aqueous sodium hydroxide in a pressurized reactor at 350 °C (Section 19.4B):



Phenol

Bromobenzene reacts with the very powerful base, $^-NH_2$, in liquid ammonia:



Aniline

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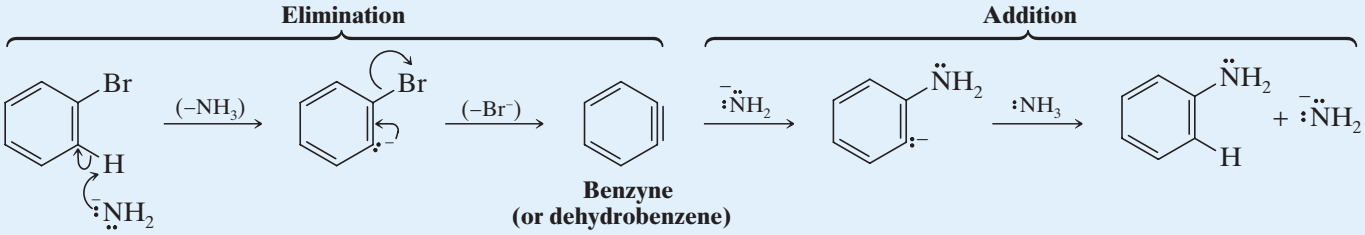
- These reactions take place through an **elimination–addition mechanism** that involves the formation of a highly unstable intermediate called *benzyne* (or *dehydrobenzene*).

We can illustrate this mechanism with the reaction of bromobenzene and amide ion. In the first step (see the following mechanism), the amide ion initiates an elimination by abstracting one of the ortho protons because they are the most acidic. The negative charge that develops on the ortho carbon is stabilized by the inductive effect of the bromine. The anion then loses a bromide ion. This elimination produces the highly unstable, and thus highly reactive, **benzyne**. Benzyne then reacts with any available nucleophile (in this case, an amide ion) by a two-step addition reaction to produce aniline.

A MECHANISM FOR THE REACTION — The Benzyne Elimination–Addition Mechanism

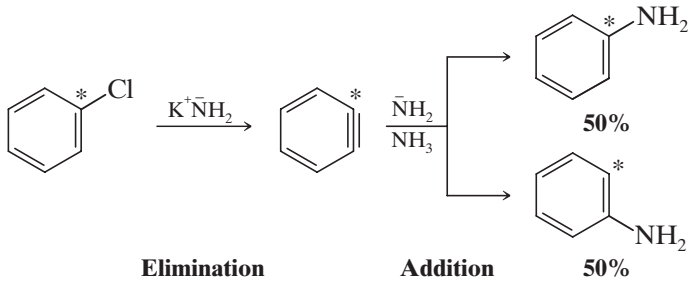


We can better understand the reactive and unstable nature of benzyne if we consider aspects of its electronic structure.

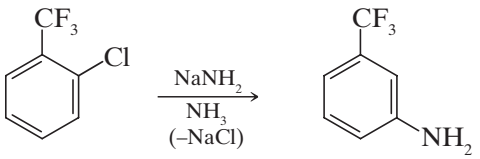
The calculated electrostatic potential map for benzyne, shows the relatively greater negative charge at the edge of the ring, corresponding to the electron density from the additional π bond in benzyne. The orbitals of the additional π bond in benzyne lie in the same plane as the ring, perpendicular to the axis of the aromatic π system. Because the carbon ring is not a perfect hexagon as in benzene, there is angle strain in the structure of benzyne. The distance between the carbons of the additional π bond in benzyne is shorter than between the other carbons, and the bond angles of the ring are therefore distorted from their ideal values. The result is that benzyne is highly unstable and highly reactive. Consequently, benzyne has never been isolated as a pure substance, but it has been detected and trapped in various ways.

What, then, is some of the evidence for an elimination–addition mechanism involving benzyne in some nucleophilic aromatic substitutions?

The first piece of clear-cut evidence was an experiment done by J. D. Roberts in 1953—one that marked the beginning of benzyne chemistry. Roberts showed that when ^{14}C-labeled (C*) chlorobenzene is treated with amide ion in liquid ammonia, the aniline that is produced has the label equally divided between the 1 and 2 positions. This result is consistent with the following elimination–addition mechanism but is, of course, not at all consistent with a direct displacement or with an addition–elimination mechanism. (Why?)



An even more striking illustration can be seen in the following reaction. When the ortho derivative **1** is treated with sodium amide, the only organic product obtained is *m*-(trifluoromethyl)aniline:



1 ***m*-(Trifluoromethyl)aniline**

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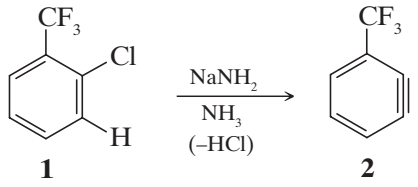
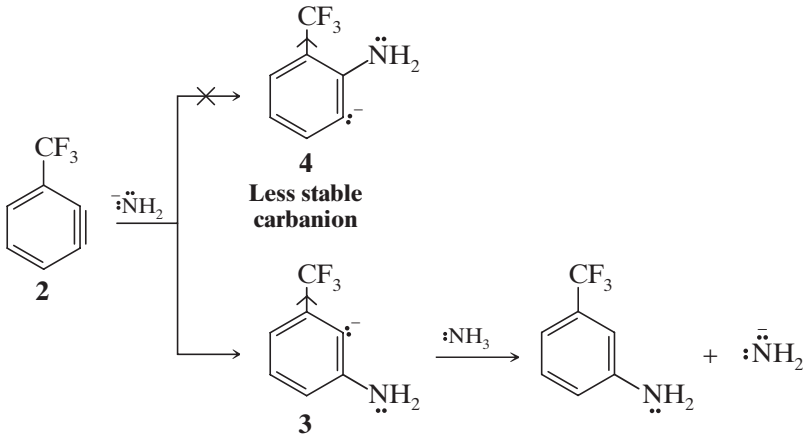
This result can also be explained by an elimination–addition mechanism. The first step produces the benzyne **2**:



1 **2**

This benzyne then adds an amide ion in the way that produces the more stable carbanion **3** rather than the less stable carbanion **4**:

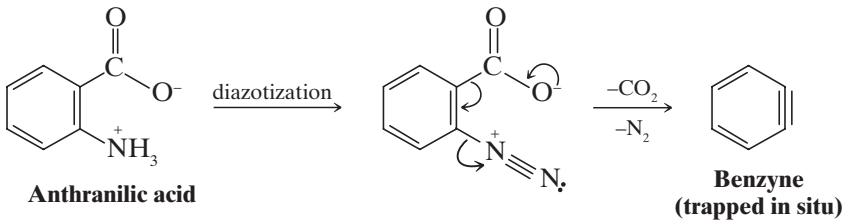


More stable carbanion (The negative charge is closer to the electronegative trifluoromethyl group.)

Carbanion **3** then accepts a proton from ammonia to form *m*-(trifluoromethyl)aniline.

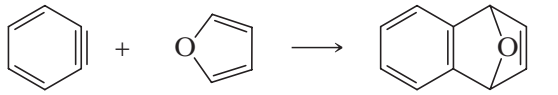
Carbanion **3** is more stable than **4** because the carbon atom bearing the negative charge is closer to the highly electronegative trifluoromethyl group. The trifluoromethyl group stabilizes the negative charge through its inductive effect. (Resonance effects are not important here because the sp^2 orbital that contains the electron pair does not overlap with the π orbitals of the aromatic system.)

Benzyne intermediates have been "trapped" through the use of Diels–Alder reactions. One convenient method for generating benzyne is the diazotization of anthranilic acid (2-aminobenzoic acid) followed by elimination of CO_2 and N_2:



Anthranilic acid **Benzyne (trapped in situ)**

When benzyne is generated in the presence of the diene *furan*, the product is a Diels–Alder adduct:



Benzyne (generated by an elimination reaction) **Furan** **Diels–Alder adduct**

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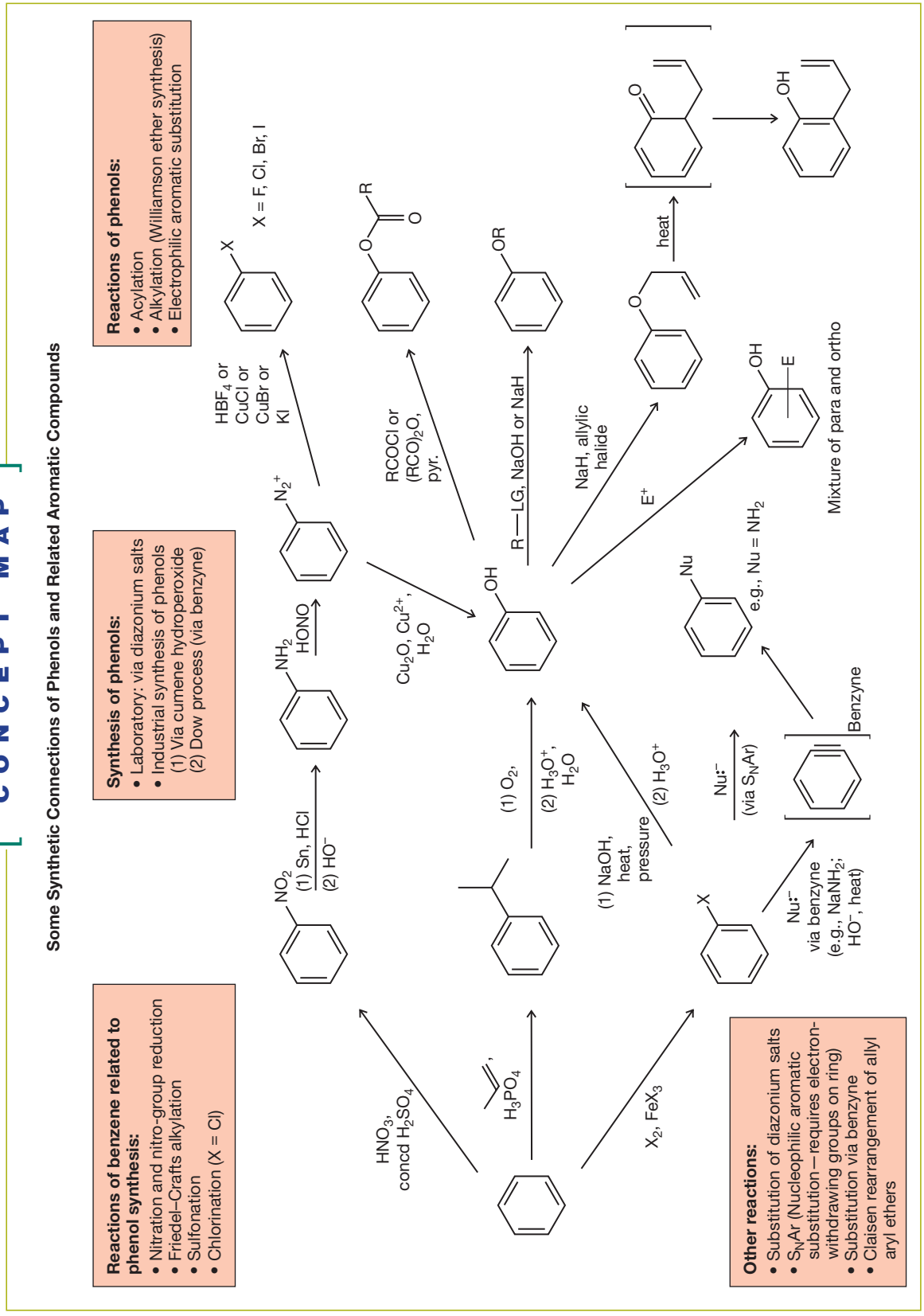
CONCEPT MAP

Some Synthetic Connections of Phenols and Related Aromatic Compounds



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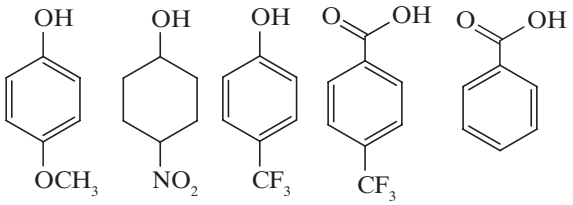
REVIEW PROBLEMS

Physical Properties

19.8 Rank the following in order of increasing acidity.



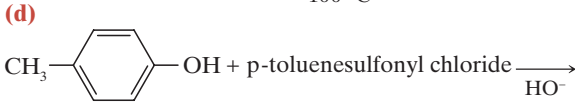
19.9 Without consulting tables, select the stronger acid from each of the following pairs:
- **(a)** 4-Methylphenol and 4-fluorophenol
- **(b)** 4-Methylphenol and 4-nitrophenol
- **(c)** 4-Nitrophenol and 3-nitrophenol
- **(d)** 4-Methylphenol and benzyl alcohol
- **(e)** 4-Fluorophenol and 4-bromophenol

19.10 What products would be obtained from each of the following acid–base reactions?
- **(a)** Sodium ethoxide in ethanol + phenol $\longrightarrow$
- **(b)** Phenol + aqueous sodium hydroxide $\longrightarrow$
- **(c)** Sodium phenoxide + aqueous hydrochloric acid $\longrightarrow$
- **(d)** Sodium phenoxide + H_2O + CO_2 $\longrightarrow$

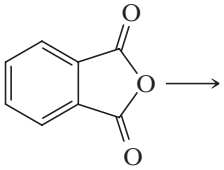
19.11 Describe a simple chemical test that could be used to distinguish between members of each of the following pairs of compounds:
- **(a)** 4-Chlorophenol and 4-chloro-1-methylbenzene
- **(b)** 4-Methylphenol and 4-methylbenzoic acid
- **(c)** 4-Methylphenol and 2,4,6-trinitrophenol
- **(d)** Ethyl phenyl ether and 4-ethylphenol

General Reactions

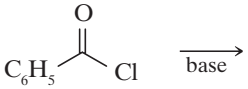
19.12 Complete the following equations:
- **(a)** Phenol + Br_2 $\xrightarrow[5\ ^\circ C,\ CS_2]{}$
- **(b)** Phenol + concd H_2SO_4 $\xrightarrow{25\ ^\circ C}$
- **(c)** Phenol + concd H_2SO_4 $\xrightarrow{100\ ^\circ C}$
- **(d)**



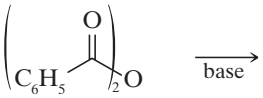
- **(e)** Phenol + Br_2 $\xrightarrow[H_2O]{}$
- **(f)** Phenol +



- **(g)** *p*-Cresol + Br_2 $\xrightarrow[H_2O]{}$
- **(h)** Phenol +



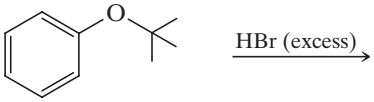
- **(i)** Phenol +



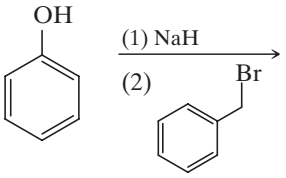
- **(j)** Phenol + NaH $\longrightarrow$
- **(k)** Product of (j) + $CH_3OSO_2OCH_3$ $\longrightarrow$
- **(l)** Product of (j) + CH_3I $\longrightarrow$
- **(m)** Product of (j) + $C_6H_5CH_2Cl$ $\longrightarrow$

19.13 Predict the product of the following reactions.

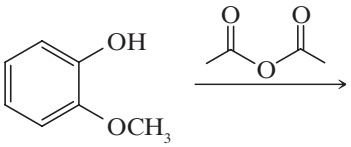
(a)



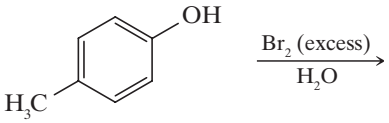
(b)



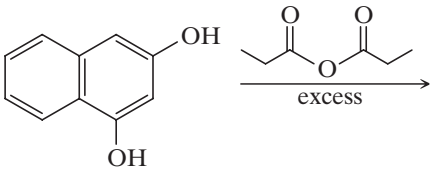
(c)



(d)



(e)



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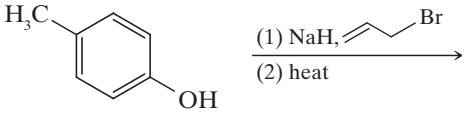
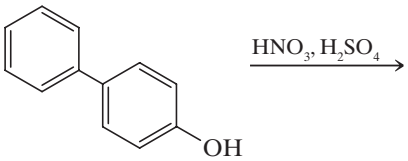
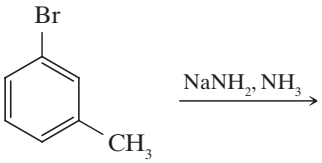


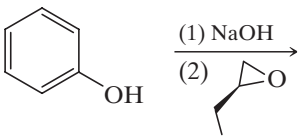
(g)



(h)



(i)



Mechanisms and Synthesis

19.14 When *m*-chlorotoluene is treated with sodium amide in liquid ammonia, the products of the reaction are *o*-, *m*-, and *p*-toluidine (i.e., *o*-$CH_3C_6H_4NH_2$, *m*-$CH_3C_6H_4NH_2$,

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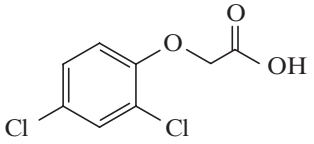
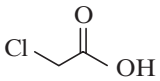
and *p*-$CH_3C_6H_4NH_2$). Propose plausible mechanisms that account for the formation of each product.

19.15 The herbicide **2,4-D** can be synthesized from phenol and chloroacetic acid. Outline the steps involved.

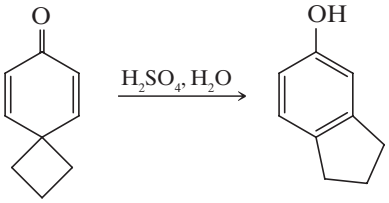


2,4-D (2,4-dichlorophenoxyacetic acid)

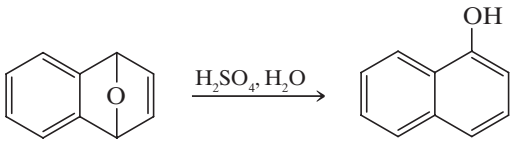


Chloroacetic acid

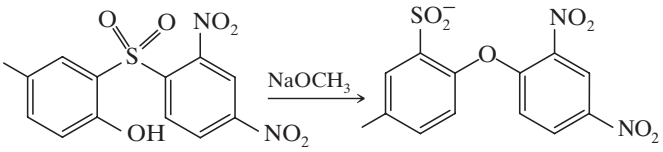
19.16 Provide a mechanism for the following reaction.



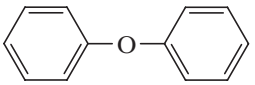
19.17 Provide a mechanism for the following reaction.



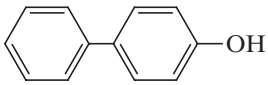
19.18 Provide a mechanism for the following reaction.



19.19 Account for the fact that the Dow process for the production of phenol produces both diphenyl ether **(1)** and 4-hydroxybiphenyl **(2)** as by-products:



1

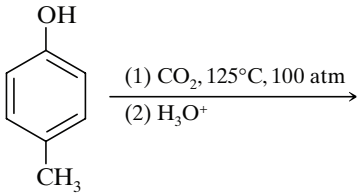


2

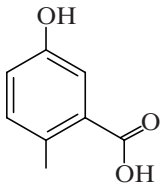
ADDITIONAL OBJECTIVE QUESTIONS

Single Correct Choice Type

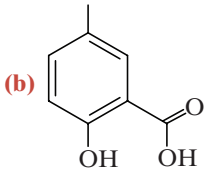
1. What is the major product of the following reaction?



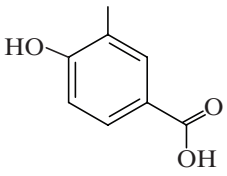
(a)



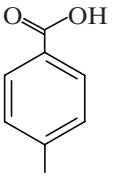
(b)



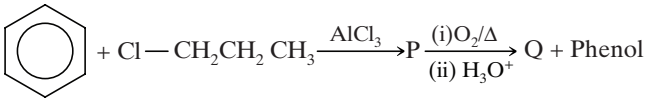
(c)



(d)

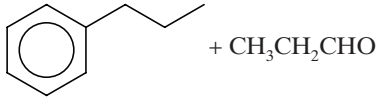


2.



P and Q are respectively

(a)



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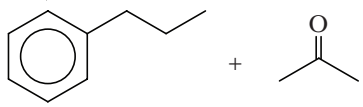
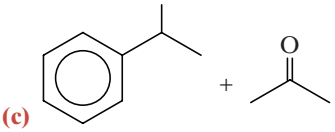


(c)



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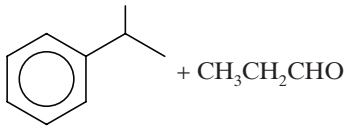
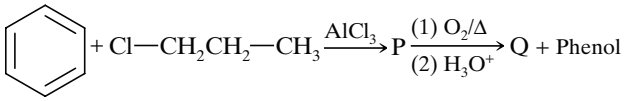
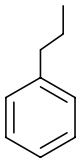


3. The major products P and Q in the following reaction are:

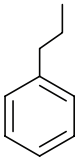


(a)



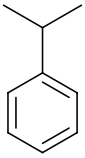
and CH_3CH_2CHO

(b)



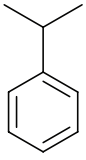
and CH_3COCH_3

(c)



and CH_3COCH_3

(d)



and CH_3CH_2CHO

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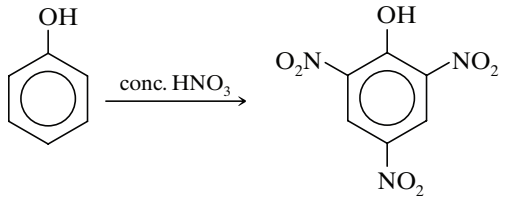
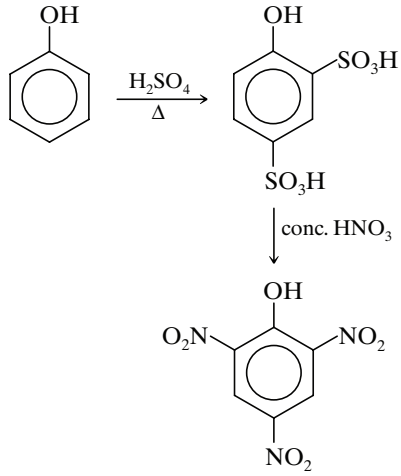
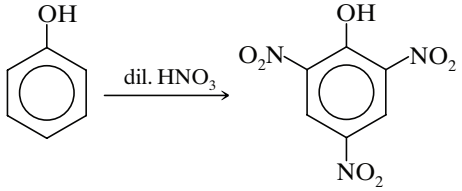
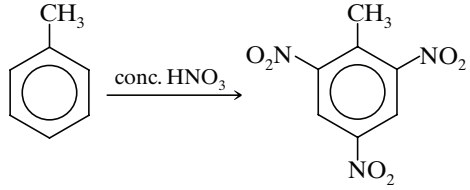
4. Which of the following is the best method for preparation of picric acid?

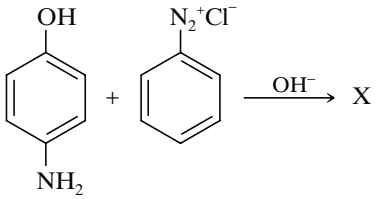
(a) 

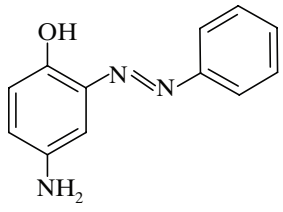
(b) 

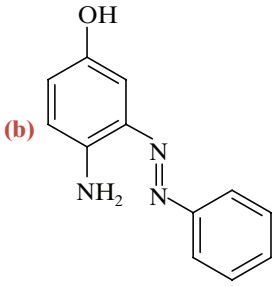
(c) 

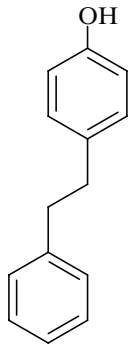
(d) 

5. Consider the following reaction and identify X:



(a) 

(b) 

(c) 

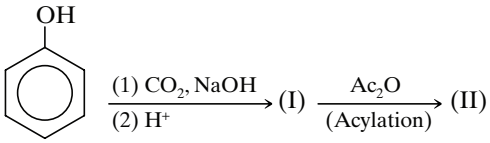
(d) None

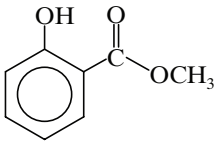
6. Phenol can be distinguished from ethanol by the reactions with _____.

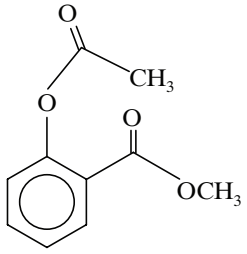
(a) Br_2/water **(b)** NaOI

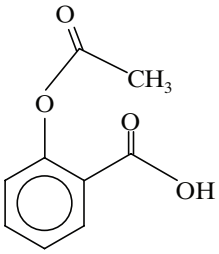
(c) Neutral $FeCl_3$ **(d)** All the above

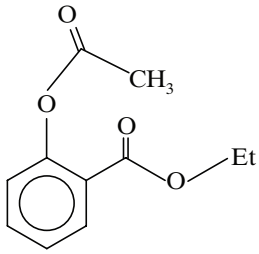
7. Major product (II) is



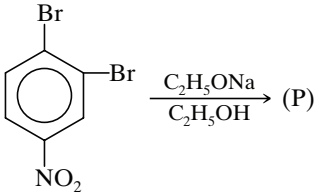
(a) 

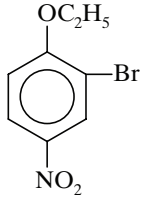
(b) 

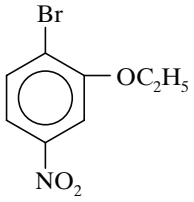
(c) 

(d) 

8. In the given reaction, P is



(a) 

(b) 

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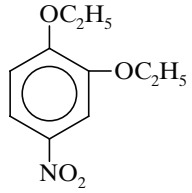
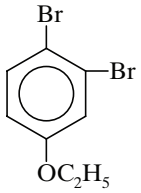
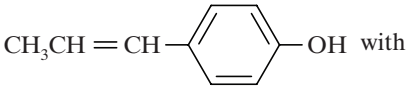
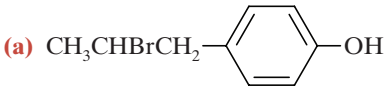
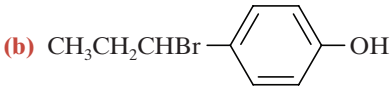
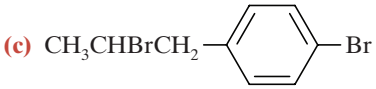
(c) 

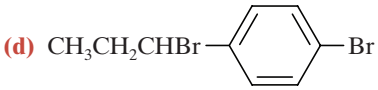
(d) 

9. The reaction of  with HBr gives

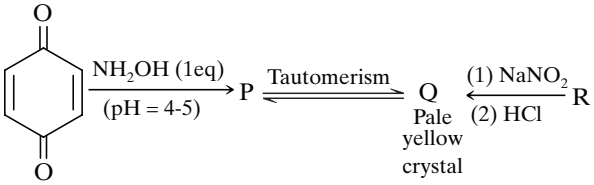
(a) 

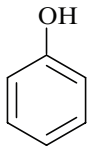
(b) 

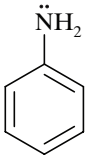
(c) 

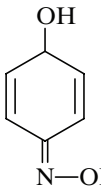
(d) 

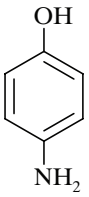
10. Identify R



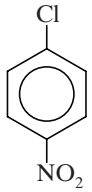
(a) 

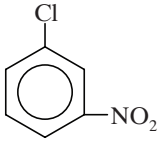
(b) 

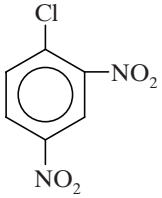
(c) 

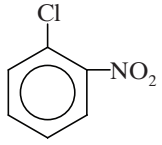
(d) 

11. Which one of the following compounds is most reactive for S_N2Ar reaction?

(a) 

(b) 

(c) 

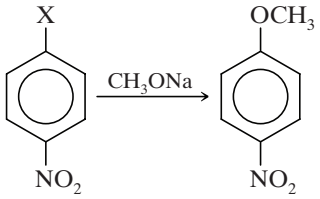
(d) 

12. Following equation illustrates

$$C_6H_5Cl + 2NaOH \xrightarrow[200\ atm]{200–250°C} C_6H_5ONa + NaCl + H_2O$$

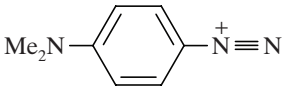
(a) Dow's process (b) Kolbe's process
(c) Carbylamine test (d) Haloform reaction

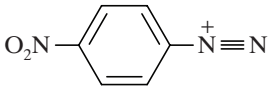
13. The following reaction has the maximum rate when

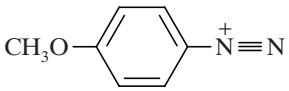


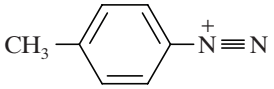
(a) X = I (b) X = Br (c) X = Cl (d) X = F

14. Consider the following ions

(i) 

(ii) 

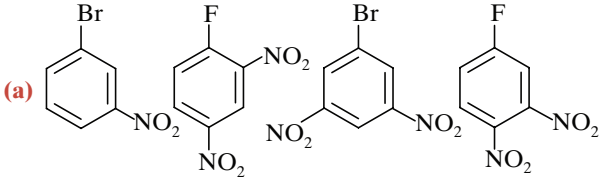
(iii) 

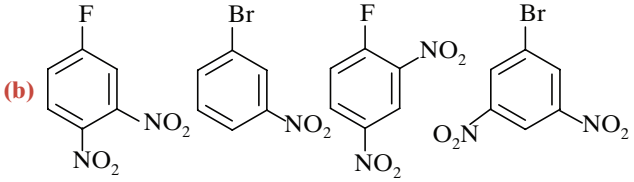
(iv) 

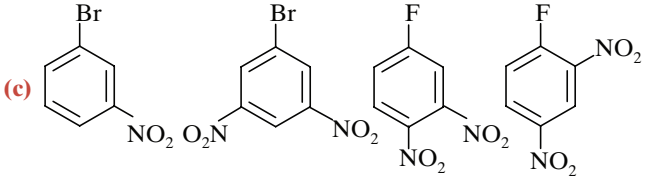
The reactivity of these ions towards azo-coupling reaction under similar conditions is

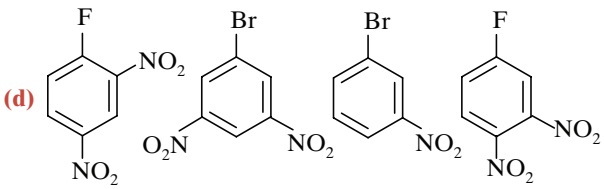
(a) (i) < (iv) < (ii) < (iii) (b) (i) < (iii) < (iv) < (ii)
(c) (iii) < (i) < (ii) < (iv) (d) (iii) < (i) < (iv) < (ii)

15. Which of the following correctly ranks the aryl halides in increasing order of reactivity towards sodium methoxide in methanol?

(a) 

(b) 

(c) 

(d) 

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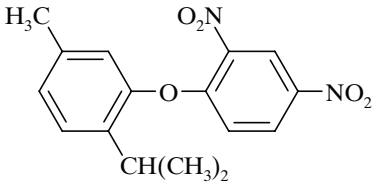
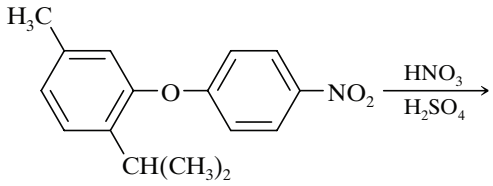
16. Which is the best synthesis of the following compound?



(a)



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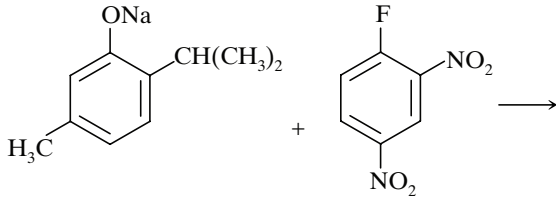

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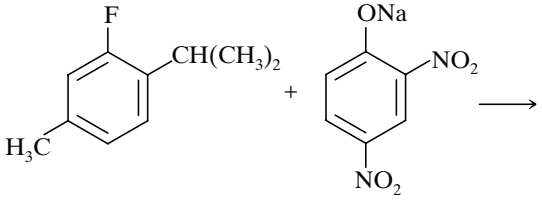

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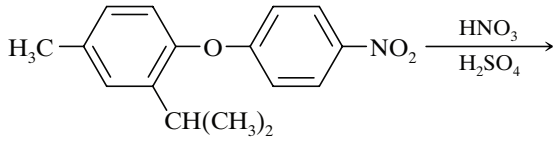
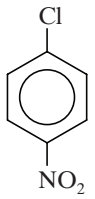


17. Phenol, when it first reacts with concentrated sulphuric acid and then with concentrated nitric acid, gives

(a) 2,4,6-trinitrobenzene. **(b)** *o*-nitrophenol.
(c) *p*-nitrophenol. **(d)** nitrobenzene.

18. Which of the following is most reactive toward S_NAr?

(a)



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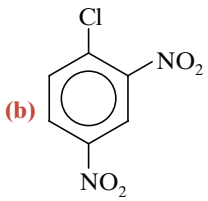

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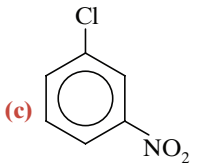

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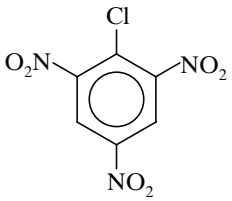
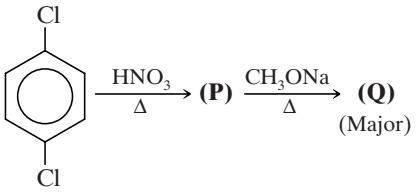


19. When phenol is treated with excess of bromine water, it gives

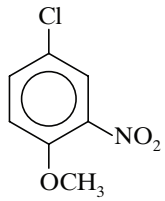
(a) *m*-bromophenol. **(b)** *o*-and *p*-bromophenol.
(c) 2, 4-dibromophenol. **(d)** 2, 4, 6-tribromophenol.

20.

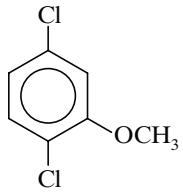


Product (Q) is

(a)



(b)



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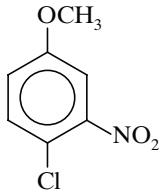
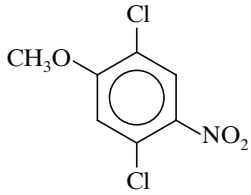


(d)



21. Benzene diazonium chloride on reaction with phenol in weakly basic medium gives

(a) diphenyl ether. **(b)** *p*-hydroxy azobenzene.
(c) chlorobenzene. **(d)** benzene.

ANSWER KEY

Single Correct Choice Type

1. (b)	**2.** (c)	**3.** (c)	**4.** (b)	**5.** (a)
6. (d)	**7.** (c)	**8.** (a)	**9.** (b)	**10.** (a)
11. (c)	**12.** (a)	**13.** (d)	**14.** (d)	**15.** (c)
16. (b)	**17.** (b)	**18.** (d)	**19.** (d)	**20.** (a)
21. (b)				

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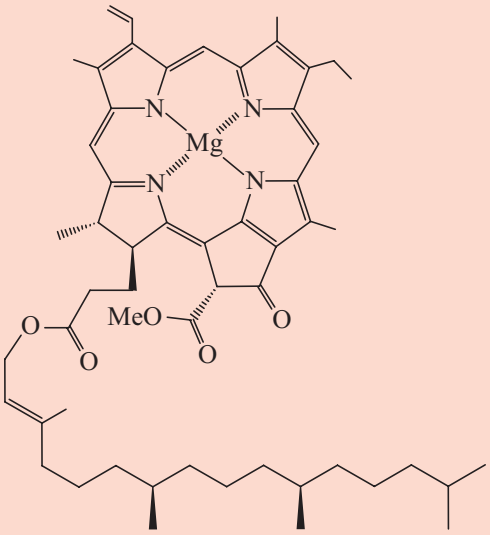
20

Carbohydrates



Chlorophyll a

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20.15 | Sugars that Contain Nitrogen
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20.1 | INTRODUCTION

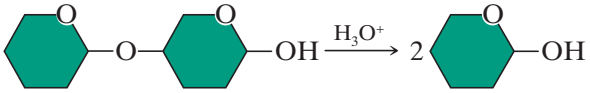
20.1A Classification of Carbohydrates

The group of compounds known as carbohydrates received their general name because of early observations that they often have the formula $C_x(H_2O)_y$—that is, they appear to be "hydrates of carbon" as noted in the chapter opener. They are also characterized by the functional groups that they contain.

- **Carbohydrates** are usually defined as polyhydroxy aldehydes and ketones or substances that hydrolyze to yield polyhydroxy aldehydes and ketones. They exist primarily in their hemiacetal or acetal forms (Section 15.7).

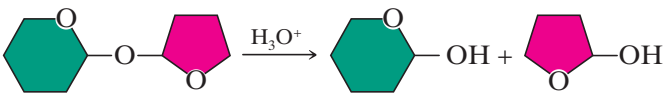
The simplest carbohydrates, those that cannot be hydrolyzed into simpler carbohydrates, are called **monosaccharides**. On a molecular basis, carbohydrates that undergo hydrolysis to produce only 2 molecules of monosaccharide are called **disaccharides**; those that yield 3 molecules of monosaccharide are called **trisaccharides**; and so on. (Carbohydrates that hydrolyze to yield 2–10 molecules of monosaccharide are sometimes called **oligosaccharides**.) Carbohydrates that yield a large number of molecules of monosaccharides (>10) are known as **polysaccharides**.

Maltose and sucrose are examples of disaccharides. On hydrolysis, 1 mol of maltose yields 2 mol of the monosaccharide glucose; sucrose undergoes hydrolysis to yield 1 mol of glucose and 1 mol of the monosaccharide fructose. Starch and cellulose are examples of polysaccharides; both are glucose polymers. Hydrolysis of either yields a large number of glucose units. The following shows these hydrolyses in a schematic way:



1 mol of maltose
A disaccharide

2 mol of glucose
A monosaccharide



1 mol of sucrose
A disaccharide

1 mol of glucose + 1 mol of fructose
Monosaccharides

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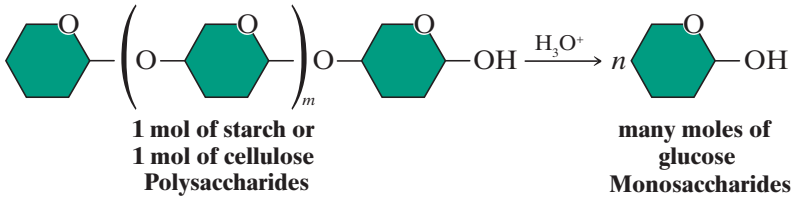

Carbohydrates are the most abundant organic constituents of plants. They not only serve as an important source of chemical energy for living organisms (sugars and starches are important in this respect), but also in plants and in some animals they serve as important constituents of supporting tissues (this is the primary function of the cellulose found in wood, cotton, and flax, for example).

We encounter carbohydrates at almost every turn of our daily lives. The paper on which this book is printed is largely cellulose; so, too, is the cotton of our clothes and the wood of our houses. The flour from which we make bread is mainly starch, and starch is also a major constituent of many other foodstuffs, such as potatoes, rice, beans, corn, an peas. Carbohydrates are central to metabolism, and they are important for cell recognition.

20.1B Photosynthesis and Carbohydrate Metabolism

Carbohydrates are synthesized in green plants by *photosynthesis*—a process that uses solar energy to reduce, or "fix," carbon dioxide. Photosynthesis in algae and higher plants occurs in cell organelles called chloroplasts. The overall equation for photosynthesis can be written as follows:

$$x\ CO_2 + y\ H_2O + \text{solar energy} \rightarrow \underset{\textbf{Carbohydrate}}{C_x(H_2O)_y} + x\ O_2$$

Many individual enzyme-catalyzed reactions take place in the general photosynthetic process and not all are fully understood. We know, however, that photosynthesis begins with the absorption of light by the important green pigment of plants, chlorophyll (Fig. 20.1). The green color of chlorophyll and, therefore, its ability to absorb sunlight in the visible region are due primarily to its extended conjugated system. As photons of sunlight are trapped by chlorophyll, energy becomes available to the plant in a chemical form that can be used to carry out the reactions that reduce carbon dioxide to carbohydrates and oxidize water to oxygen.

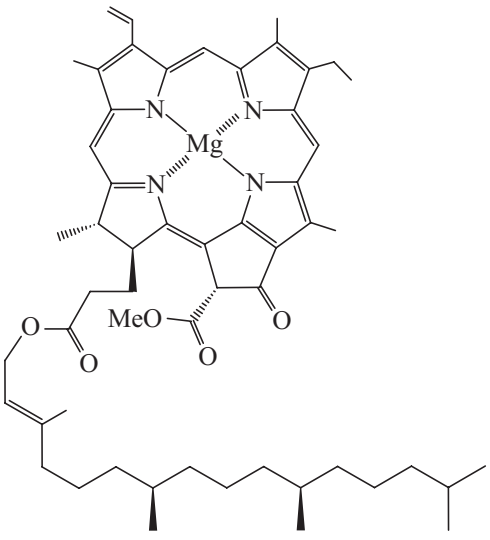

Figure 20.1 Chlorophyll a. [The structure of chlorophyll a was established largely through the work of H. Fischer (Munich), R. Willstätter (Munich), and J. B. Conant (Harvard). A synthesis of chlorophyll a from simple organic compounds was achieved by R. B. Woodward (Harvard) in 1960, who won the Nobel prize in 1965 for his outstanding contributions to synthetic organic chemistry.]

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Carbohydrates act as a major chemical repository for solar energy. Their energy is released when animals or plants metabolize carbohydrates to carbon dioxide and water:

$$C_x(H_2O)_y + x\ O_2 \rightarrow x\ CO_2 + y\ H_2O + \text{energy}$$

The metabolism of carbohydrates also takes place through a series of enzyme-catalyzed reactions in which each energy-yielding step is an oxidation (or the consequence of an oxidation).

Although some of the energy released in the oxidation of carbohydrates is inevitably converted to heat, much of it is conserved in a new chemical form through reactions that are coupled to the synthesis of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) and inorganic phosphate (P_i) (Fig. 20.2). The phosphoric anhydride bond that forms between the terminal phosphate group of ADP and the phosphate ion becomes another repository of chemical energy. Plants and animals can use the conserved energy of ATP (or very similar substances) to carry out all of their energy-requiring processes: the contraction of a muscle, the synthesis of a macromolecule, and so on. When the energy in ATP is used, a coupled reaction takes place in which ATP is hydrolyzed,

$$ATP + H_2O \rightarrow ADP + P_i + \text{energy}$$

or a new anhydride linkage is created,

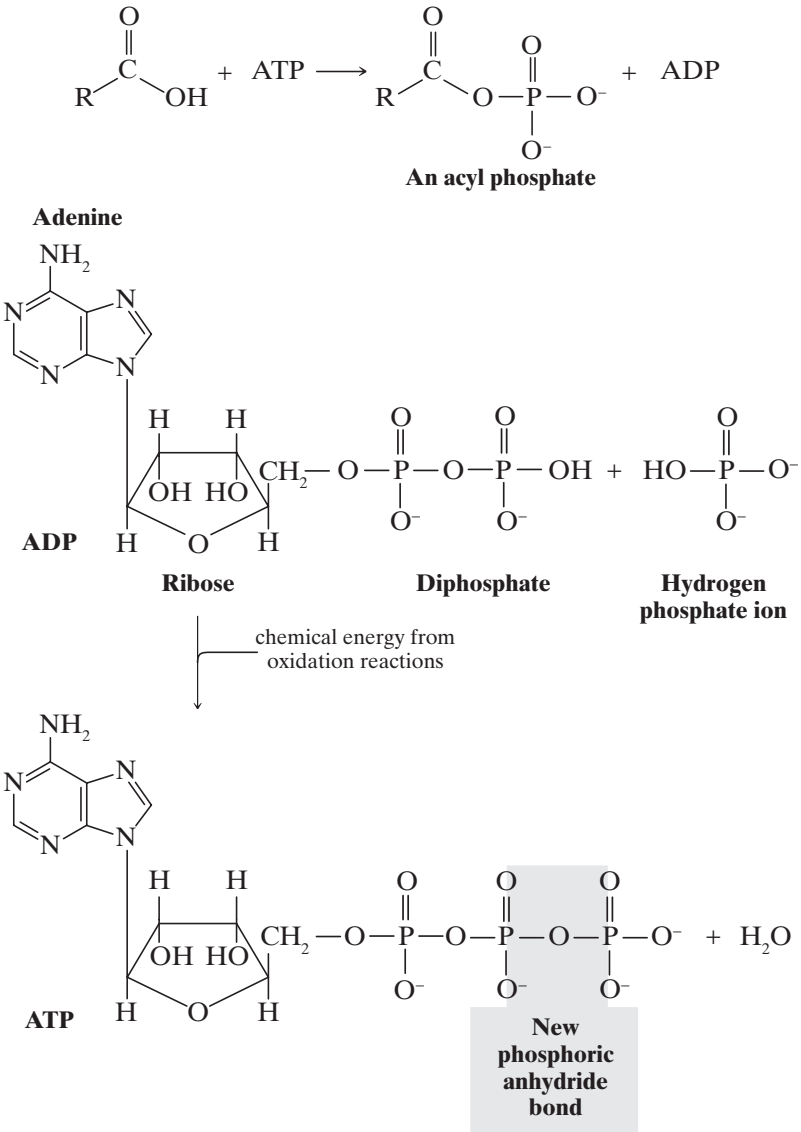

Figure 20.2 The synthesis of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) and hydrogen phosphate ion. This reaction takes place in all living organisms, and adenosine triphosphate is the major compound into which the chemical energy released by biological oxidations is transformed.

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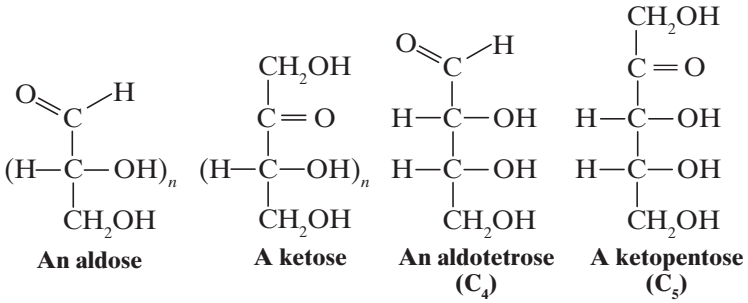
20.2 | MONOSACCHARIDES

20.2A Classification of Monosaccharides

Monosaccharides are classified according to (1) the number of carbon atoms present in the molecule and (2) whether they contain an aldehyde or keto group. Thus, a monosaccharide containing three carbon atoms is called a *triose*; one containing four carbon atoms is called a *tetrose*; one containing five carbon atoms is a *pentose*; and one containing six carbon atoms is a *hexose*. A monosaccharide containing an aldehyde group is called an **aldose**; one containing a keto group is called a **ketose**. These two classifications are frequently combined. A C_4 aldose, for example, is called an *aldotetrose*; a C_5 ketose is called a *ketopentose*.

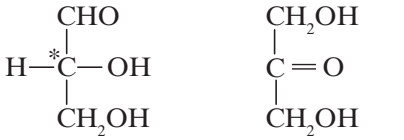


Practice Problem 20.1

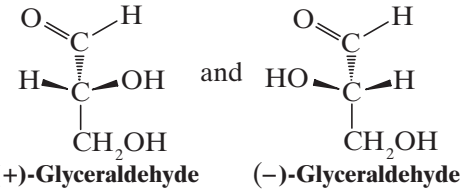
How many chirality centers are contained in **(a)** the aldotetrose and **(b)** the ketopentose just given? **(c)** How many stereoisomers would you expect from each general structure?

20.2B D and L Designations of Monosaccharides

The simplest monosaccharides are the compounds glyceraldehyde and dihydroxyacetone (see the following structures). Of these two compounds, only glyceraldehyde contains a chirality center.



Glyceraldehyde exists, therefore, in two enantiomeric forms that are known to have the absolute configurations shown here:



We saw in Section 4.7 that, according to the Cahn–Ingold–Prelog convention, (+)-glyceraldehyde should be designated (*R*)-(+)-glyceraldehyde and (−)-glyceraldehyde should be designated (*S*)-(−)-glyceraldehyde.

Early in the twentieth century, before the absolute configurations of any organic compounds were known, another system of stereochemical designations was introduced. According to this system (first suggested by M. A. Rosanoff of New York University in 1906), (+)-glyceraldehyde is designated D-(+)-glyceraldehyde and (−)-glyceraldehyde is designated L-(−)-glyceraldehyde. These two compounds, moreover, serve as configurational standards for all monosaccharides. A monosaccharide *whose highest numbered chirality center* (the penultimate carbon) has the same configuration as D-(+)-glyceraldehyde is designated as a D sugar; one whose highest numbered chirality

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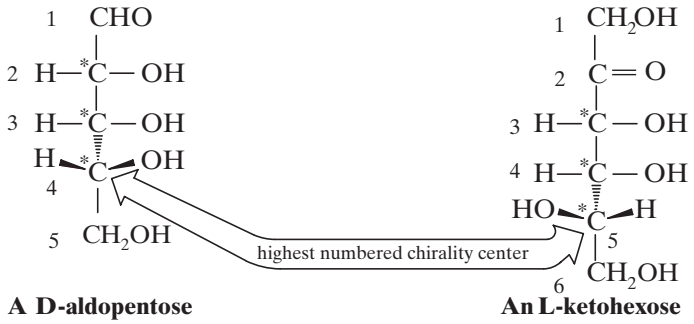
center has the same configuration as L-glyceraldehyde is designated as an L sugar. By convention, acyclic forms of monosaccharides are drawn vertically with the aldehyde or keto group at or nearest the top. When drawn in this way, D sugars have the —OH on their penultimate carbon on the right:



A D-aldopentose **An L-ketohexose**

The **D and L nomenclature** designations are like (*R*) and (*S*) designations in that they are not necessarily related to the optical rotations of the sugars to which they are applied. Thus, one may encounter other sugars that are D-(+) or D-(−) and ones that are L-(+) or L-(−).

The D–L system of stereochemical designations is thoroughly entrenched in the literature of carbohydrate chemistry, and even though it has the disadvantage of specifying the configuration of only one chirality center—that of the highest numbered chirality center—we shall employ the D–L system in our designations of carbohydrates.

Practice Problem 20.2

Write three-dimensional formulas for each aldotetrose and ketopentose isomer in Practice Problem 20.1 and designate each as a D or L sugar.

20.2C Structural Formulas for Monosaccharides

Later in this chapter we shall see how the great carbohydrate chemist Emil Fischer was able to establish the stereochemical configuration of the aldohexose D-(+)-glucose, the most abundant monosaccharide. In the meantime, however, we can use D-(+)-glucose as an example illustrating the various ways of representing the structures of monosaccharides.

Fischer represented the structure of D-(+)-glucose with the cross formulation **(1)** in Fig. 20.3. This type of formulation is now called a **Fischer projection** (Section 4.13) and is still useful for carbohydrates. In Fischer projections, by convention, *horizontal lines project out toward the reader and vertical lines project behind the plane of the page. When we use Fischer projections, however, we must not* (in our mind's eye) *remove them from the plane of the page in order to test their superposability and we must not rotate them by 90°*. In terms of more familiar formulations, the Fischer projection translates into formulas **6** and **7**. In IUPAC nomenclature and with the Cahn–Ingold–Prelog system of stereochemical designations, the open-chain form of D-(+)-glucose is (2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexanal.

> The meaning of formulas **1**, **2**, and **3** can be seen best through the use of molecular models: we first construct a chain of six carbon atoms with the —CHO group at the top and a —CH_2OH group at the bottom. We then bring the CH_2OH group up behind the chain until it almost touches the —CHO group. Holding this model so that the —CHO and —CH_2OH groups are directed generally away from us, we then begin placing —H and —OH groups on each of the four remaining carbon atoms. The —OH group of C2 is placed on the right; that of C3 on the left; and those of C4 and C5 on the right.

Although many of the properties of D-(+)-glucose can be explained in terms of an open-chain structure (**1**, **2**, or **3**), a considerable body of evidence indicates that the open-chain structure exists, primarily, in equilibrium with two cyclic forms. These can be represented by structures **4** and **5** or **6** and **7**. The cyclic forms of D-(+)-glucose are **hemiacetals** formed by an intramolecular reaction of the —OH group at C5 with the aldehyde group (Fig. 20.4). Cyclization creates a new chirality center at C1, and this chirality center explains how two cyclic forms are possible. These two cyclic forms are *diastereomers* that differ only in the configuration of C1.

- In carbohydrate chemistry diastereomers differing only at the hemiacetal or acetal carbon are called **anomers**, and the hemiacetal or acetal carbon atom is called the **anomeric carbon atom**.

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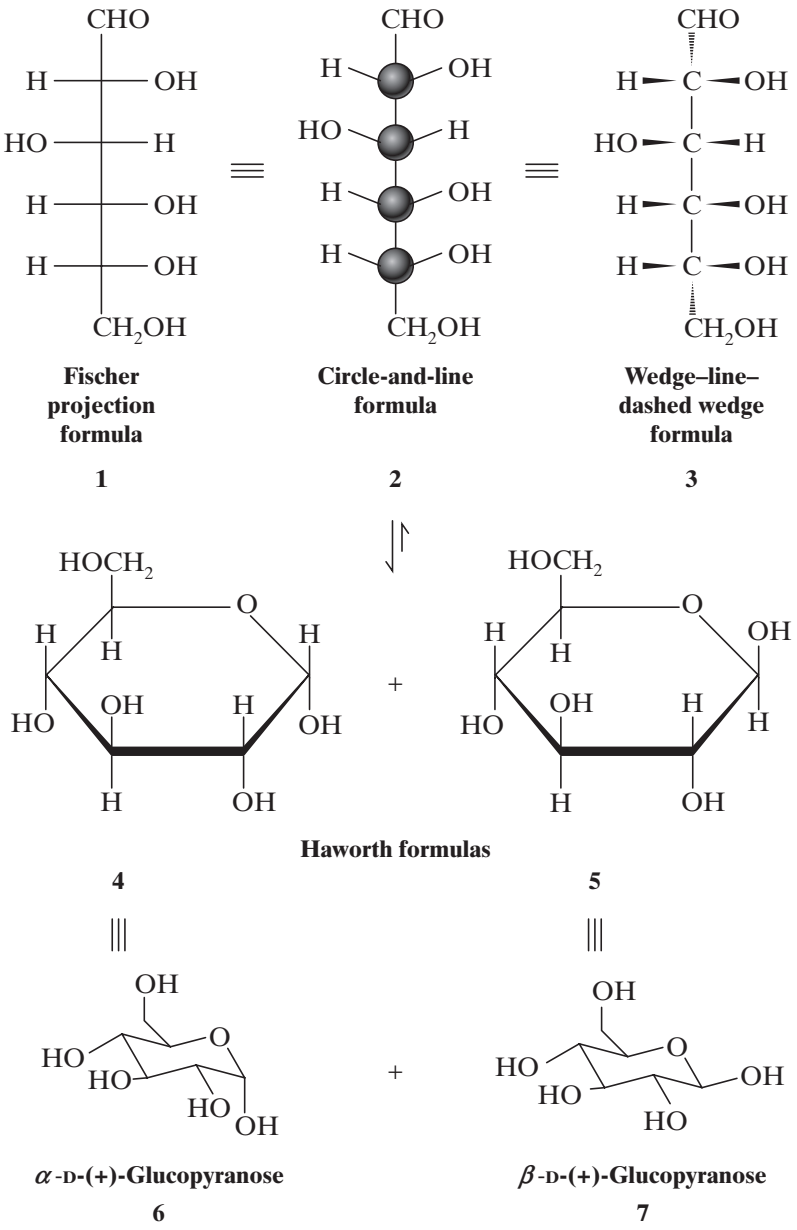

Figure 20.3 Formulas 1–3 are used for the open-chain structure of D-(+)-glucose. Formulas 4–7 are used for the two cyclic hemiacetal forms of D-(+)-glucose.

Structures **4** and **5** for the glucose anomers are called **Haworth formulas*** and, although they do not give an accurate picture of the shape of the six-membered ring, they have many practical uses. Figure 20.4 demonstrates how the representation of each chirality center of the open-chain form can be correlated with its representation in the Haworth formula.

Each glucose anomer is designated as an **α anomer** or a **β anomer** depending on the location of the —OH group of C1. When we draw the cyclic forms of a D sugar in the orientation shown in Figs. 20.3 or 20.4, the α anomer has the —OH trans to the —CH_2OH group and the β anomer has the —OH cis to the —CH_2OH group.

Studies of the structures of the cyclic hemiacetal forms of D-(+)-glucose using X-ray analysis have demonstrated that the actual conformations of the rings are the chair forms represented by conformational formulas

*Haworth formulas are named after the English chemist W. N. Haworth (University of Birmingham), who, in 1926, along with E. L. Hirst, demonstrated that the cyclic form of glucose acetals consists of a six-membered ring. Haworth received the Nobel Prize for his work in carbohydrate chemistry in 1937. For an excellent discussion of Haworth formulas and their relation to open-chain forms, see "The Conversion of Open Chain Structures of Monosaccharides into the Corresponding Haworth Formulas," Wheeler, D. M. S., Wheeler, M. M., and Wheeler, T. S., *J. Chem. Educ.* **1982**, *59*, 969–970.

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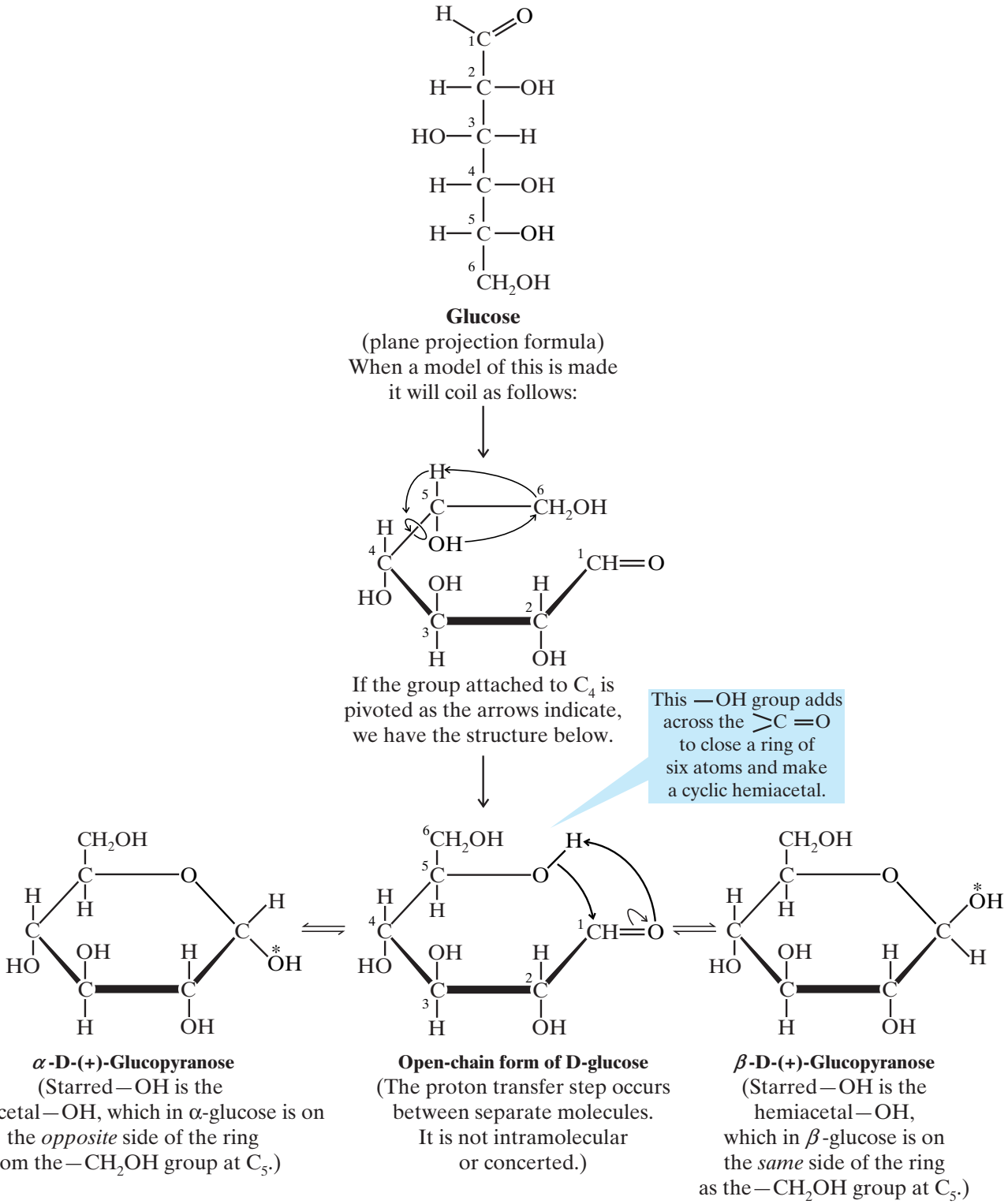

Figure 20.4 Haworth formulas for the cyclic hemiacetal forms of D-(+)-glucose and their relation to the open-chain polyhydroxy aldehyde structure. (Reprinted with permission of John Wiley & Sons, Inc., from Holum, J. R., *Organic Chemistry: A Brief Course*, p. 316. Copyright 1975.)

6 and **7** in Fig. 20.3. This shape is exactly what we would expect from our studies of the conformations of cyclohexane (Chapter 4), and it is especially interesting to notice that in the β anomer of D-glucose all of the large substituents, —OH and —CH_2OH, are equatorial. In the α anomer, the only bulky axial substituent is the —OH at C1.

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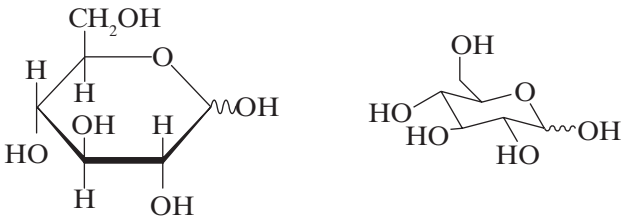
It is convenient at times to represent the cyclic structures of a monosaccharide without specifying whether the configuration of the anomeric carbon atom is α or β. When we do this, we shall use formulas such as the following:



The symbol ∿ indicates α or β (three-dimensional view not specified).

Not all carbohydrates exist in equilibrium with six-membered hemiacetal rings; in several instances the ring is five membered. (Even glucose exists, to a small extent, in equilibrium with five-membered hemiacetal rings.) Because of this variation, a system of nomenclature has been introduced to allow designation of the ring size.

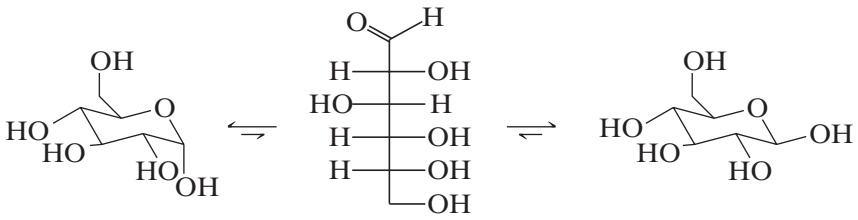
- If the monosaccharide ring is six membered, the compound is called a **pyranose**; if the ring is five membered, the compound is designated as a **furanose**.

20.3 | MUTAROTATION

Part of the evidence for the cyclic hemiacetal structure for D-(+)-glucose comes from experiments in which both α or β forms have been isolated. Ordinary D-(+)-glucose has a melting point of 146 °C. However, when D-(+)-glucose is crystallized by evaporating an aqueous solution kept above 98 °C, a second form of D-(+)-glucose with a melting point of 150 °C can be obtained. When the optical rotations of these two forms are measured, they are found to be significantly different, but when an aqueous solution of either form is allowed to stand, its rotation changes. The specific rotation of one form decreases and the rotation of the other increases, *until both solutions show the same value*. A solution of ordinary D-(+)-glucose (mp 146 °C) has an initial specific rotation of +112, but, ultimately, the specific rotation of this solution falls to +52.7. A solution of the second form of D-(+)-glucose (mp 150 °C) has an initial specific rotation of +18.7, but, slowly, the specific rotation of this solution rises to +52.7.

- This change in specific rotation toward an equilibrium value is called **mutarotation**.

The explanation for this mutarotation lies in the existence of an equilibrium between the open-chain form of D-(+)-glucose and the α and β forms of the cyclic hemiacetals:



α-D-(+)-Glucopyranose (mp 146 °C; $[\alpha]_D^{25}$ = +112) | **Open-chain form of D-(+)-glucose** | **β-D-(+)-Glucopyranose (mp 150 °C; $[\alpha]_D^{25}$ = +18.7)**

X-ray analysis has confirmed that ordinary D-(+)-glucose has the α configuration at the anomeric carbon atom and that the higher melting form has the β configuration.

The concentration of open-chain D-(+)-glucose in solution at equilibrium is very small. Solutions of D-(+)-glucose give no observable UV or IR absorption band for a carbonyl group, and solutions of D-(+)-glucose give a negative test with Schiff's reagent—a special reagent that requires a relatively high concentration of a free aldehyde group (rather than a hemiacetal) in order to give a positive test.

Assuming that the concentration of the open-chain form is negligible, one can, by use of the specific rotations in the preceding figures, calculate the percentages of the α and β anomers present at equilibrium. These percentages, 36% α anomer and 64% β anomer, are in accord with a greater stability for β-D-(+)-glucopyranose. This preference is what we might expect on the basis of its having only equatorial groups:

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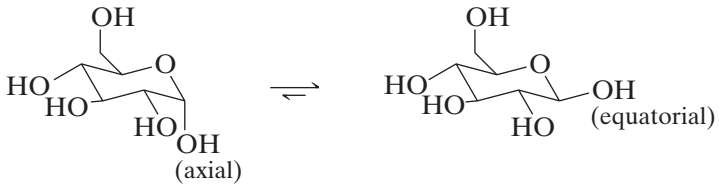
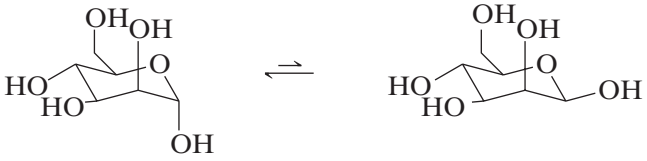


α-D-(+)-Glucopyranose (36% at equilibrium) ⇌ **β-D-(+)-Glucopyranose (64% at equilibrium)**

The β anomer of a pyranose is not always the more stable, however. With D-mannose, the equilibrium favors the α anomer, and this result is called an *anomeric effect*:

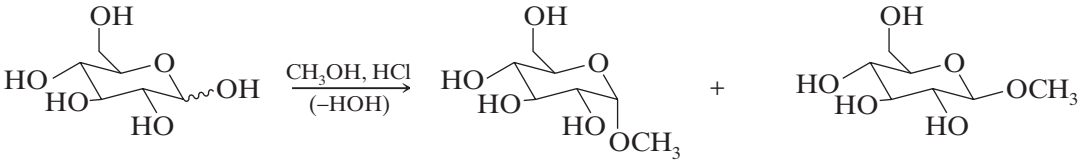


α-D-Mannopyranose (69% at equilibrium) ⇌ **β-D-Mannopyranose (31% at equilibrium)**

The anomeric effect is widely believed to be caused by hyperconjugation. An axially oriented orbital associated with nonbonding electrons of the ring oxygen can overlap with a σ* orbital of the axial exocyclic C—O hemiacetal bond. This effect is similar to that which helps cause the lowest energy conformation of ethane to be the anti conformation (Section 5.8). An anomeric effect will frequently cause an electronegative substituent, such as a hydroxyl or alkoxyl group, to prefer the axial orientation.

20.4 | GLYCOSIDE FORMATION

When a small amount of gaseous hydrogen chloride is passed into a solution of D-(+)-glucose in methanol, a reaction takes place that results in the formation of anomeric methyl *acetals*:



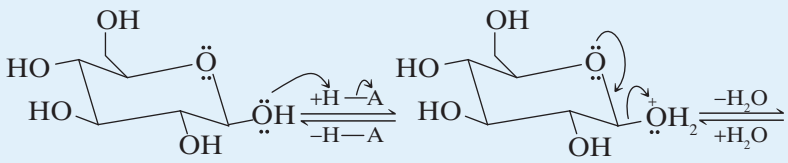
D-(+)-Glucose → **Methyl α-D-glucopyranoside (mp 165 °C; $[\alpha]_D^{25}$ = +158)** + **Methyl β-D-glucopyranoside (mp 107 °C; $[\alpha]_D^{25}$ = –33)**

- Carbohydrate acetals are generally called **glycosides** (see the following mechanism), and an acetal of glucose is called a *glucoside*. (Acetals of mannose are *mannosides*, acetals of fructose are *fructosides*, and so on.)

The methyl D-glucosides have been shown to have six-membered rings (Section 20.2C) so they are properly named methyl α-D-glucopyranoside and methyl β-D-glucopyranoside.

The mechanism for the formation of the methyl glucosides (starting arbitrarily with β-D-glucopyranose) is as follows:

A MECHANISM FOR THE REACTION — Formation of a Glycoside



β-D-Glucopyranose

(*Mechanism continues on next page*)

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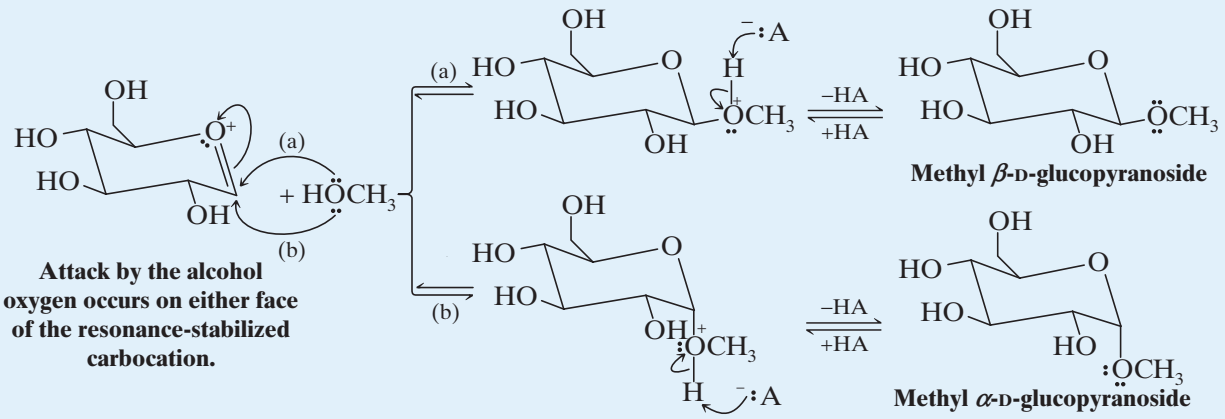
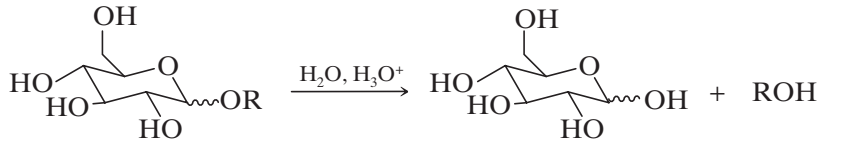


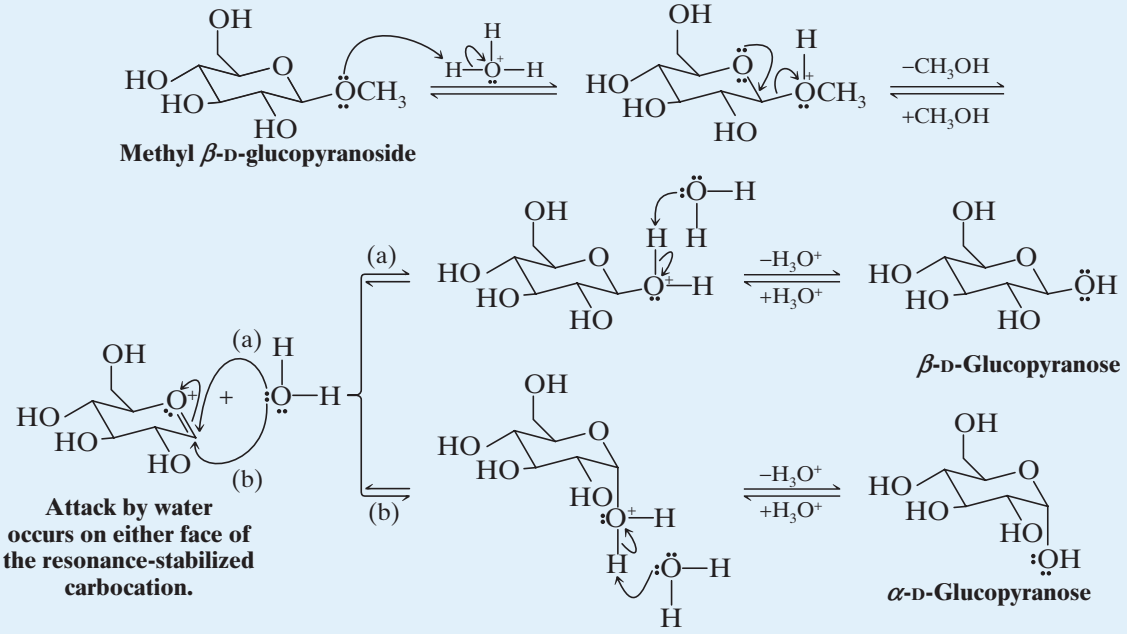
You should review the mechanism for acetal formation given in Section 15.7B and compare it with the steps given here. Notice, again, the important role played by the electron pair of the adjacent oxygen atom in stabilizing the carbocation that forms in the second step.

Glycosides are stable in basic solutions because they are acetals. In acidic solutions, however, glycosides undergo hydrolysis to produce a sugar and an alcohol (again, because they are acetals, Section 15.7B). The alcohol obtained by hydrolysis of a glycoside is known as an **aglycone**:



For example, when an aqueous solution of methyl β-D-glucopyranoside is made acidic, the glycoside undergoes hydrolysis to produce D-glucose as a mixture of the two pyranose forms (in equilibrium with a small amount of the open-chain form).

A MECHANISM FOR THE REACTION — Hydrolysis of a Glycoside



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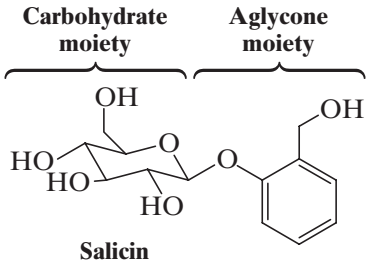
Glycosides may be as simple as the methyl glucosides that we have just studied or they may be considerably more complex. Many naturally occurring compounds are glycosides. An example is *salicin*, a compound found in the bark of willow trees:



Salicin

As early as the time of the ancient Greeks, preparations made from willow bark were used in relieving pain. Eventually, chemists isolated salicin from other plant materials and were able to show that it was responsible for the analgesic effect of the willow bark preparations. Salicin can be converted to salicylic acid, which in turn can be converted into the most widely used modern analgesic, *aspirin* (Section 19.8).

Solved Problem 20.1

In neutral or basic solutions, glycosides do not show mutarotation. However, if the solutions are made acidic, glycosides show mutarotation. Explain.

Answer

Because glycosides are acetals, they undergo hydrolysis in aqueous acid to form cyclic hemiacetals that then undergo mutarotation. Acetals are stable to base, and therefore in basic solution they do not show mutarotation.

Practice Problem 20.3

(a) What products would be formed if salicin were treated with dilute aqueous HCl?
(b) Outline a mechanism for the reactions involved in their formation.

Practice Problem 20.4

How would you convert D-glucose to a mixture of ethyl α-D-glucopyranoside and ethyl β-D-glucopyranoside? Show all steps in the mechanism for their formation.

20.5 | OTHER REACTIONS OF MONOSACCHARIDES

20.5A Enolization, Tautomerization, and Isomerization

Dissolving monosaccharides in aqueous base causes them to undergo a series of enolizations and keto–enol tautomerizations that lead to isomerizations. For example, if a solution of D-glucose containing calcium hydroxide is allowed to stand for several days, a number of products can be isolated, including D-fructose and D-mannose (Fig. 20.5). This type of reaction is called the **Lobry de Bruyn–Alberda van Ekenstein transformation** after the two Dutch chemists who discovered it in 1895.

When carrying out reactions with monosaccharides, it is usually important to prevent these isomerizations and thereby to preserve the stereochemistry at all of the chirality centers. One way to do this is to convert the monosaccharide to the methyl glycoside first. We can then safely carry out reactions in basic media because the aldehyde group has been converted to an acetal and acetals are stable in aqueous base. Preparation of the methyl glycoside serves to "protect" the monosaccharide from undesired reactions that could occur with the anomeric carbon in its hemiacetal form.

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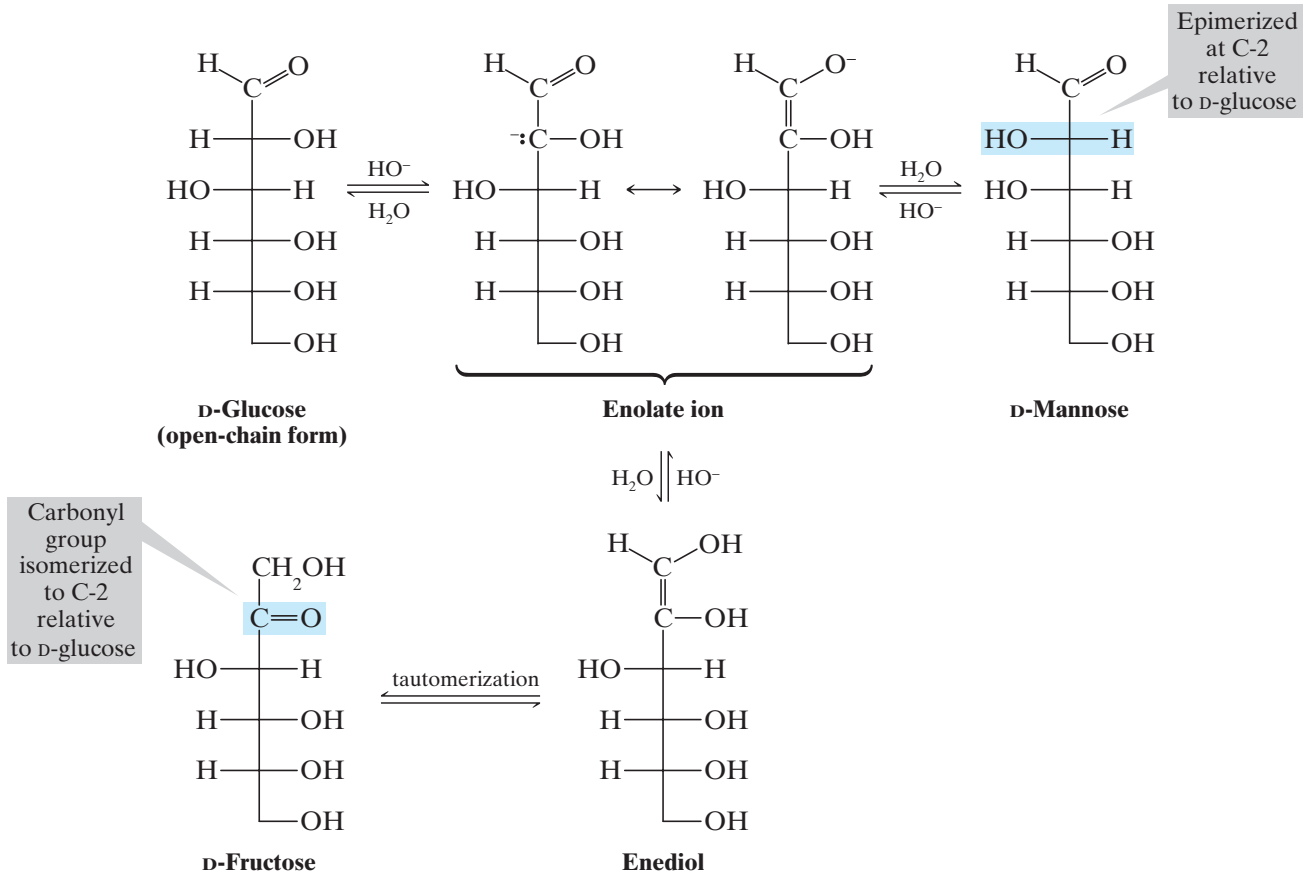


Figure 20.5 Monosaccharides undergo isomerizations via enolates and enediols when placed in aqueous base. Here we show how D-glucose isomerizes to D-mannose and to D-fructose.

20.5B Use of Protecting Groups in Carbohydrate Synthesis

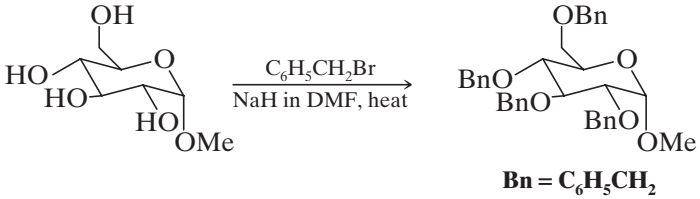
Protecting groups are functional groups introduced selectively to block the reactivity of certain sites in a molecule while desired transformations are carried on elsewhere. After the desired transformations are accomplished, the protecting groups are removed. Laboratory reactions involving carbohydrates often require the use of protecting groups due to the multiple sites of reactivity present in carbohydrates. As we have just seen, formation of a glycoside (an acetal) can be used to prevent undesired reactions that would involve the anomeric carbon in its hemiacetal form. Common protecting groups for the alcohol functional groups in carbohydrates include ethers, esters, and acetals.

20.5C Formation of Ethers

- Hydroxyl groups of sugars can be converted to ethers using a base and an alkyl halide by a version of the Williamson ether synthesis (Section 10.10B).

Benzyl ethers are commonly used to protect hydroxyl groups in sugars. Benzyl halides are easily introduced because they are highly reactive in S_N2 reactions. Sodium or potassium hydride is typically used as the base in an aprotic solvent such as DMF or DMSO. The benzyl groups can later be easily removed by hydrogenolysis using a palladium catalyst.

Benzyl Ether Formation



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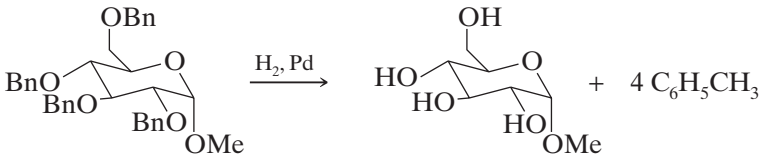
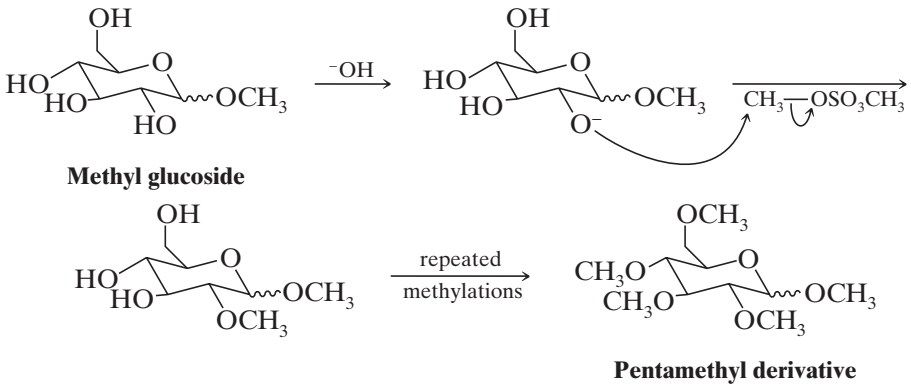
Benzyl Ether Cleavage



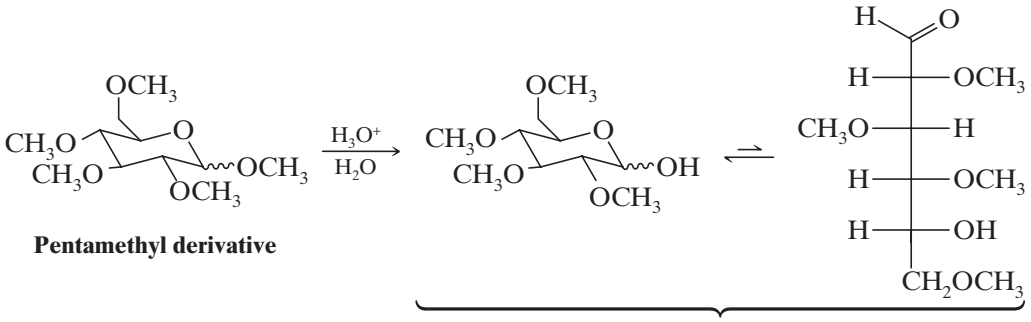
Methyl ethers can also be prepared. The pentamethyl derivative of glucopyranose, for example, can be synthesized by treating methyl glucoside with excess dimethyl sulfate in aqueous sodium hydroxide. Sodium hydroxide is a competent base in this case because the hydroxyl groups of monosaccharides are more acidic than those of ordinary alcohols due to the many electronegative atoms in the sugar, all of which exert electron-withdrawing inductive effects on nearby hydroxyl groups. In aqueous NaOH the hydroxyl groups are all converted to alkoxide ions, and each of these, in turn, reacts with dimethyl sulfate in an S_N2 reaction to yield a methyl ether. The process is called *exhaustive methylation*:



Methyl glucoside

Pentamethyl derivative

Although not often used as protecting groups for alcohols in carbohydrates, methyl ethers have been useful in the structure elucidation of sugars. For example, evidence for the pyranose form of glucose can be obtained by exhaustive methylation followed by aqueous hydrolysis of the acetal linkage. Because the C2, C3, C4, and C6 methoxy groups of the pentamethyl derivative are ethers, they are not affected by aqueous hydrolysis. (To cleave them requires heating with concentrated HBr or HI, Section 10.11.) The methoxyl group at C1, however, is part of an acetal linkage, and so it is labile under the conditions of aqueous hydrolysis. Hydrolysis of the pentamethyl derivative of glucose gives evidence that the C5 oxygen was the one involved in the cyclic hemiacetal form because in the open-chain form of the product (which is in equilibrium with the cyclic hemiacetal) it is the C5 oxygen that is not methylated:

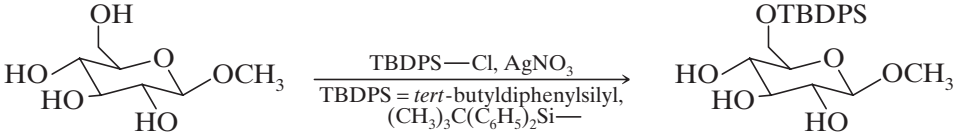


Pentamethyl derivative

2,3,4,6-Tetra-*O*-methyl-D-glucose

Silyl ethers, including *tert*-butyldimethylsilyl (TBS) ethers (Section 10.11E) and phenyl-substituted ethers, are also used as protecting groups in carbohydrate synthesis. *tert*-Butyldiphenylsilyl (TBDPS) ethers show excellent regioselectivity for primary hydroxyl groups in sugars, such as at C6 in a hexopyranose.

Regioselective TBDPS Ether Formation



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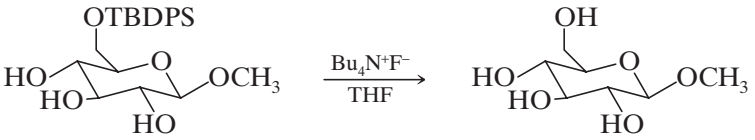
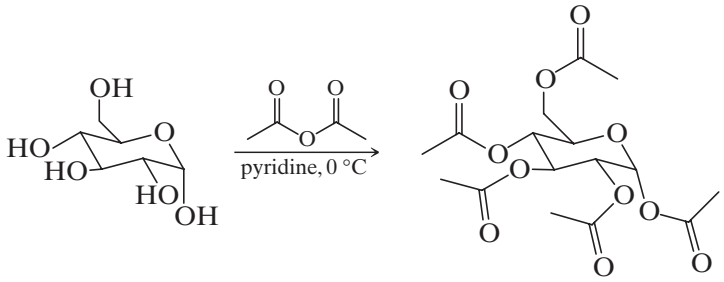
TBDPS Ether Cleavage



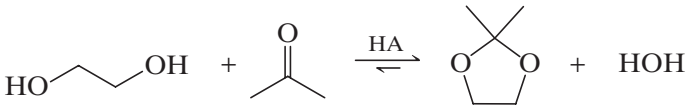
20.5D Conversion to Esters

Treating a monosaccharide with excess acetic anhydride and a weak base (such as pyridine or sodium acetate) converts all of the hydroxyl groups, including the anomeric hydroxyl, to ester groups. If the reaction is carried out at a low temperature (e.g., 0 °C), the reaction occurs stereospecifically; the α anomer gives the α-acetate and the β anomer gives the β-acetate. Acetate esters are common protecting groups for carbohydrate hydroxyls.



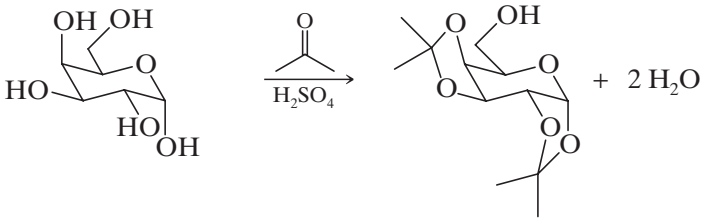
20.5E Conversion to Cyclic Acetals

In Section 15.7B we learned that aldehydes and ketones react with open-chain 1,2-diols to produce **cyclic acetals**:



1,2-Diol **Cyclic acetal**

If the 1,2-diol is attached to a ring, as in a monosaccharide, **formation of the cyclic acetals occurs only when the vicinal hydroxyl groups are cis to each other**. For example, α-D-galactopyranose reacts with acetone in the following way:



Cyclic acetals are commonly used to protect vicinal cis hydroxyl groups of a sugar while reactions are carried out on other parts of the molecule. When acetals such as these are formed from acetone, they are called **acetonides**.

20.6 | OXIDATION REACTIONS OF MONOSACCHARIDES

A number of oxidizing agents are used to identify functional groups of carbohydrates, in elucidating their structures, and for syntheses. The most important are (1) Benedict's or Tollens' reagents, (2) bromine water, (3) nitric acid, and (4) periodic acid. Each of these reagents produces a different and usually specific effect when it is allowed to react with a monosaccharide. We shall now examine what these effects are.

20.6A Benedict's or Tollens' Reagents: Reducing Sugars

Benedict's reagent (an alkaline solution containing a cupric citrate complex ion) and Tollens' solution [$Ag^+(NH_3)_2\bar{O}H$] oxidize and thus give positive tests with *aldoses and ketoses*. The tests are positive even though aldoses and ketoses exist primarily as cyclic hemiacetals.

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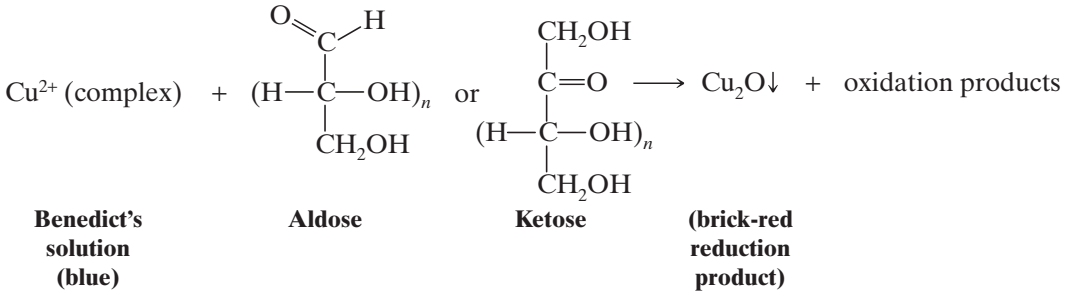
We studied the use of Tollens' silver mirror test in Section 15.13B. Benedict's solution and the related Fehling's solution (which contains a cupric tartrate complex ion) give brick-red precipitates of Cu_2O when they oxidize an aldose. [In alkaline solution ketoses are converted to aldoses (Section 20.5A), which are then oxidized by the cupric complexes.] Since the solutions of cupric tartrates and citrates are blue, the appearance of a brick-red precipitate is a vivid and unmistakable indication of a positive test.

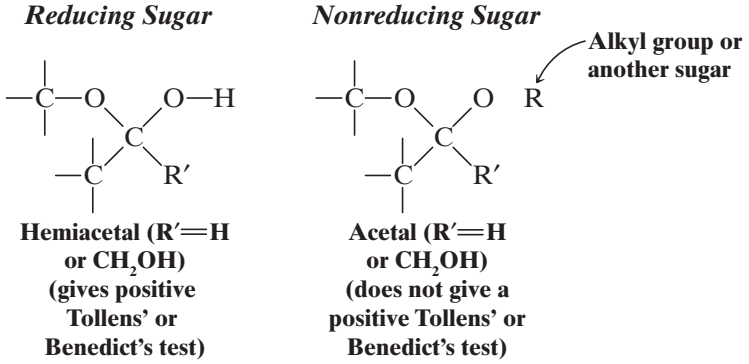


- Sugars that give positive tests with Tollens' or Benedict's solutions are known as **reducing sugars**, and all carbohydrates that contain a *hemiacetal group* give positive tests.

In aqueous solution the hemiacetal form of sugars exists in equilibrium with relatively small, but not insignificant, concentrations of noncyclic aldehydes or α-hydroxy ketones. It is the latter two that undergo the oxidation, perturbing the equilibrium to produce more aldehyde or α-hydroxy ketone, which then undergoes oxidation until one reactant is exhausted.

- Carbohydrates that contain only acetal groups do not give positive tests with Benedict's or Tollens' solutions, and they are called *nonreducing sugars*.

Acetals do not exist in equilibrium with aldehydes or α-hydroxy ketones in the basic aqueous media of the test reagents.



Practice Problem 20.5

How might you distinguish between α-D-glucopyranose (i.e., D-glucose) and methyl α-D-glucopyranoside?

Although Benedict's and Tollens' reagents have some use as diagnostic tools [Benedict's solution can be used in quantitative determinations of reducing sugars (reported as glucose) in blood or urine], neither of these reagents is useful as a preparative reagent in carbohydrate oxidations. Oxidations with both reagents take place in alkaline solution, *and in alkaline solutions sugars undergo a complex series of reactions that lead to isomerizations* (Section 20.5A).

20.6B Bromine Water: The Synthesis of Aldonic Acids

Monosaccharides do not undergo isomerization and fragmentation reactions in mildly acidic solution. Thus, a useful oxidizing reagent for preparative purposes is bromine in water (pH 6.0).

- Bromine water is a general reagent that selectively oxidizes the —CHO group to a $—CO_2H$ group, thus converting an aldose to an **aldonic acid**:

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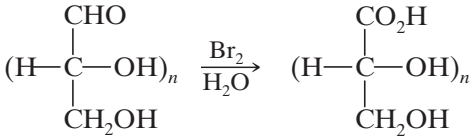
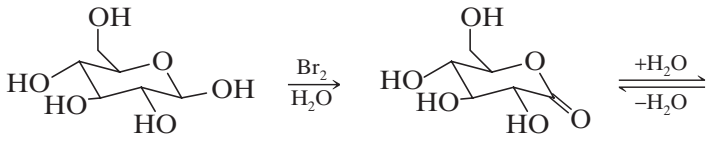
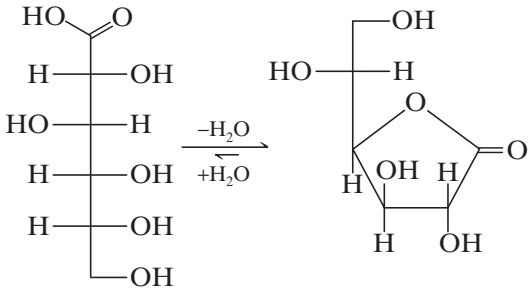


Aldose **Aldonic acid**

Experiments with aldopyranoses have shown that the actual course of the reaction is somewhat more complex than we have indicated. Bromine water specifically oxidizes the β anomer, and the initial product that forms is a *δ-aldonolactone*. This compound may then hydrolyze to an aldonic acid, and the aldonic acid may undergo a subsequent ring closure to form a *γ-aldonolactone:*



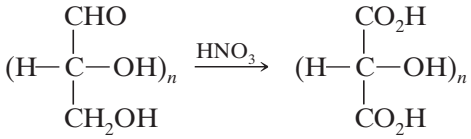
β-D-Glucopyranose **D-Glucono-δ-lactone**



D-Gluconic acid **D-Gluconic-γ-lactone**

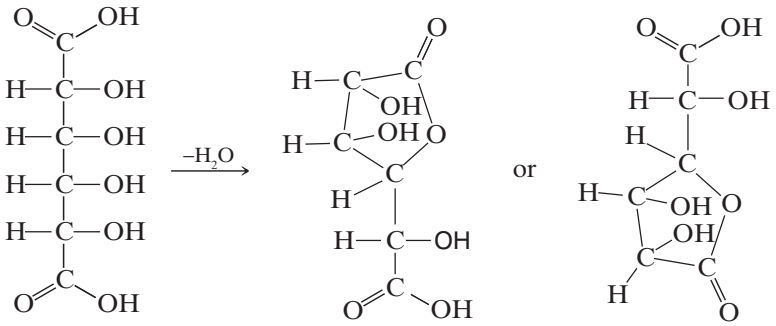
20.6C Nitric Acid Oxidation: Aldaric Acids

- Dilute nitric acid—a stronger oxidizing agent than bromine water—oxidizes both the —CHO group and the terminal —CH_2OH group of an aldose to —CO_2H groups, forming dicarboxylic acids are known as **aldaric acids**:



Aldose **Aldaric acid**

It is not known whether a lactone is an intermediate in the oxidation of an aldose to an aldaric acid; however, aldaric acids form γ- and δ-lactones readily:



Aldaric acid (from an aldohexose) **γ-Lactones of an aldaric acid**

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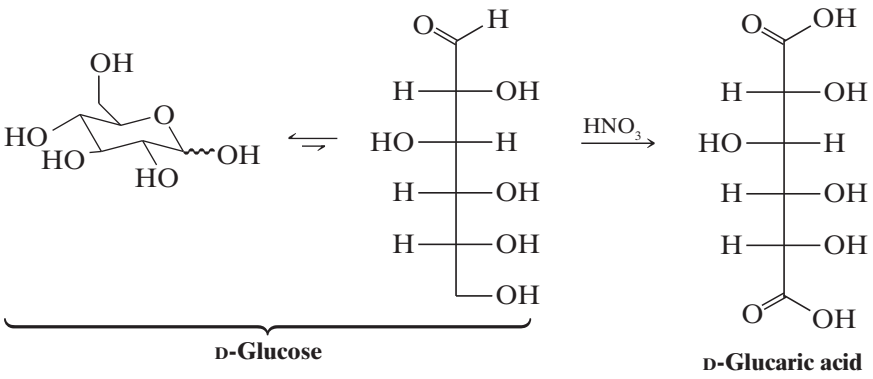
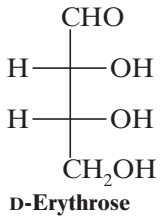
The aldaric acid obtained from D-glucose is called D-glucaric acid*:



Practice Problem 20.6

(a) Would you expect D-glucaric acid to be optically active?
(b) Write the open-chain structure for the aldaric acid (mannaric acid) that would be obtained by nitric acid oxidation of D-mannose.
(c) Would you expect mannaric acid to be optically active?
(d) What aldaric acid would you expect to obtain from D-erythrose?



D-Erythrose

(e) Would the aldaric acid in (d) show optical activity?
(f) D-Threose, a diastereomer of D-erythrose, yields an optically active aldaric acid when it is subjected to nitric acid oxidation. Write Fischer projection formulas for D-threose and its nitric acid oxidation product.
(g) What are the names of the aldaric acids obtained from D-erythrose and D-threose?

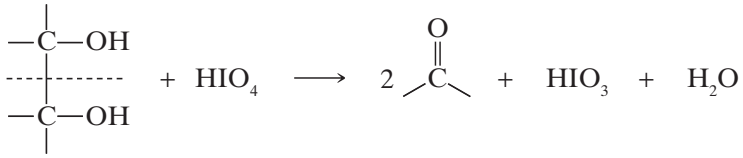
Practice Problem 20.7

D-Glucaric acid undergoes lactonization to yield two different γ-lactones. What are their structures?

20.6D Periodate Oxidations: Oxidative Cleavage of Polyhydroxy Compounds

- Compounds that have hydroxyl groups on adjacent atoms undergo oxidative cleavage when they are treated with aqueous periodic acid (HIO_4). The reaction breaks carbon–carbon bonds and produces carbonyl compounds (aldehydes, ketones, or acids).

The stoichiometry of oxidative cleavage by periodic acid is



Since the reaction usually takes place in quantitative yield, valuable information can often be gained by measuring the number of molar equivalents of periodic acid consumed in the reaction as well as by identifying the carbonyl products.

*Older terms for an aldaric acid are a *glycaric* acid or a *saccharic* acid.

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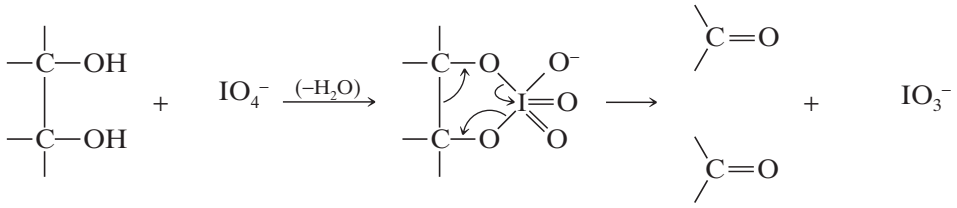
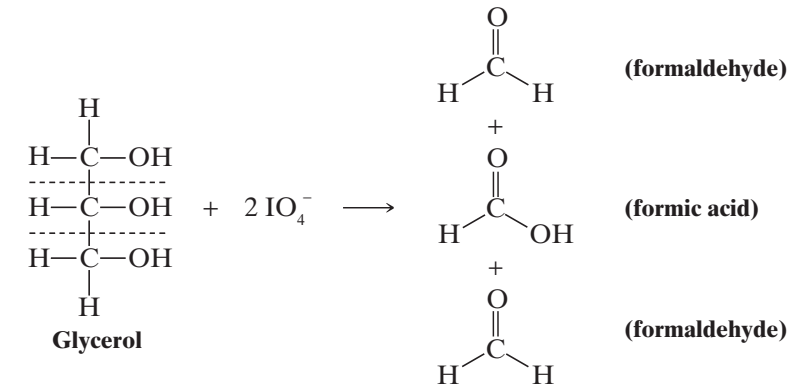
Periodate oxidations are thought to take place through a cyclic intermediate:

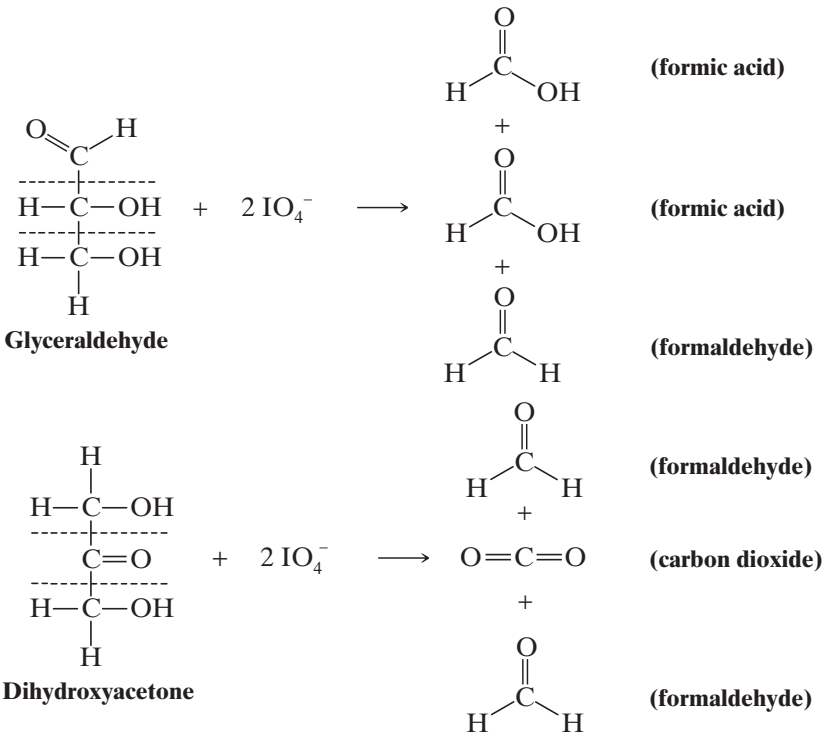


Before we discuss the use of periodic acid in carbohydrate chemistry, we should illustrate the course of the reaction with several simple examples. Notice in these periodate oxidations that *for every C—C bond broken, a C—O bond is formed at each carbon*.

1. When three or more —CHOH groups are contiguous, the internal ones are obtained as *formic acid*. Periodate oxidation of glycerol, for example, gives two molar equivalents of formaldehyde and one molar equivalent of formic acid:



2. Oxidative cleavage also takes place when an —OH group is adjacent to the carbonyl group of an aldehyde or ketone (but not that of an acid or an ester). Glyceraldehyde yields two molar equivalents of formic acid and one molar equivalent of formaldehyde, while dihydroxyacetone gives two molar equivalents of formaldehyde and one molar equivalent of carbon dioxide:



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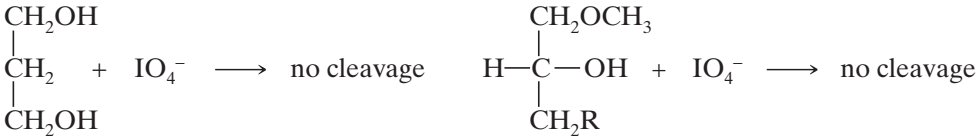
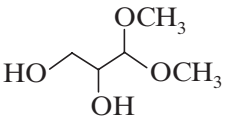
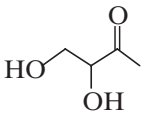
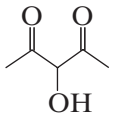
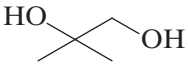
3. Periodic acid does not cleave compounds in which the hydroxyl groups are separated by an intervening —CH_2— group, nor those in which a hydroxyl group is adjacent to an ether or acetal function:



Practice Problem 20.8

What products would you expect to be formed when each of the following compounds is treated with an appropriate amount of periodic acid? How many molar equivalents of HIO_4 would be consumed in each case?

(a) 2,3-Butanediol **(b)** 1,2,3-Butanetriol **(c)**  **(d)** 

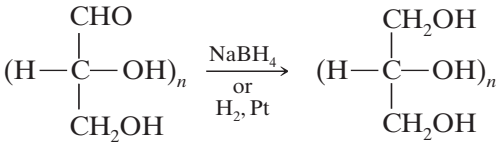
(e)  **(f)** *cis*-1,2-Cyclopentanediol **(g)**  **(h)** D-Erythrose

Practice Problem 20.9

Show how periodic acid could be used to distinguish between an aldohexose and a ketohexose. What products would you obtain from each, and how many molar equivalents of HIO_4 would be consumed?

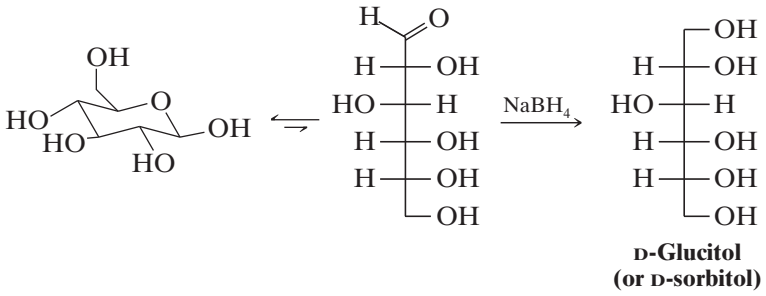
20.7 | REDUCTION OF MONOSACCHARIDES: ALDITOLS

- Aldoses (and ketoses) can be reduced with sodium borohydride to give compounds called **alditols**:



Aldose **Alditol**

Reduction of D-glucose, for example, yields D-glucitol:



D-Glucitol (or D-sorbitol)

Practice Problem 20.10

(a) Would you expect D-glucitol to be optically active? **(b)** Write Fischer projection formulas for all of the D-aldohexoses that would yield *optically inactive alditols*.

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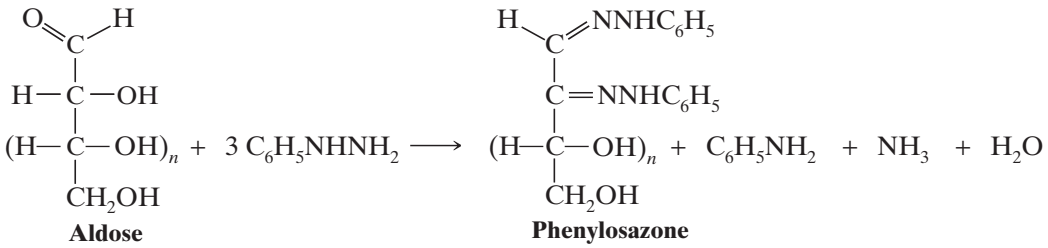
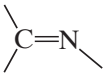
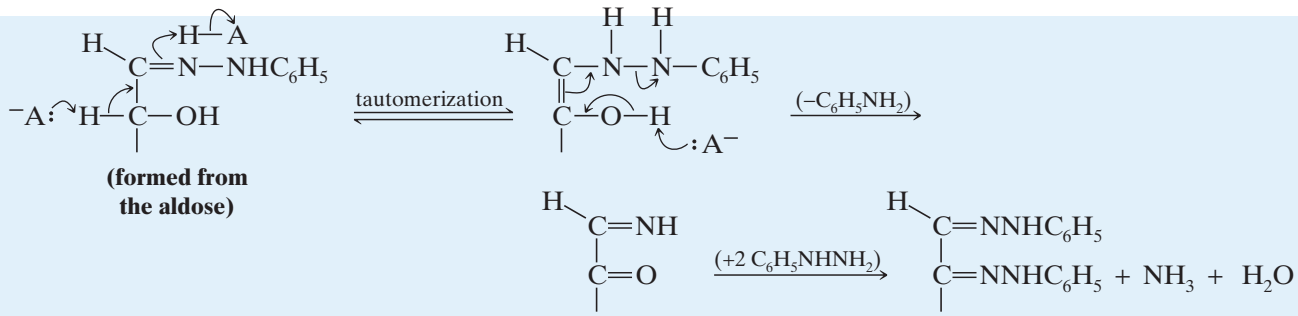
20.8 | REACTIONS OF MONOSACCHARIDES WITH PHENYLHYDRAZINE: OSAZONES

The aldehyde group of an aldose reacts with such carbonyl reagents as hydroxylamine and phenylhydrazine. With hydroxylamine, the product is the expected oxime. With enough phenylhydrazine, however, three molar equivalents of phenylhydrazine are consumed and a second phenylhydrazone group is introduced at C2. The product is called a *phenylosazone*. Phenylosazones crystallize readily (unlike sugars) and are useful derivatives for identifying sugars.

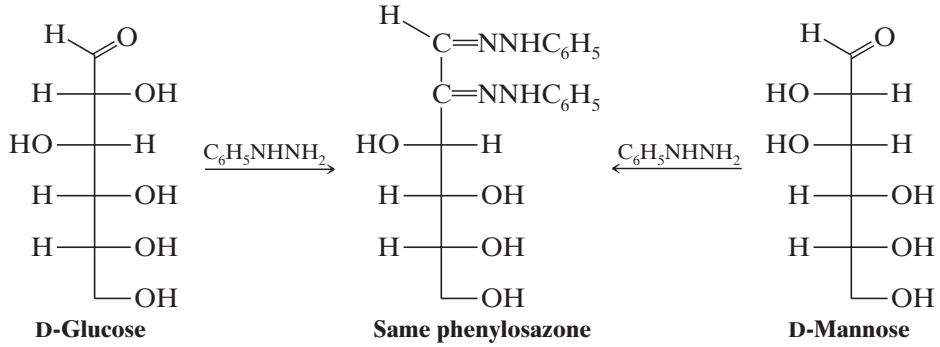


The mechanism for osazone formation probably depends on a series of reactions in which  behaves very much like  in giving a nitrogen version of an enol.

A MECHANISM FOR THE REACTION — Phenylosazone Formation



Osazone formation results in a loss of the chirality center at C2 but does not affect other chirality centers; D-glucose and D-mannose, for example, yield the same phenylosazone:



This experiment, first done by Emil Fischer, established that D-glucose and D-mannose have the same configurations about C3, C4, and C5. Diastereomeric aldoses that differ in configuration at only one carbon (such as D-glucose and D-mannose) are called epimers. In general, any pair of diastereomers that differ in configuration at only a single tetrahedral chirality center can be called **epimers**.

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Practice Problem 20.11

Although D-fructose is not an epimer of D-glucose or D-mannose (D-fructose is a ketohexose), all three yield the same phenylosazone. **(a)** Using Fischer projection formulas, write an equation for the reaction of fructose with phenylhydrazine. **(b)** What information about the stereochemistry of D-fructose does this experiment yield?

20.9 | SYNTHESIS AND DEGRADATION OF MONOSACCHARIDES

20.9A Kiliani–Fischer Synthesis

In 1885, Heinrich Kiliani (Freiburg, Germany) discovered that an aldose can be converted to the epimeric aldonic acids having one additional carbon through the addition of hydrogen cyanide and subsequent hydrolysis of the epimeric cyanohydrins. Fischer later extended this method by showing that aldonolactones obtained from the aldonic acids can be reduced to aldoses. Today, this method for lengthening the carbon chain of an aldose is called the Kiliani–Fischer synthesis.

We can illustrate the Kiliani–Fischer synthesis with the synthesis of D-threose and D-erythrose (aldotetroses) from D-glyceraldehyde (an aldotriose) in Fig. 20.6.

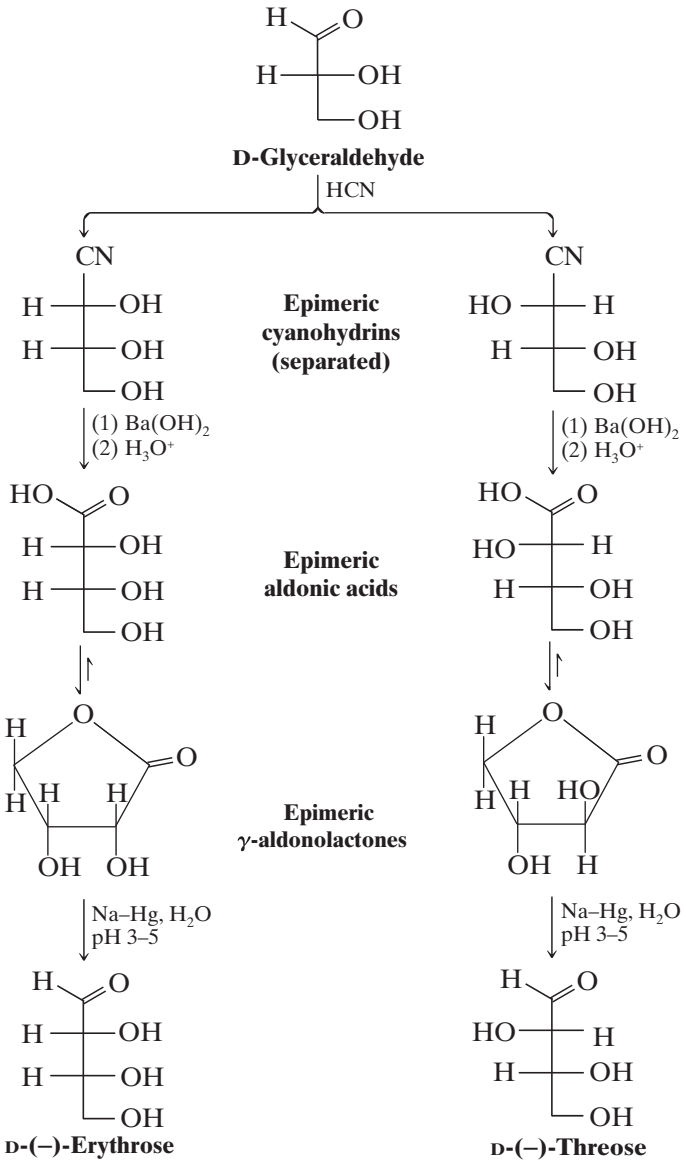

Figure 20.6 A Kiliani–Fischer synthesis of D-(–)-erythrose and D-(–)-threose from D-glyceraldehyde.

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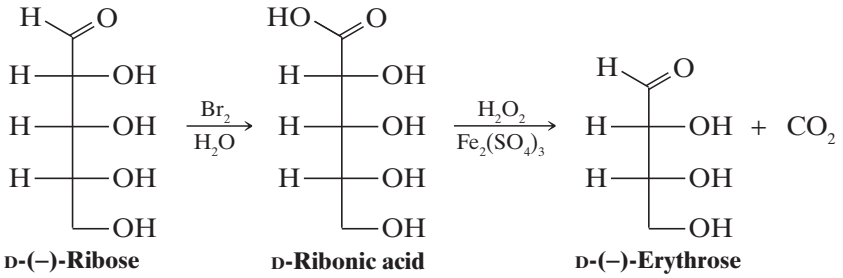
Addition of hydrogen cyanide to glyceraldehyde produces two epimeric cyanohydrins because the reaction creates a new chirality center. The cyanohydrins can be separated easily (since they are diastereomers), and each can be converted to an aldose through hydrolysis, acidification, lactonization, and reduction with Na–Hg at pH 3–5. One cyanohydrin ultimately yields D-(−)-erythrose and the other yields D-(−)-threose.

We can be sure that the aldotetroses that we obtain from this Kiliani–Fischer synthesis are both D sugars because the starting compound is D-glyceraldehyde and its chirality center is unaffected by the synthesis. On the basis of the Kiliani–Fischer synthesis, we cannot know just which aldotetrose has both —OH groups on the right and which has the top —OH on the left in the Fischer projection. However, if we oxidize both aldotetroses to aldaric acids, one [D-(−)-erythrose] will yield an *optically inactive* (meso) product while the other [D-(−)-threose] will yield a product that is *optically active* (see Practice Problem 20.6).

20.9B The Ruff Degradation

Just as the Kiliani–Fischer synthesis can be used to lengthen the chain of an aldose by one carbon atom, the Ruff degradation* can be used to shorten the chain by a similar unit. The Ruff degradation involves (1) oxidation of the aldose to an aldonic acid using bromine water and (2) oxidative decarboxylation of the aldonic acid to the next lower aldose using hydrogen peroxide and ferric sulfate. D-(−)-Ribose, for example, can be degraded to D-(−)-erythrose:



D-(−)-Ribose D-Ribonic acid D-(−)-Erythrose

20.10 | THE D FAMILY OF ALDOSES

The Ruff degradation and the Kiliani–Fischer synthesis allow us to place all of the aldoses into families or "family trees" based on their relation to D- or L-glyceraldehyde. Such a tree is constructed in Fig. 20.7 and includes the structures of the D-aldohexoses, **1–8**.

- Most, but not all, of the naturally occurring aldoses belong to the D family, with D-(+)-glucose being by far the most common.

D-(+)-Galactose can be obtained from milk sugar (lactose), but L-(−)-galactose occurs in a polysaccharide obtained from the vineyard snail, *Helix pomatia*. L-(+)-Arabinose is found widely, but D-(−)-arabinose is scarce, being found only in certain bacteria and sponges. Threose, lyxose, gulose, and allose do not occur naturally, but one or both forms (D or L) of each have been synthesized.

20.11 | FISCHER'S PROOF OF THE CONFIGURATION OF D-(+)-GLUCOSE

Emil Fischer began his work on the stereochemistry of (+)-glucose in 1888, only 12 years after van't Hoff and Le Bel had made their proposal concerning the tetrahedral structure of carbon. Only a small body of data was available to Fischer at the beginning. Only a few monosaccharides were known, including (+)-glucose, (+)-arabinose, and (+)-mannose. [(+)-Mannose had just been synthesized by Fischer.] The sugars (+)-glucose and (+)-mannose were known to be aldohexoses; (+)-arabinose was known to be an aldopentose.

Since an aldohexose has four chirality centers, 2^4 (or 16) stereoisomers are possible—*one of which is* (+)-*glucose*. Fischer arbitrarily decided to limit his attention to the eight structures with the D configuration given in Fig. 20.7 (structures **1–8**). Fischer realized that he would be unable to differentiate between enantiomeric configurations

*Developed by Otto Ruff, 1871–1939, a German chemist.

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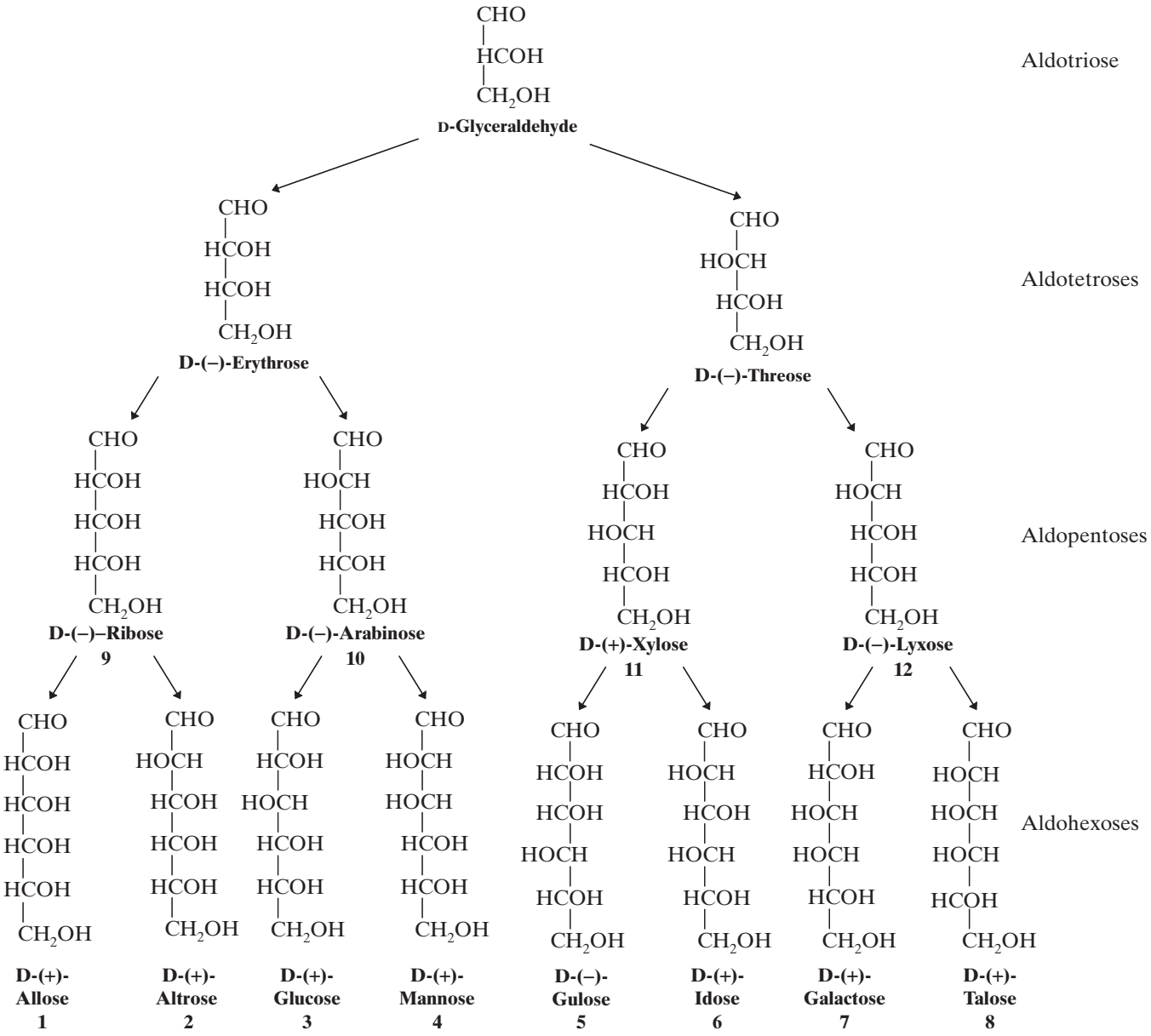

Figure 20.7 The D family of aldohexoses.

because methods for determining the absolute configuration of organic compounds had not been developed. It was not until 1951, when Bijvoet (Section 4.15A) determined the absolute configuration of L-(+)-tartaric acid [and, hence, D-(+)-glyceraldehyde], that Fischer's arbitrary assignment of (+)-glucose to the family we call the D family was known to be correct.

Fischer's assignment of structure **3** to (+)-glucose was based on the following reasoning:

1. Nitric acid oxidation of (+)-glucose gives an optically active aldaric acid. This eliminates structures **1** and **7** from consideration because both compounds would yield *meso*-aldaric acids.
2. *Degradation of* (+)*-glucose gives* (−)*-arabinose, and nitric acid oxidation of* (−)*-arabinose gives an optically active aldaric acid.* This means that (−)-arabinose cannot have configuration **9** or **11** and must have either structure **10** or **12**. It also establishes that (+)-glucose cannot have configuration **2**, **5**, or **6**. This leaves structures **3**, **4**, and **8** as possibilities for (+)-glucose.
3. Kiliani–Fischer synthesis beginning with (−)-arabinose gives (+)-glucose and (+)-mannose; nitric acid oxidation of (+)-mannose gives an optically active aldaric acid. This, together with the fact that (+)-glucose yields a

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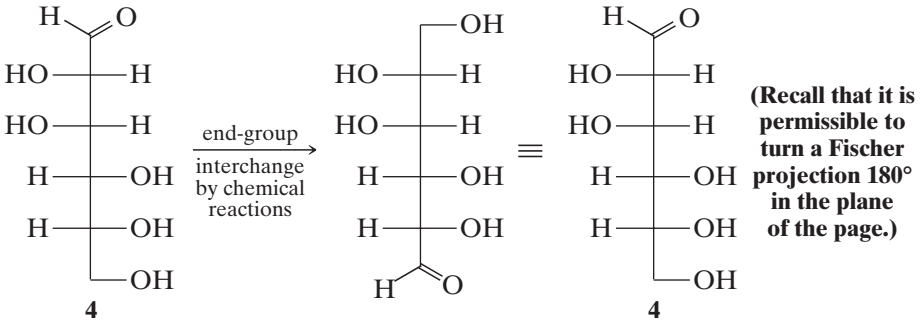
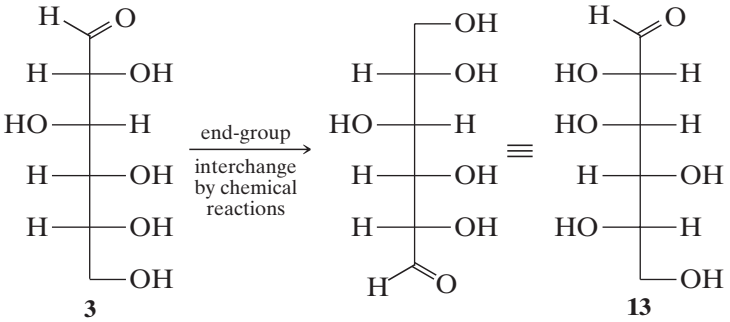
different but also optically active aldaric acid, establishes **10** as the structure of (−)-arabinose and eliminates **8** as a possible structure for (+)-glucose. Had (−)-arabinose been represented by structure **12**, a Kiliani–Fischer synthesis would have given the two aldohexoses, **7** and **8**, one of which (**7**) would yield an optically inactive aldaric acid on nitric acid oxidation.

4. Two structures now remain, **3** and **4**; one structure represents (+)-glucose and one represents (+)-mannose. Fischer realized that (+)-glucose and (+)-mannose were epimeric (at C2), but a decision as to which compound was represented by which structure was most difficult.
5. Fischer had already developed a method for effectively *interchanging the two end groups* (aldehyde and primary alcohol) *of an aldose chain*. And, with brilliant logic, Fischer realized that if (+)-glucose had structure **4**, an interchange of end groups *would yield the same aldohexose*:



4 **4**

On the other hand, if (+)-glucose has structure **3**, *an end-group interchange will yield a different aldohexose*, **13**:

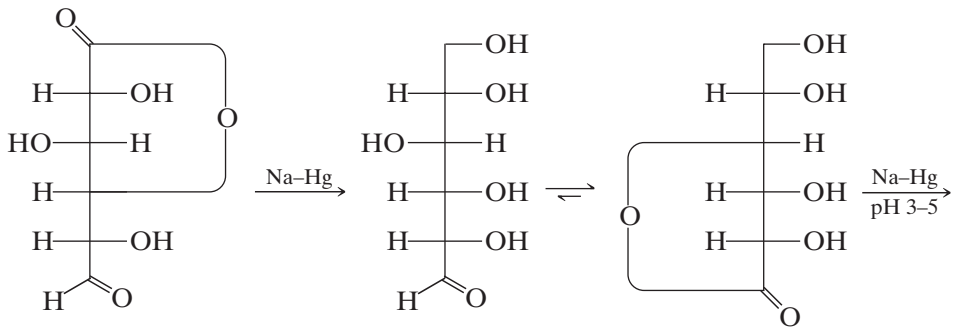


3 **13**
L-Gulose

This new aldohexose, if it were formed, would be an L sugar and it would be the mirror reflection of D-gulose. Thus its name would be L-gulose.

Fischer carried out the end-group interchange starting with (+)-glucose and *the product was the new aldohexose* **13**. This outcome proved that (+)-glucose has structure **3**. It also established **4** as the structure for (+)-mannose, and it proved the structure of L-(+)-gulose as **13**.

The procedure Fischer used for interchanging the ends of the (+)-glucose chain began with one of the γ-lactones of D-glucaric acid (see Practice Problem 20.7) and was carried out as follows:



A γ-lactone of D-glucaric acid **L-Gulonic acid** **A γ-aldonolactone**

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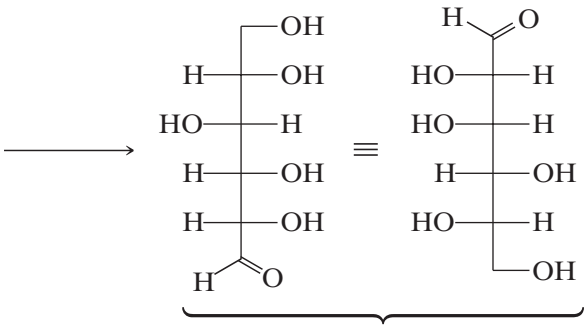


L-(+)-Gulose
13

Notice in this synthesis that the second reduction with Na–Hg is carried out at pH 3–5. Under these conditions, reduction of the lactone yields an aldehyde and not a primary alcohol.

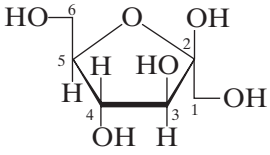
20.12 | DISACCHARIDES

20.12A Sucrose

Ordinary table **sugar** is a **disaccharide** called *sucrose*. Sucrose, the most widely occurring disaccharide, is found in all photosynthetic plants and is obtained commercially from sugarcane or sugar beets. Sucrose has the structure shown in Fig. 20.8.

The structure of sucrose is based on the following evidence:

1. Sucrose has the molecular formula $C_{12}H_{22}O_{11}$.
2. Acid-catalyzed hydrolysis of 1 mol of sucrose yields 1 mol of D-glucose and 1 mol of D-fructose.



Fructose
(as a β-furanose)

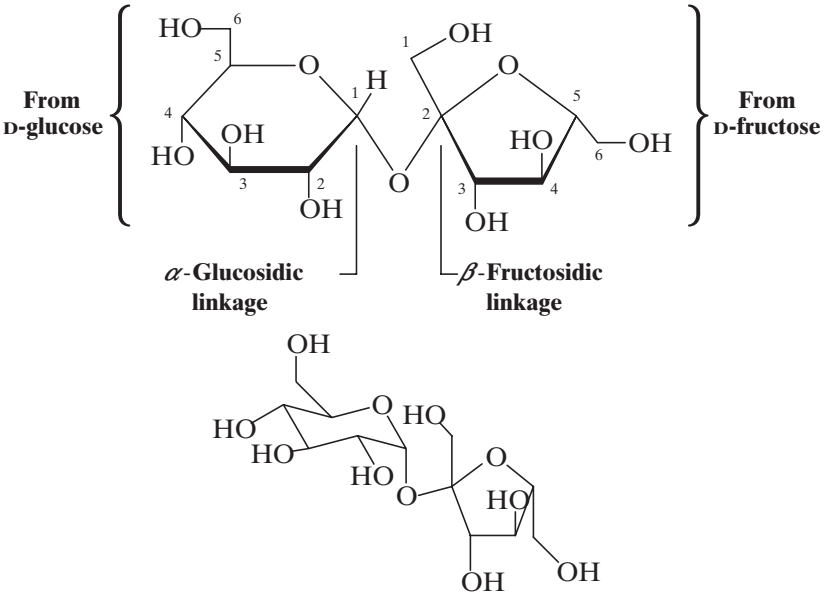


Figure 20.8 Two representations of the formula for (+)-sucrose (α-D-glucopyranosyl β-D-fructofuranoside).

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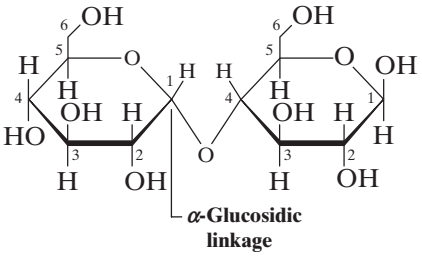
3. Sucrose is a nonreducing sugar; it gives negative tests with Benedict's and Tollens' solutions. Sucrose does not form an osazone and does not undergo mutarotation. These facts mean that neither the glucose nor the fructose portion of sucrose has a hemiacetal group. Thus, the two hexoses must have a glycosidic linkage that involves C1 of glucose and C2 of fructose, for only in this way will both carbonyl groups be present as full acetals (i.e., as glycosides).
4. The stereochemistry of the glycosidic linkages can be inferred from experiments done with enzymes. Sucrose is hydrolyzed by an *α-glucosidase* obtained from yeast but not by *β*-glucosidase enzymes. This hydrolysis indicates *an α configuration at the glucoside portion*. Sucrose is also hydrolyzed by *sucrase*, an enzyme known to hydrolyze *β*-fructofuranosides but not *α*-fructofuranosides. This hydrolysis indicates a *β configuration at the fructoside portion*.
5. Methylation of sucrose gives an octamethyl derivative that, on hydrolysis, gives 2,3,4,6-tetra-*O*-methyl-D-glucose and 1,3,4,6-tetra-*O*-methyl-D-fructose. The identities of these two products demonstrate that the glucose portion is a *pyranoside* and that the fructose portion is a *furanoside*.

The structure of sucrose has been confirmed by X-ray analysis and by an unambiguous synthesis.

20.12B Maltose

When starch (Section 20.13A) is hydrolyzed by the enzyme *diastase*, one product is a disaccharide known as *maltose* (Fig. 20.9). The structure of maltose was deduced based on the following evidence:



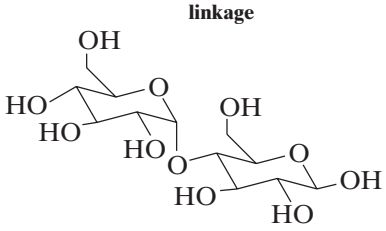


Figure 20.9 Two representations of the structure of the *β* anomer of (+)-maltose, 4-*O*-(*α*-D-glucopyranosyl)-*β*-D-glucopyranose.

1. When 1 mol of maltose is subjected to acid-catalyzed hydrolysis, it yields 2 mol of D-(+)-glucose.
2. Unlike sucrose, *maltose is a reducing sugar*; it gives positive tests with Fehling's, Benedict's, and Tollens' solutions. Maltose also reacts with phenylhydrazine to form a monophenylosazone (i.e., it incorporates two molecules of phenylhydrazine).
3. Maltose exists in two anomeric forms: *α*-(+)-maltose, $[\alpha]_D^{25} = +168$, and *β*-(+)-maltose, $[\alpha]_D^{25} = +112$. The maltose anomers undergo mutarotation to yield an equilibrium mixture, $[\alpha]_D^{25} = +136$.

Facts 2 and 3 demonstrate that one of the glucose residues of maltose is present in a hemiacetal form; the other, therefore, must be present as a glucoside. The configuration of this glucosidic linkage can be inferred as *α*, because maltose is hydrolyzed by *α*-glucosidase enzymes and not by *β*-glucosidase enzymes.

4. Maltose reacts with bromine water to form a monocarboxylic acid, maltonic acid (Fig. 20.10*a*). This fact, too, is consistent with the presence of only one hemiacetal group.
5. Methylation of maltonic acid followed by hydrolysis gives 2,3,4,6-tetra-*O*-methyl-D-glucose and 2,3,5,6-tetra-*O*-methyl-D-gluconic acid. That the first product has a free —OH at C5 indicates that the nonreducing glucose portion is present as a pyranoside; that the second product, 2,3,5,6-tetra-*O*-methyl-D-gluconic acid, has a free —OH at C4 indicates that this position was involved in a glycosidic linkage with the nonreducing glucose. Only the size of the reducing glucose ring needs to be determined.
6. Methylation of maltose itself, followed by hydrolysis (Fig. 20.10*b*), gives 2,3,4,6-tetra-*O*-methyl-D-glucose and 2,3,6-tri-*O*-methyl-D-glucose. The free —OH at C5 in the latter product indicates that it must have been involved in the oxide ring and that the reducing glucose is present as a *pyranose*.

20.12C Cellobiose

Partial hydrolysis of cellulose (Section 20.13C) gives the disaccharide cellobiose ($C_{12}H_{22}O_{11}$) (Fig. 20.11). Cellobiose resembles maltose in every respect except one: the configuration of its glycosidic linkage.

Cellobiose, like maltose, is a reducing sugar that, on acid-catalyzed hydrolysis, yields two molar equivalents of D-glucose. Cellobiose also undergoes mutarotation and forms a monophenylosazone. Methylation studies show that C1 of one glucose unit is connected in glycosidic linkage with C4 of the other and that both rings are six membered. Unlike maltose, however, cellobiose is hydrolyzed by *β-glucosidase* enzymes and not by *α*-glucosidase enzymes: This indicates that the glycosidic linkage in cellobiose is *β* (Fig. 20.11).

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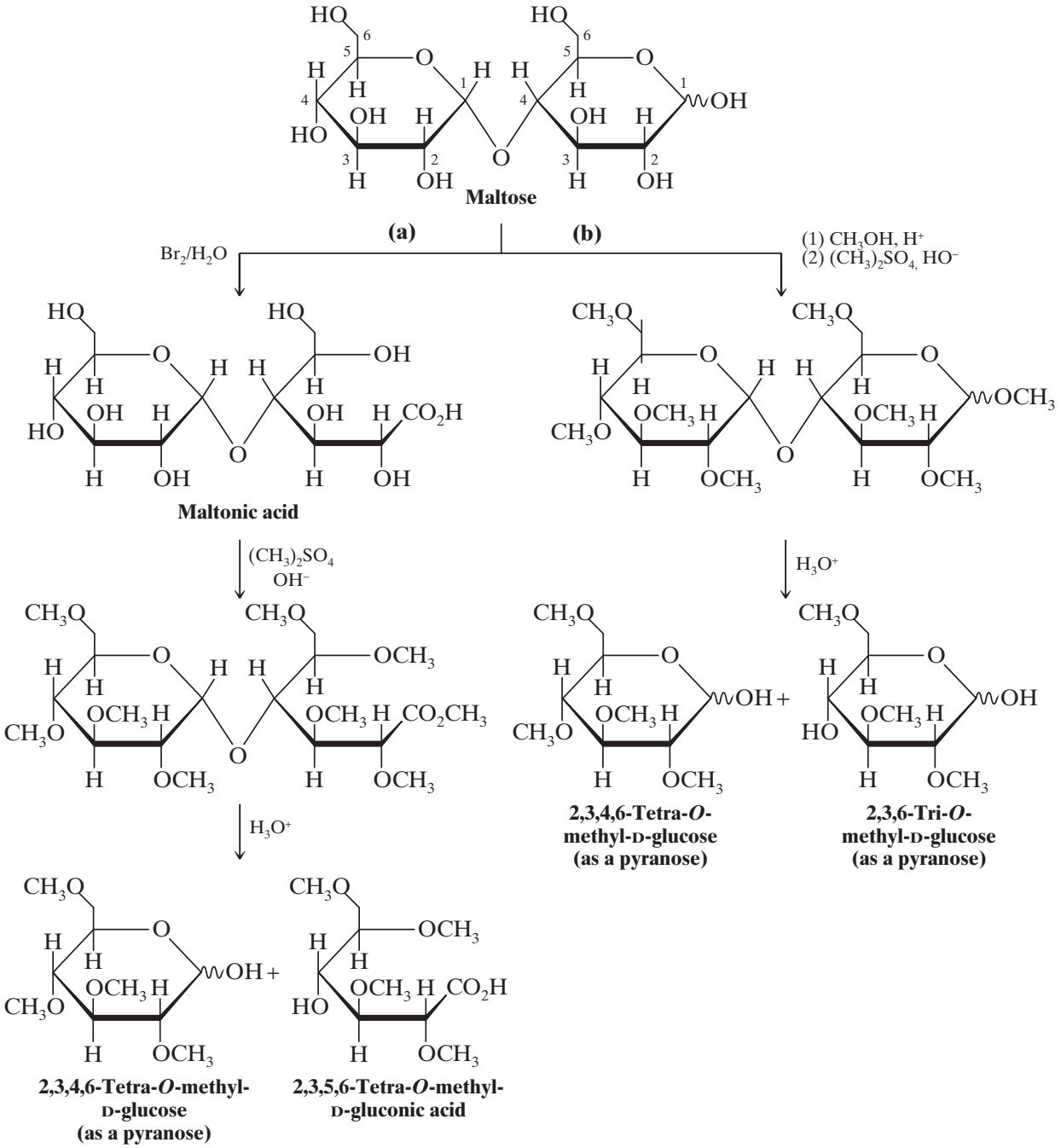

Figure 20.10 (*a*) Oxidation of maltose to maltonic acid followed by methylation and hydrolysis. (*b*) Methylation and subsequent hydrolysis of maltose itself.

20.12D Lactose

Lactose (Fig. 20.12) is a disaccharide present in the milk of humans, cows, and almost all other mammals. Lactose is a reducing sugar that hydrolyzes to yield D-glucose and D-galactose; the glycosidic linkage is *β*.

20.13 | POLYSACCHARIDES

- **Polysaccharides**, also known as **glycans**, consist of monosaccharides joined together by glycosidic linkages.

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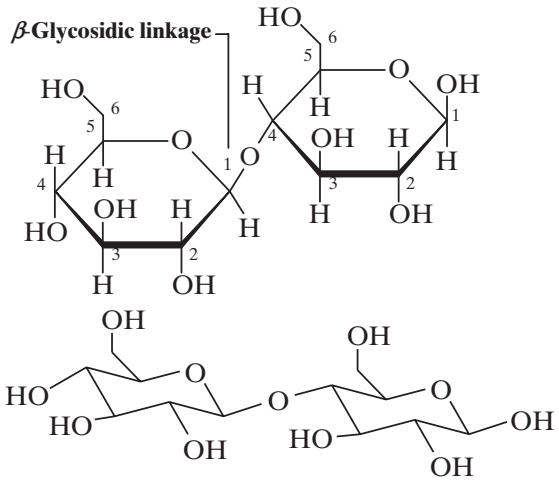

Figure 20.11 Two representations of the β anomer of cellobiose, 4-*O*-(β-D-glucopyranosyl)-β-D-glucopyranose.

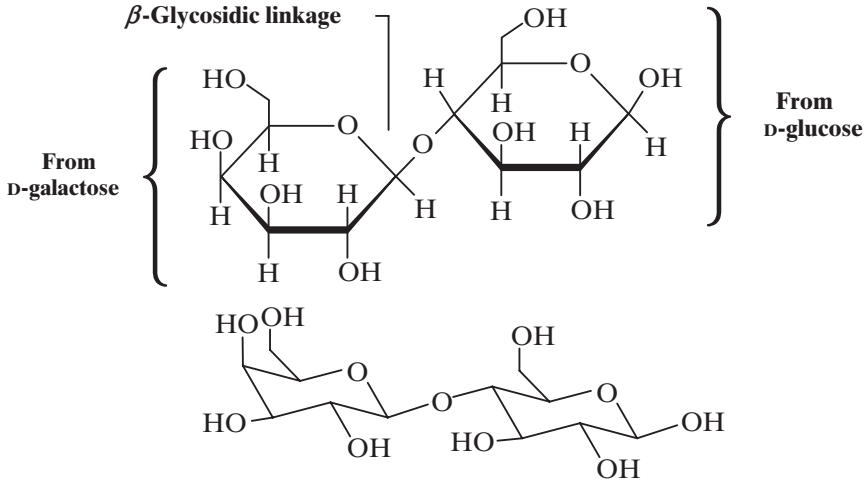

Figure 20.12 Two representations of the β anomer of lactose, 4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranose.

Polysaccharides that are polymers of a single monosaccharide are called **homopolysaccharides**; those made up of more than one type of monosaccharide are called **heteropolysaccharides**. Homopolysaccharides are also classified on the basis of their monosaccharide units. A homopolysaccharide consisting of glucose monomeric units is called a **glucan**; one consisting of galactose units is a **galactan**, and so on.

Three important polysaccharides, all of which are glucans, are starch, glycogen, and cellulose.

- Starch is the principal food reserve of plants, glycogen functions as a carbohydrate reserve for animals, and cellulose serves as structural material in plants.

As we examine the structures of these three polysaccharides, we shall be able to see how each is especially suited for its function.

20.13A Starch

Starch occurs as microscopic granules in the roots, tubers, and seeds of plants. Corn, potatoes, wheat, and rice are important commercial sources of starch. Heating starch with water causes the granules to swell and produce a colloidal suspension from which two major components can be isolated. One fraction is called *amylose* and the other *amylopectin*. Most starches yield 10–20% amylose and 80–90% amylopectin.

- Amylose typically consists of more than 1000 D-glucopyranoside units *connected in α linkages* between C1 of one unit and C4 of the next (Fig. 20.13).

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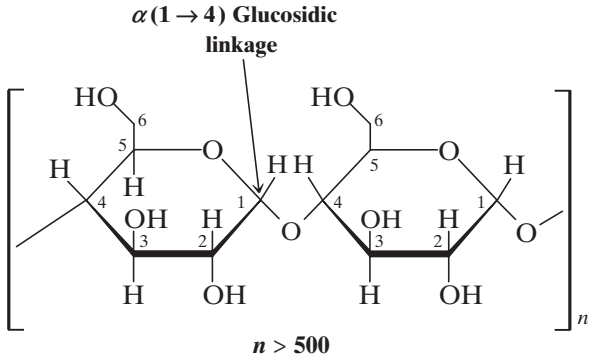

Figure 20.13 Partial structure of amylose, an unbranched polymer of D-glucose connected in $\alpha(1 \rightarrow 4)$ glycosidic linkages.

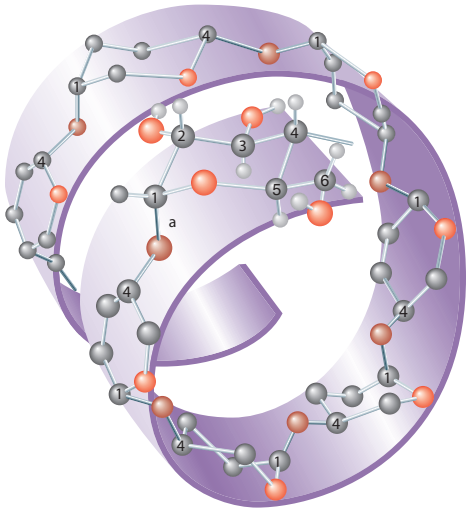

Figure 20.14 Amylose. The $\alpha(1 \rightarrow 4)$ linkages cause it to assume the shape of a left-handed helix. (Illustration, Irving Geis. Image from the Irving Geis Collection, HHMI. Rights owned by Howard Hughes Medical Institute. Not to be reproduced without permission.)

Thus, in the ring size of its glucose units and in the configuration of the glycosidic linkages between them, amylose resembles maltose.

Chains of D-glucose units with α-glycosidic linkages such as those of amylose tend to assume a helical arrangement (Fig. 20.14). This arrangement results in a compact shape for the amylose molecule even though its molecular weight is quite large (150,000–600,000).

- Amylopectin has a structure similar to that of amylose [i.e., $\alpha(1 \rightarrow 4)$ links], except that in amylopectin the chains are branched. Branching takes place between C6 of one glucose unit and C1 of another and occurs at intervals of 20–25 glucose units (Fig. 20.15).

Physical measurements indicate that amylopectin has a molecular weight of 1–6 million; thus amylopectin consists of hundreds of interconnecting chains of 20–25 glucose units each.

20.13B Glycogen

- Glycogen has a structure very much like that of amylopectin; however, in glycogen the chains are much more highly branched.

Methylation and hydrolysis of glycogen indicate that there is one end group for every 10–12 glucose units; branches may occur as often as every 6 units. Glycogen has a very high molecular weight. Studies of glycogens isolated under conditions that minimize the likelihood of hydrolysis indicate molecular weights as high as 100 million.

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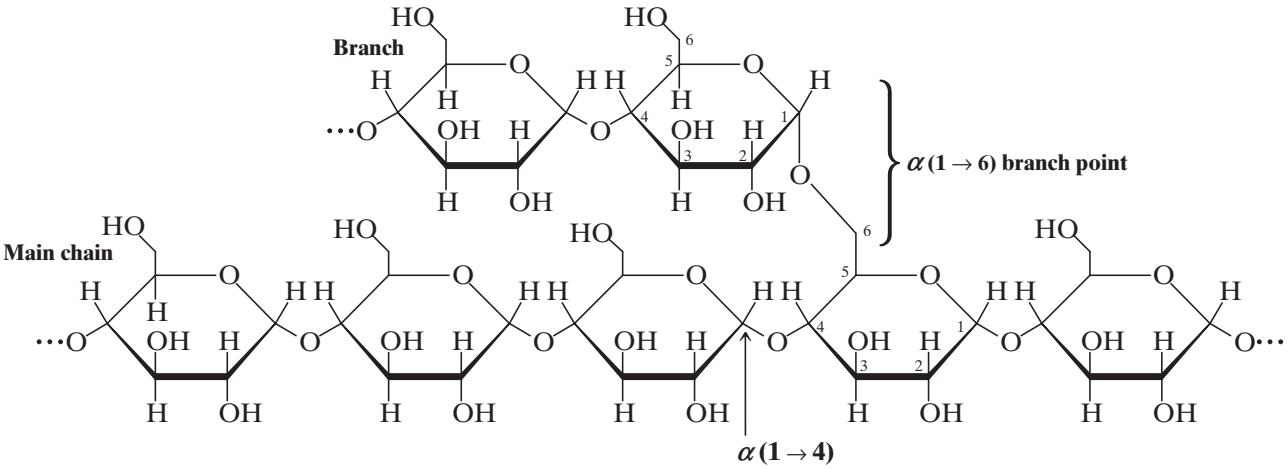

Figure 20.15 Partial structure of amylopectin.

The size and structure of glycogen beautifully suit its function as a reserve carbohydrate for animals. First, its size makes it too large to diffuse across cell membranes; thus, glycogen remains inside the cell, where it is needed as an energy source. Second, because glycogen incorporates tens of thousands of glucose units in a single molecule, it solves an important osmotic problem for the cell. Were so many glucose units present in the cell as individual molecules, the osmotic pressure within the cell would be enormous—so large that the cell membrane would almost certainly break. Finally, the localization of glucose units within a large, highly branched structure simplifies one of the cell's logistical problems: that of having a ready source of glucose when cellular glucose concentrations are low and of being able to store glucose rapidly when cellular glucose concentrations are high. There are enzymes within the cell that catalyze the reactions by which glucose units are detached from (or attached to) glycogen. These enzymes operate at end groups by hydrolyzing (or forming) $\alpha(1 \rightarrow 4)$ glycosidic linkages. Because glycogen is so highly branched, a very large number of end groups is available at which these enzymes can operate. At the same time the overall concentration of glycogen (in moles per liter) is quite low because of its enormous molecular weight.

Amylopectin presumably serves a similar function in plants. The fact that amylopectin is less highly branched than glycogen is, however, not a serious disadvantage. Plants have a much lower metabolic rate than animals—and plants, of course, do not require sudden bursts of energy.

Animals store energy as fats (triacylglycerols) as well as glycogen. Fats, because they are more highly reduced, are capable of furnishing much more energy. The metabolism of a typical fatty acid, for example, liberates more than twice as much energy per carbon as glucose or glycogen. Why, then, we might ask, have two different energy repositories evolved? Glucose (from glycogen) is readily available and is highly water soluble. Glucose, as a result, diffuses rapidly through the aqueous medium of the cell and serves as an ideal source of "ready energy." Long-chain fatty acids, by contrast, are almost insoluble in water, and their concentration inside the cell could never be very high. They would be a poor source of energy if the cell were in an energy pinch. On the other hand, fatty acids (as triacylglycerols), because of their caloric richness, are an excellent energy repository for long-term energy storage.

20.13C Cellulose

When we examine the structure of cellulose, we find another example of a polysaccharide in which nature has arranged monomeric glucose units in a manner that suits its function.

- Cellulose contains D-glucopyranoside units linked in $(1 \rightarrow 4)$ fashion in very long unbranched chains. Unlike starch and glycogen, however, the linkages in cellulose are *β-glycosidic linkages* (Fig. 20.16).

The β-glycosidic linkages of cellulose make cellulose chains essentially linear; they do not tend to coil into helical structures as do glucose polymers when linked in an $\alpha(1 \rightarrow 4)$ manner.

The linear arrangement of β-linked glucose units in cellulose presents a uniform distribution of —OH groups on the outside of each chain. When two or more cellulose chains make contact, the hydroxyl groups are ideally situated to "zip" the chains together by forming hydrogen bonds (Fig. 20.17). Zipping many cellulose chains together in this way gives a highly insoluble, rigid, and fibrous polymer that is ideal as cell-wall material for plants.

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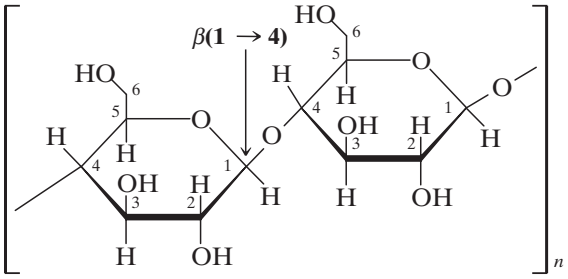

Figure 20.16 A portion of a cellulose chain. The glycosidic linkages are $\alpha(1 \rightarrow 4)$.

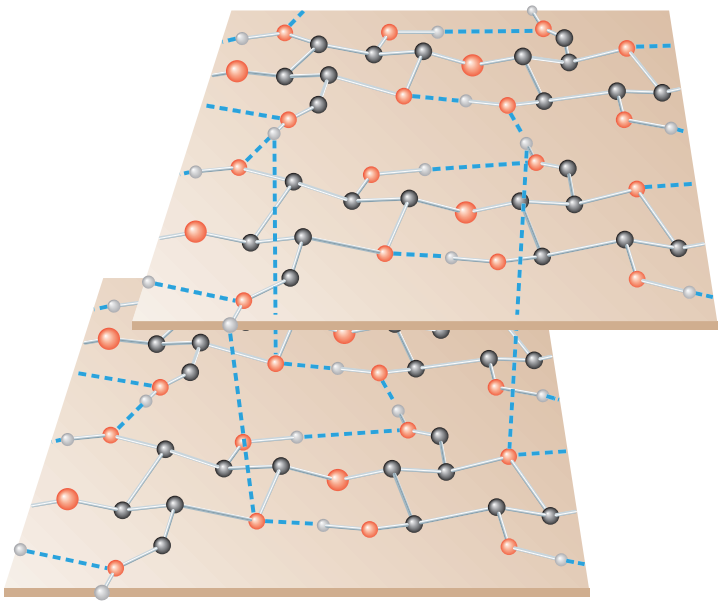

Figure 20.17 A proposed structure for cellulose. A fiber of cellulose may consist of about 40 parallel strands of glucose molecules linked in a $\beta(1 \rightarrow 4)$ fashion. Each glucose unit in a chain is turned over with respect to the preceding glucose unit and is held in this position by hydrogen bonds (dashed lines) between the chains. The glucan chains line up laterally to form sheets, and these sheets stack vertically so that they are staggered by one-half of a glucose unit. (Hydrogen atoms that do not participate in hydrogen bonding have been omitted for clarity.) (Illustration, Irving Geis. Image from the Irving Geis Collection, HHMI. Rights owned by Howard Hughes Medical Institute. Not to be reproduced without permission.)

This special property of cellulose chains, we should emphasize, is not just a result of $\beta(1 \rightarrow 4)$ glycosidic linkages; it is also a consequence of the precise stereochemistry of D-glucose at each chirality center. Were D-galactose or D-allose units linked in a similar fashion, they almost certainly would not give rise to a polymer with properties like cellulose. Thus, we get another glimpse of why D-glucose occupies such a special position in the chemistry of plants and animals. Not only is it the most stable aldohexose (because it can exist in a chair conformation that allows all of its bulky groups to occupy equatorial positions), but its special stereochemistry also allows it to form helical structures when α linked as in starches, and rigid linear structures when β linked as in cellulose.

There is another interesting and important fact about cellulose: the digestive enzymes of humans cannot attack its $\beta(1 \rightarrow 4)$ linkages. Hence, cellulose cannot serve as a food source for humans, as can starch. Cows and termites, however, can use cellulose (of grass and wood) as a food source because symbiotic bacteria in their digestive systems furnish β-glucosidase enzymes.

Perhaps we should ask ourselves one other question: Why has D-(+)-glucose been selected for its special role rather than L-(−)-glucose, its mirror image? Here an answer cannot be given with any certainty. The selection of D-(+)-glucose may simply have been a random event early in the course of the evolution of enzyme catalysts. Once

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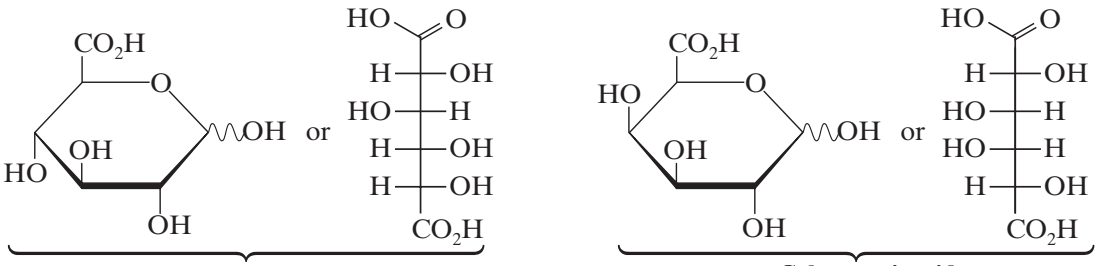
this selection was made, however, the chirality of the active sites of the enzymes involved would retain a bias toward D-(+)-glucose and against L-(−)-glucose (because of the improper fit of the latter). Once introduced, this bias would be perpetuated and extended to other catalysts.

Finally, when we speak about evolutionary selection of a particular molecule for a given function, we do not mean to imply that evolution operates on a molecular level. Evolution, of course, takes place at the level of organism populations, and molecules are selected only in the sense that their use gives the organism an increased likelihood of surviving and procreating.

20.14 | OTHER BIOLOGICALLY IMPORTANT SUGARS

Monosaccharide derivatives in which the $-CH_2OH$ group at C6 has been specifically oxidized to a carboxyl group are called **uronic acids**. Their names are based on the monosaccharide from which they are derived. For example, specific oxidation of C6 of glucose to a carboxyl group converts *glucose* to **glucuronic acid**. In the same way, specific oxidation of C6 of *galactose* would yield **galacturonic acid**:

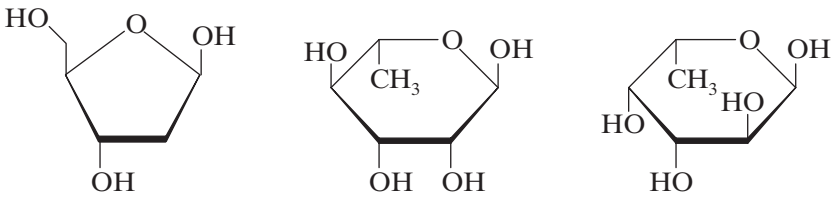


Practice Problem 20.12

Direct oxidation of an aldose affects the aldehyde group first, converting it to a carboxylic acid (Section 20.6B), and most oxidizing agents that will attack 1° alcohol groups will also attack 2° alcohol groups. Clearly, then, a laboratory synthesis of a uronic acid from an aldose requires protecting these groups from oxidation. Keeping this in mind, suggest a method for carrying out a specific oxidation that would convert D-galactose to D-galacturonic acid. (*Hint*: See Section 20.5E.)

- Monosaccharides in which an —OH group has been replaced by —H are known as **deoxy sugars**.

The most important deoxy sugar, because it occurs in DNA, is **deoxyribose**. Other deoxy sugars that occur widely in polysaccharides are L-rhamnose and L-fucose:



20.15 | SUGARS THAT CONTAIN NITROGEN

20.15A Glycosylamines

A sugar in which an amino group replaces the anomeric —OH is called a glycosylamine. Examples are β-D-glucopyranosylamine and adenosine:

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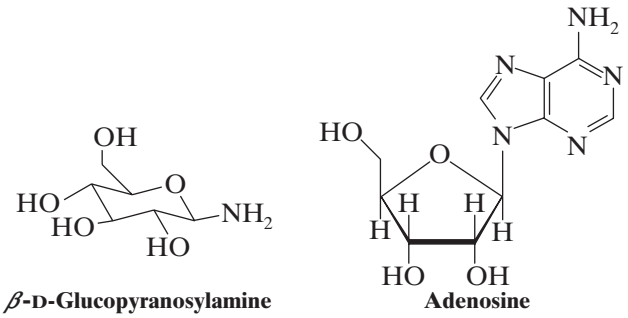


β-D-Glucopyranosylamine Adenosine

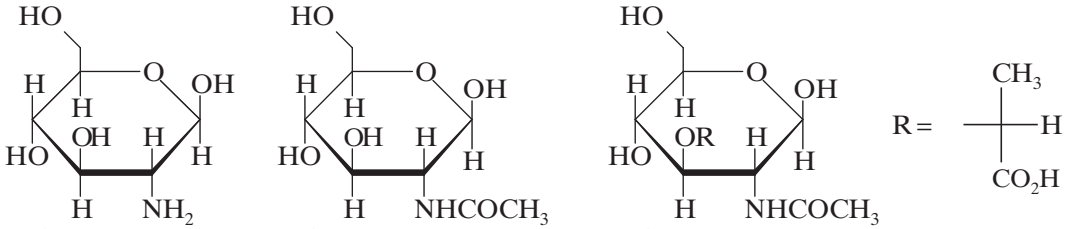
Adenosine is an example of a glycosylamine that is also called a nucleoside.

- **Nucleosides** are glycosylamines in which the amino component is a pyrimidine or a purine (Section 20.1B) and in which the sugar component is either D-ribose or 2-deoxy-D-ribose (i.e., D-ribose minus the oxygen at the 2 position).

20.15B Amino Sugars

- A sugar in which an amino group replaces a nonanomeric —OH group is called an **amino sugar**.

D-Glucosamine is an example of an amino sugar. In many instances the amino group is acetylated as in ***N*-acetyl-D-glucosamine**. ***N*-Acetylmuramic acid** is an important component of bacterial cell walls.



β-D-Glucosamine β-*N*-Acetyl-D-glucosamine (NAG) β-*N*-Acetylmuramic acid (NAM)

D-Glucosamine can be obtained by hydrolysis of **chitin**, a polysaccharide found in the shells of lobsters and crabs and in the external skeletons of insects and spiders. The amino group of D-glucosamine as it occurs in chitin, however, is acetylated; thus, the repeating unit is actually *N*-acetylglucosamine (Fig. 20.18). The glycosidic linkages in chitin are $\beta(1 \rightarrow 4)$. X-Ray analysis indicates that the structure of chitin is similar to that of cellulose.

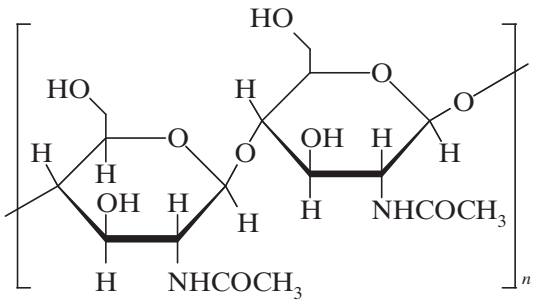


Figure 20.18 A partial structure of chitin. The repeating units are *N*-acetylglucosamines linked $\beta(1 \rightarrow 4)$.

D-Glucosamine can also be isolated from **heparin**, a sulfated polysaccharide that consists predominately of alternating units of D-glucuronate-2-sulfate and *N*-sulfo-D-glucosamine-6-sulfate (Fig. 20.19). Heparin occurs in intracellular granules of mast cells that line arterial walls, where, when released through injury, it inhibits the clotting

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of blood. Its purpose seems to be to prevent runaway clot formation. Heparin is widely used in medicine to prevent blood clotting in postsurgical patients.

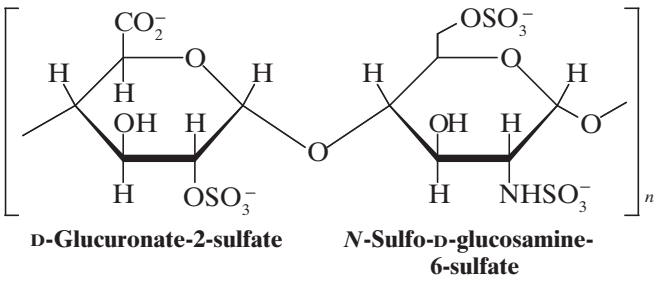
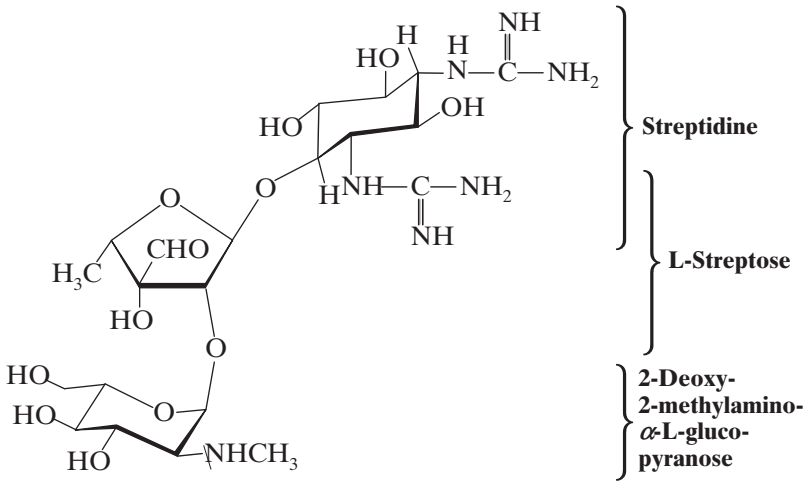


Figure 20.19 A partial structure of heparin, a polysaccharide that prevents blood clotting.

20.16 | CARBOHYDRATE ANTIBIOTICS

One of the important discoveries in carbohydrate chemistry was the isolation (in 1944) of the carbohydrate antibiotic called *streptomycin*. Streptomycin disrupts bacterial protein synthesis. Its structure is made up of the following three subunits:



All three components are unusual: the amino sugar is based on L-glucose; streptose is a branched-chain monosaccharide; and streptidine is not a sugar at all, but a cyclohexane derivative called an amino cyclitol.

Other members of this family are antibiotics called kanamycins, neomycins, and gentamicins (not shown). All are based on an amino cyclitol linked to one or more amino sugars. The glycosidic linkage is nearly always α. These antibiotics are especially useful against bacteria that are resistant to penicillins.

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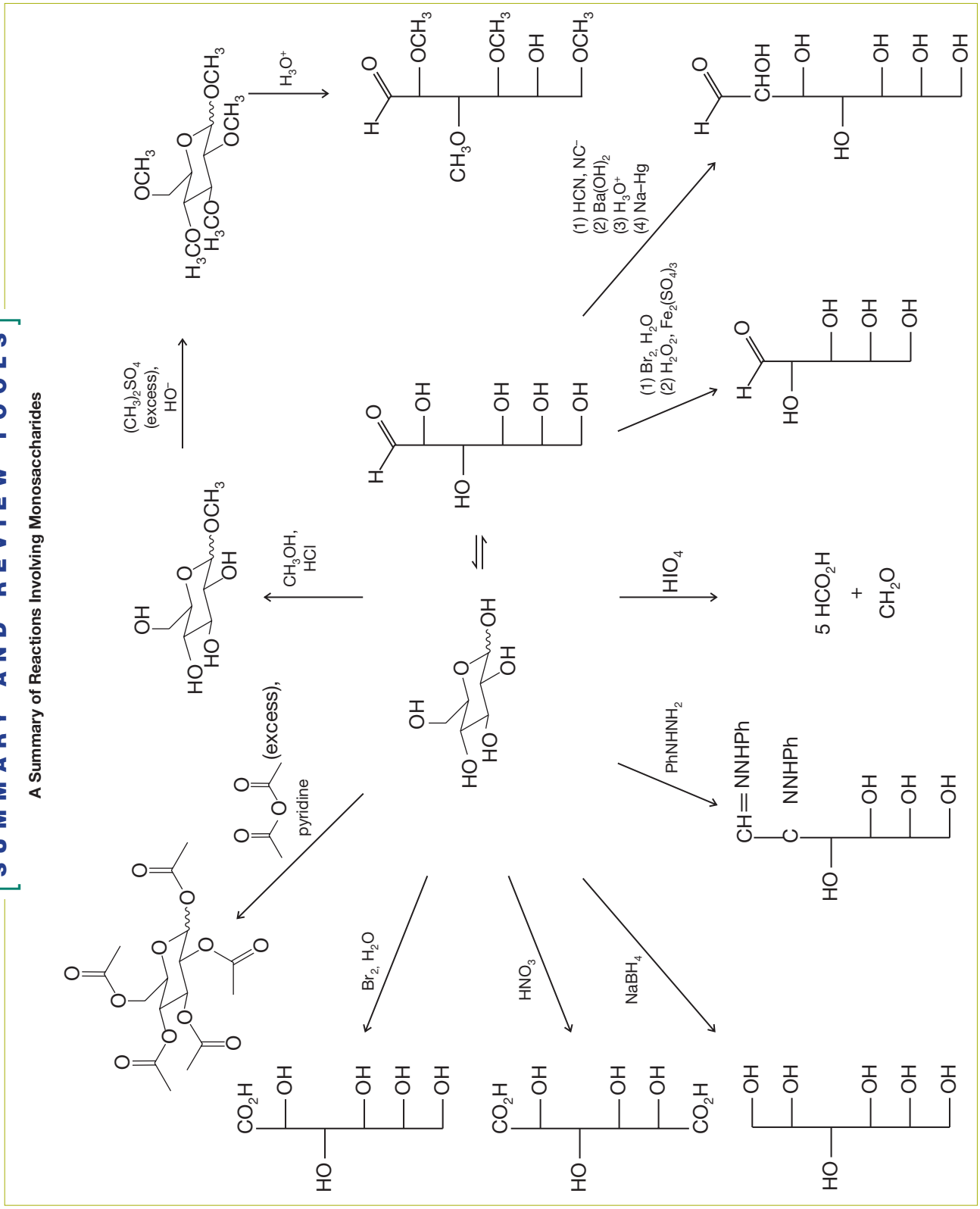
SUMMARY AND REVIEW TOOLS

A Summary of Reactions Involving Monosaccharides



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REVIEW PROBLEMS

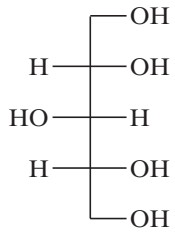
Carbohydrate Structure and Reactions

20.13 Give appropriate structural formulas to illustrate each of the following:

- **(a)** An aldopentose
- **(b)** A ketohexose
- **(c)** An L-monosaccharide
- **(d)** A glycoside
- **(e)** An aldonic acid
- **(f)** An aldaric acid
- **(g)** An aldonolactone
- **(h)** A pyranose
- **(i)** A furanose
- **(j)** A reducing sugar
- **(k)** A pyranoside
- **(l)** A furanoside
- **(m)** Epimers
- **(n)** Anomers
- **(o)** A phenylosazone
- **(p)** A disaccharide
- **(q)** A polysaccharide
- **(r)** A nonreducing sugar

20.14 **A**, **B**, and **C** are three aldohexoses. Compounds **A** and **B** yield the same optically active alditol when they are reduced with hydrogen and a catalyst; **A** and **B** yield different phenylosazones when treated with phenylhydrazine; **B** and **C** give the same phenylosazone but different alditols. Assuming that all are D sugars, give names and structures for **A**, **B**, and **C**.

20.15 Xylitol is a sweetener that is used in sugarless chewing gum. Starting with an appropriate monosaccharide, outline a possible synthesis of xylitol.

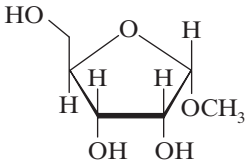


Xylitol

20.16 Although monosaccharides undergo complex isomerizations in base (see Section 20.5A), aldonic acids are epimerized specifically at C2 when they are heated with pyridine. Show how you could make use of this reaction in a synthesis of D-mannose from D-glucose.

20.17 Outline chemical tests that will distinguish between members of each of the following pairs:

- **(a)** D-Glucose and D-glucitol
- **(b)** D-Glucitol and D-glucaric acid
- **(c)** D-Glucose and D-fructose
- **(d)** D-Glucose and D-galactose
- **(e)** Sucrose and maltose
- **(f)** Maltose and maltonic acid
- **(g)** Methyl β-D-glucopyranoside and 2,3,4,6-tetra-*O*-methyl-β-D-glucopyranose
- **(h)** Methyl α-D-ribofuranoside (**I**) and methyl 2-deoxy-α-D-ribofuranoside (**II**):



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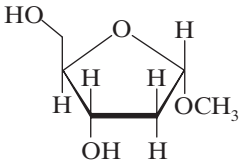


II

ADDITIONAL OBJECTIVE QUESTIONS

Single Correct Choice Type

1. Cellulose is a polymer of

- **(a)** glucose.
- **(b)** fructose.
- **(c)** ribose.
- **(d)** sucrose.

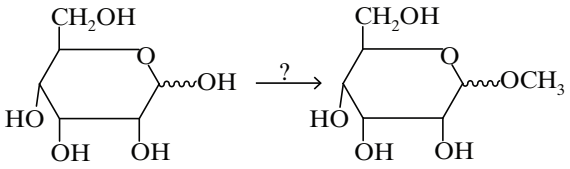
2. Glucose molecule reacts with X number of molecules of phenylhydrazine to yield osazone. The value of X is

- **(a)** three.
- **(b)** two.
- **(c)** one.
- **(d)** four.

3. All monosaccharide _____ Tollen's reagent.

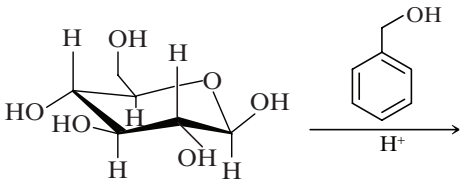
- **(a)** oxidizes
- **(b)** reduces
- **(c)** condense with
- **(d)** add to

4. Select the reagent needed to perform the following transformation:



- **(a)** CH_3OH, KOH
- **(b)** $(CH_3C)_2O$ (with O double-bonded)
- **(c)** $(CH_3)_2SO_4$, OH^-
- **(d)** CH_3OH, HCl

5. Choose the correct compound that is formed as the major product of the following reaction.



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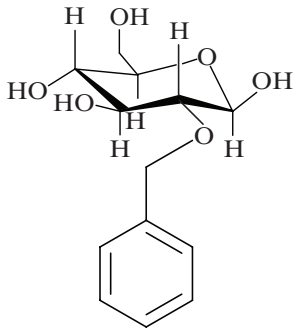
(a)



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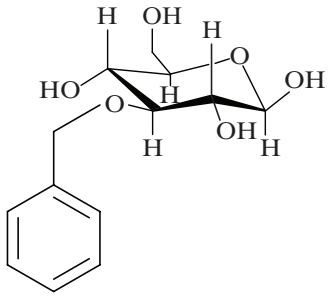
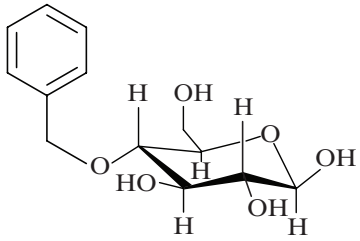
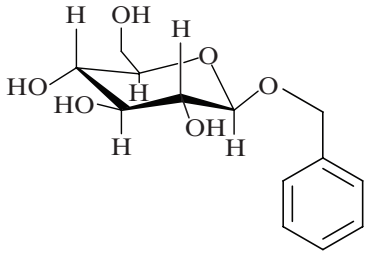


(c)



(d)



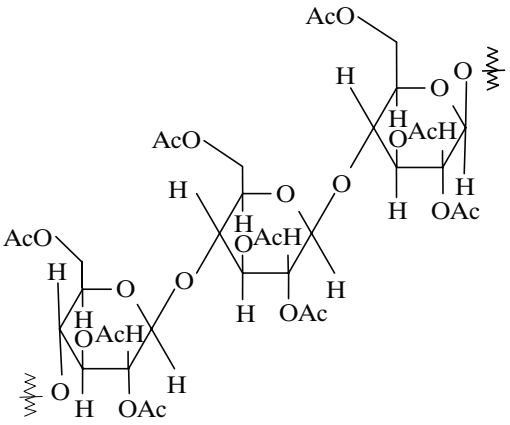
6. Which of the following statements is not true about glucose?
   - (a) It is an aldohexose.
   - (b) On heating with HI, it forms *n*-hexane.
   - (c) It is present in furanose form.
   - (d) It does not give 2,4-DNP test.

7. The pair of compounds in which both the compounds give positive test with Tollen's reagent is
   - (a) glucose and sucrose.
   - (b) fructose and sucrose.
   - (c) acetophenone and hexanal.
   - (d) glucose and fructose.

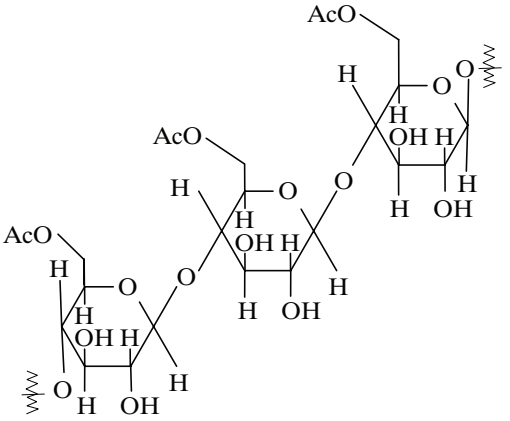
8. Identify the pair of epimers in the following.
   - (a) D-Glucose and D-Fructose.
   - (b) D-Glucose and L-Glucose.
   - (c) D-Glucose and D-Mannose.
   - (d) D-Glucose and D-Gulose.

9. Cellulose upon acetylation with excess acetic anhydride/H_2SO_4 (catalytic) gives cellulose triacetate whose structure is

(a)



(b)



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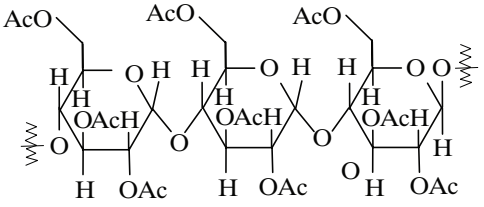
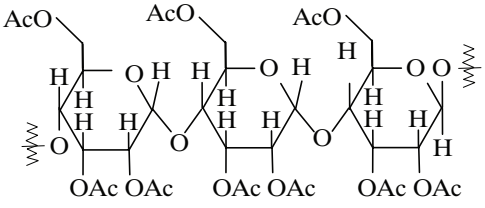
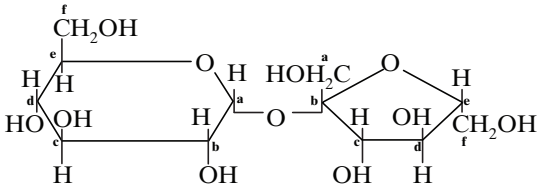


(d)



10. Structure of a disaccharide formed by glucose and fructose is given below. Identify anomeric carbon atoms in the monosaccharide units.



   - (a) carbon **a** of glucose and carbon **a** of fructose.
   - (b) carbon **a** of glucose and carbon **e** of fructose.
   - (c) carbon **a** of glucose and carbon **b** of fructose.
   - (d) carbon **f** of glucose and carbon **f** of fructose.

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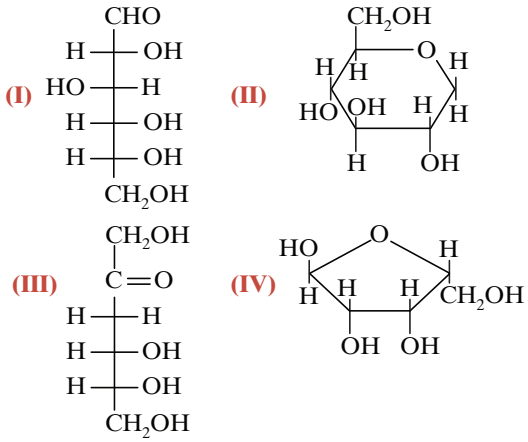
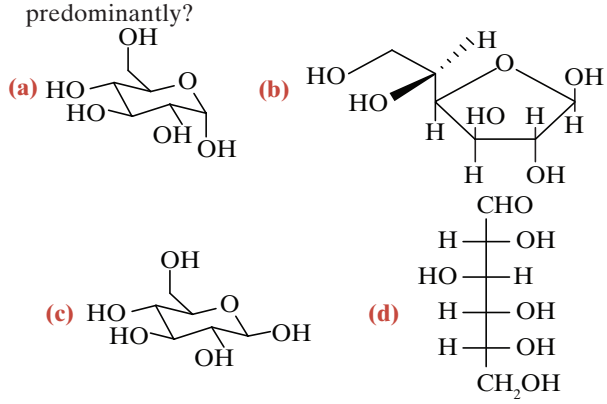
11. Which of the following carbohydrate is/are reducing sugar?



(a) I, II, III, IV **(b)** I, III, IV **(c)** I, II, IV **(d)** II, III, IV

12. In what structural form does D-glucose exist predominantly?



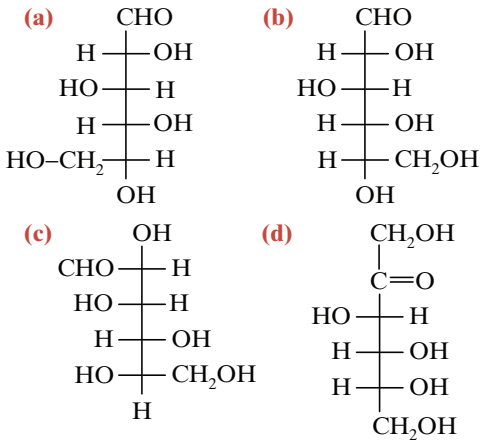
13. Which of following is an oligosaccharide?
(a) Glucose **(b)** Fructose **(c)** Sucrose **(d)** Starch

14. Which of following pairs will form the same osazone?
(a) D-Glucose, D-Allose **(b)** D-Glucose, D-Altrose
(c) D-Allose, D-Altrose **(d)** D-Fructose, D-Galactose

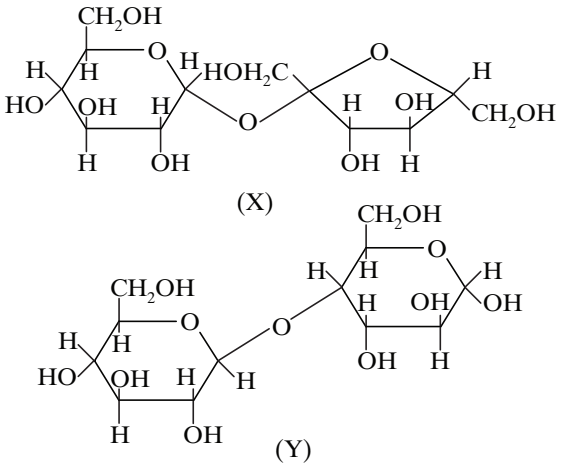
15. Hydrolysis of (+)-sucrose (ordinary table sugar) yields
(a) D-glucose. **(b)** D-fructose.
(c) D-galactose. **(d)** More than one of the above.

Multiple Correct Choice Type

1. Which of the following are D sugars?



2. The correct statement(s) about the following sugars X and Y are

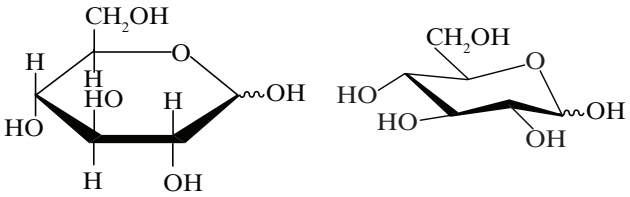


(a) X is a reducing sugar and Y is a non-reducing sugar.
(b) X is a non-reducing sugar and Y is a reducing sugar.
(c) The glycosidic linkages in X and Y are α and β, respectively.
(d) The glycosidic linkages in X and Y are β and α, respectively.

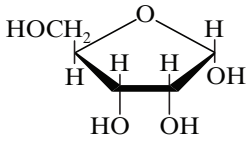
Linked Comprehension Type

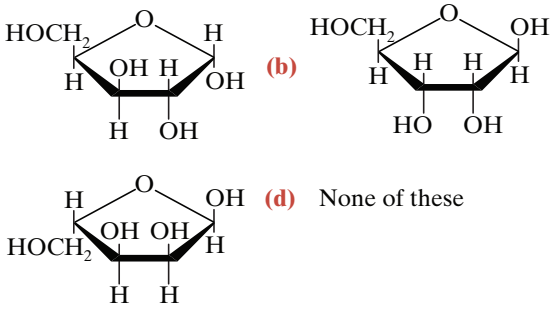
Paragraph for Questions 1 to 3

It is convenient at times to represent the cyclic structures of a monosaccharide without specifying whether the configuration of the anomeric carbon atom is α or β. When we do this, we shall use formulas such as the following:



1. Which of the following represents the anomer of the compound shown?





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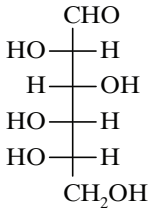
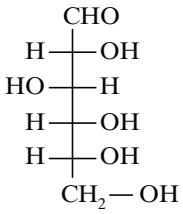
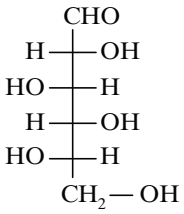
2. Which of the following are the structure of L-glucose?

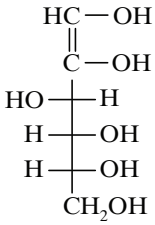
(a)


(b)


(c)


(d) None of these

3. The given enol form is



(a) D-glucose. **(b)** D-mannose.
(c) D-fructose. **(d)** All of these.

Integer Type

1. How many compounds from the following list are isomers of D-glucose?

D-Mannose, D-Fructose, D-Gulose, D-Idose, D-Galactose, D-Arabinose, D-Ribose

ANSWER KEY

Single Correct Choice Type

1. (a)	**2.** (a)	**3.** (b)	**4.** (d)	**5.** (d)
6. (c)	**7.** (d)	**8.** (c)	**9.** (a)	**10.** (c)
11. (b)	**12.** (c)	**13.** (c)	**14.** (c)	**15.** (d)

Multiple Correct Choice Type

1. (a), (c), (d) **2.** (b), (c)

Linked Comprehension Type

1. (b) **2.** (a) **3.** (d)

Integer Type

1. (5)

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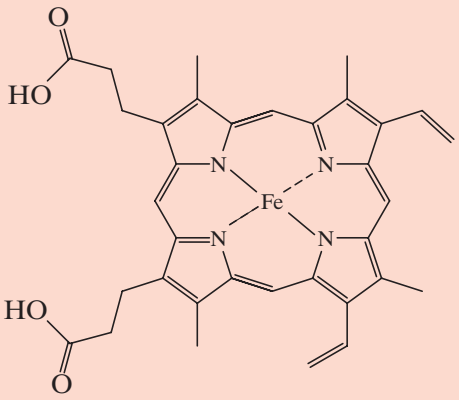
21

Amino Acids and Proteins



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21.1 | Introduction
21.2 | Amino Acids
21.3 | Synthesis of α-Amino Acids
21.4 | Polypeptides and Proteins
21.5 | Primary Structure of Polypeptides and Proteins
21.6 | Secondary, Tertiary, and Quaternary Structures of Proteins

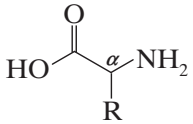
21.1 | INTRODUCTION

The three groups of biological polymers are polysaccharides, proteins, and nucleic acids. We studied polysaccharides in Chapter 20 and saw that they function primarily as energy reserves, as biochemical labels on cell surfaces, and, in plants, as structural materials. Of the three groups of biopolymers, proteins have the most diverse functions. As enzymes and hormones, proteins catalyze and regulate the reactions that occur in the body; as muscles and tendons they provide the body with the means for movement; as skin and hair they give it an outer covering; as hemoglobin molecules they transfer all-important oxygen to its most remote corners; as antibodies they provide it with a means of protection against disease; and in combination with other substances in bone they provide it with structural support.

Given such diversity of functions, we should not be surprised to find that proteins come in all sizes and shapes. By the standard of most of the molecules we have studied, even small proteins have very high molecular weights. Lysozyme, an enzyme, is a relatively small protein and yet its molecular weight is 14,600. The molecular weights of most proteins are much larger. Their shapes cover a range from the globular proteins such as lysozyme and hemoglobin to the helical coils of α-keratin (hair, nails, and wool) and the pleated sheets of silk fibroin.

And yet, in spite of such diversity of size, shape, and function, all proteins have common features that allow us to deduce their structures and understand their properties. Later in this chapter we shall see how this is done.

- Proteins are **polyamides**, and their monomeric units are composed of about 20 different α-amino acids:



An α-amino acid

R is a side chain at the α carbon that determines the identity of the amino acid (Table 21.1).

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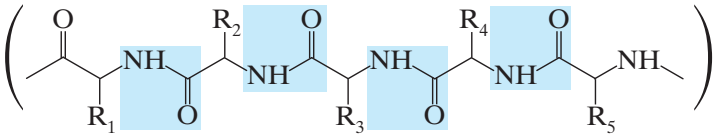


A portion of a protein molecule

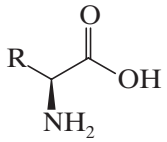
Amide (peptide) linkages are shaded.
R_1 to R_5 may be any of the possible side chains.

- The exact sequence of the different α-amino acids along the protein chain is called the **primary structure** of the protein.

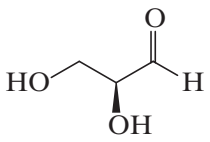
A protein's primary structure, as its name suggests, is of fundamental importance. For the protein to carry out its particular function, the primary structure must be correct. We shall see later that when the primary structure is correct, the protein's polyamide chain folds in particular ways to give it the shape it needs for its particular task.

- Folding of the polyamide chain gives rise to higher levels of complexity called the **secondary** and **tertiary structures** of the protein.
- **Quaternary structure** results when a protein contains an aggregate of more than one polyamide chain.
- Hydrolysis of proteins with acid or base yields a mixture of amino acids.

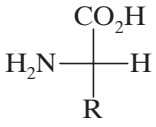
Although hydrolysis of naturally occurring proteins may yield as many as 22 different amino acids, the amino acids have an important structural feature in common: with the exception of glycine (whose molecules are achiral), almost all naturally occurring amino acids have the L configuration at the α carbon. That is, they have the same relative configuration as L-glyceraldehyde:

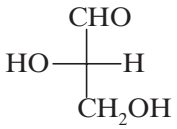


An L-α-amino acid
[usually an (*S*)-α-amino acid]



L-Glyceraldehyde
[(*S*)-glyceraldehyde]





Fischer projections for an L-α-amino acid and L-glyceraldehyde

21.2 | AMINO ACIDS

21.2A Structures and Names

- The 22 α-amino acids that can be obtained from proteins can be subdivided into three different groups on the basis of the structures of their side chains, R. These are given in Table 21.1.

Only 20 of the 22 α-amino acids in Table 21.1 are actually used by cells when they synthesize proteins. Two amino acids are synthesized after the polyamide chain is intact. Hydroxyproline (present mainly in collagen) is synthesized by oxidation of proline, and cystine (present in most proteins) is synthesized from cysteine.

The conversion of cysteine to cystine requires additional comment. The —SH group of cysteine makes cysteine a *thiol*. One property of thiols is that they can be converted to disulfides by mild oxidizing agents. This conversion, moreover, can be reversed by mild reducing agents:

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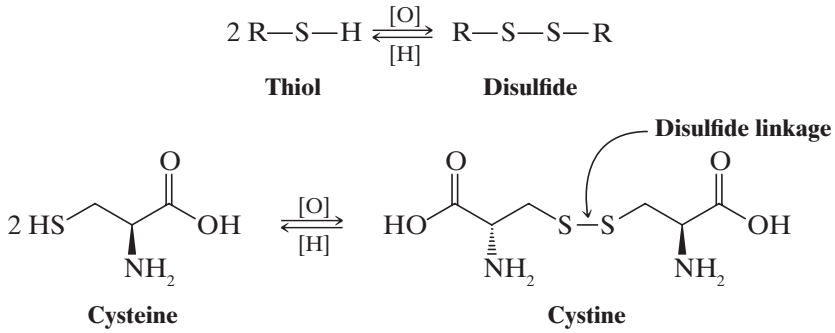
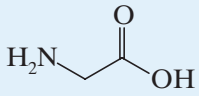
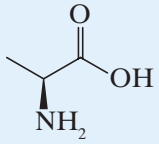
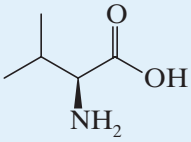
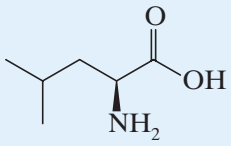
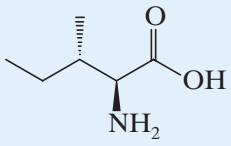
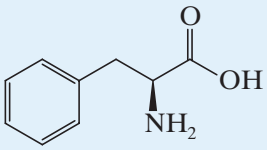


We shall see later how the **disulfide linkage** between cysteine units in a protein chain contributes to the overall structure and shape of the protein.

Table 21.1 L-Amino Acids Found in Proteins

Structure	Name	Abbreviations[a]	pK_{a_1} α-CO_2H	pK_{a_2} α-NH_3^+	pK_{a_3} R group	pI
Neutral Amino Acids						
	Glycine	G or Gly	2.3	9.6		6.0
	Alanine	A or Ala	2.3	9.7		6.0
	Valine[b]	V or Val	2.3	9.6		6.0
	Leucine[b]	L or Leu	2.4	9.6		6.0
	Isoleucine[b]	I or Ile	2.4	9.7		6.1
	Phenylalanine[b]	F or Phe	1.8	9.1		5.5

(*Continued*)

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Table 21.1 Continued

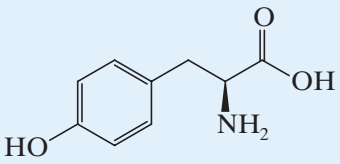
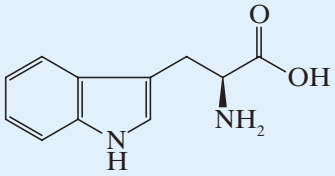
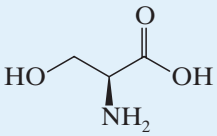
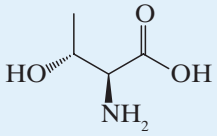
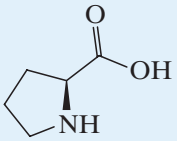
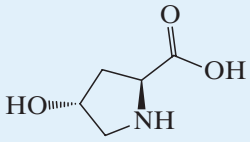
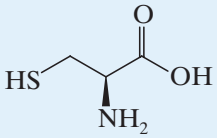
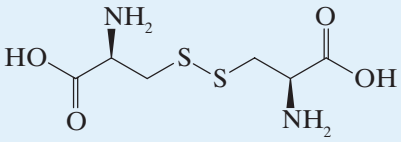
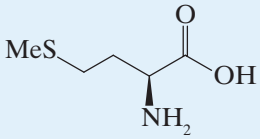
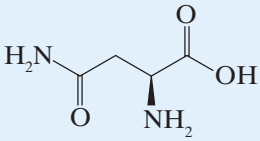
Structure	Name	Abbreviations[a]	pK_{a_1} α-CO_2H	pK_{a_2} α-NH_3^+	pK_{a_3} R group	pI
	Tyrosine	Y or Tyr	2.2	9.1	10.1	5.7
	Tryptophan[b]	W or Trp	2.4	9.4		5.9
	Serine	S or Ser	2.2	9.2		5.7
	Threonine[b]	T or Thr	2.6	10.4		6.5
	Proline	P or Pro	2.0	10.6		6.3
	4-Hydroxyproline (cis and trans)	O or Hyp	1.9	9.7		6.3
	Cysteine	C or Cys	1.7	10.8	8.3	5.0
	Cystine	Cys-Cys	1.6 2.3	7.9 9.9		5.1
	Methionine[b]	M or Met	2.3	9.2		5.8
	Asparagine	N or Asn	2.0	8.8		5.4

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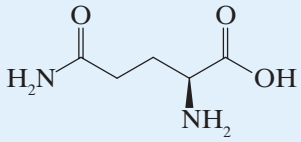
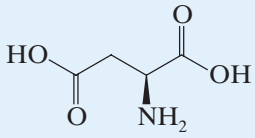
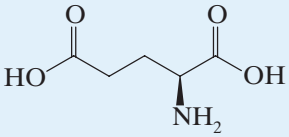
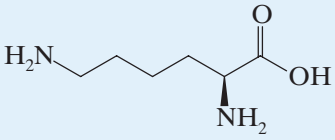
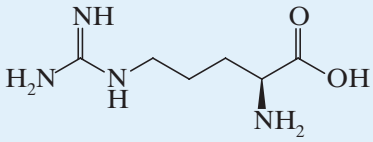
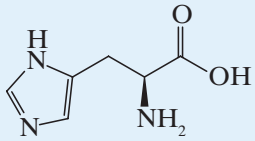
Table 21.1 Continued

Structure	Name	Abbreviations[a]	pK_{a_1} α-CO_2H	pK_{a_2} α-NH_3^+	pK_{a_3} R group	pI
	Glutamine	Q or Gln	2.2	9.1		5.7
Side Chains Containing an Acidic (Carboxyl) Group						
	Aspartic acid	D or Asp	2.1	9.8	3.9	3.0
	Glutamic acid	E or Glu	2.2	9.7	4.3	3.2
Side Chains Containing a Basic Group						
	Lysine[b]	K or Lys	2.2	9.0	10.5[c]	9.8
	Arginine	R or Arg	2.2	9.0	12.5[c]	10.8
	Histidine	H or His	1.8	9.2	6.0[c]	7.6

[a]Single-letter abbreviations are now the most commonly used form in current biochemical literature.
[b]An essential amino acid.
[c]pK_a is of protonated amine of R group.

21.2B Essential Amino Acids

Amino acids can be synthesized by all living organisms, plants and animals. Many higher animals, however, are deficient in their ability to synthesize all of the amino acids they need for their proteins. Thus, these higher animals require certain amino acids as a part of their diet. For adult humans there are eight **essential amino acids**; these are identified in Table 21.1 by a footnote.

21.2C Amino Acids as Dipolar Ions

- Amino acids contain both a basic group ($-NH_2$) and an acidic group ($-CO_2H$).
- In the dry solid state, amino acids exist as **dipolar ions**, a form in which the carboxyl group is present as a carboxylate ion, $-CO_2^-$, and the amino group is present as an aminium ion, $-NH_3^+$. (Dipolar ions are also called **zwitterions**.)
- In aqueous solution, an equilibrium exists between the dipolar ion and the anionic and cationic forms of an amino acid.

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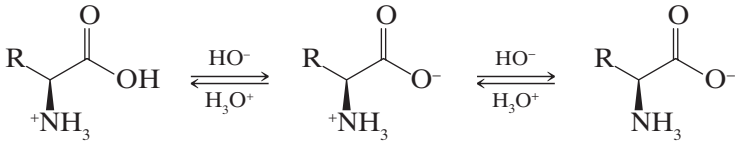


Cationic form (predominant in strongly acidic solutions, e.g., at pH 0) | **Dipolar ion** | **Anionic form (predominant in strongly basic solutions, e.g., at pH 14)**

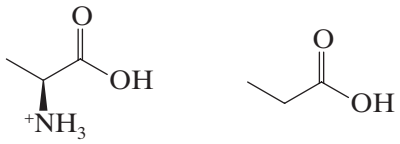
The predominant form of the amino acid present in a solution depends on the pH of the solution and on the nature of the amino acid. In strongly acidic solutions all amino acids are present primarily as cations; in strongly basic solutions they are present as anions.

- The **isoelectric point (p*I*)** is the pH at which the concentration of the dipolar ion is at its maximum and the concentrations of the anions and cations are equal.

Each amino acid has a particular isoelectric point. These are given in Table 21.1.

Let us consider first an amino acid with a side chain that contains neither acidic nor basic groups—an amino acid, for example, such as alanine.

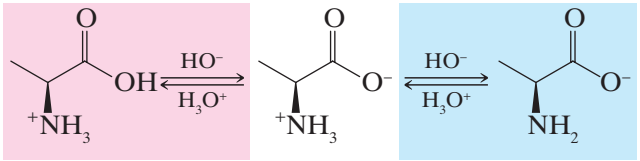
If alanine is dissolved in a strongly acidic solution (e.g., pH 0), it is present in mainly a net cationic form. In this state the amino group is protonated (bears a formal +1 charge) and the carboxylic acid group is neutral (has no formal charge). As is typical of α-amino acids, the pK_a for the carboxylic acid hydrogen of alanine is considerably lower (2.3) than the pK_a of an ordinary carboxylic acid (e.g., propanoic acid, pK_a 4.89):



Cationic form of alanine $pK_{a_1} = 2.3$ | **Propanoic acid** $pK_a = 4.89$

The reason for this enhanced acidity of the carboxyl group in an α-amino acid is the inductive effect of the neighboring aminium cation, which helps to stabilize the carboxylate anion formed when it loses a proton. Loss of a proton from the carboxyl group in a cationic α-amino acid leaves the molecule electrically neutral (in the form of a dipolar ion). This equilibrium is shown in the red-shaded portion of the equation below.

The protonated amino group of an α-amino acid is also acidic, but less so than the carboxylic acid group. The pK_a of the aminium group in alanine is 9.7. The equilibrium for loss of an aminium proton is shown in the blue-shaded portion of the equation below. The carboxylic acid proton is always lost before a proton from the aminium group in an α-amino acid.



Cationic form ($pK_{a_1} = 2.3$) | **Dipolar ion** ($pK_{a_2} = 9.7$) | **Anionic form**

The state of an α-amino acid at any given pH is governed by a combination of two equilibria, as shown in the above equation for alanine. The isoelectric point (p*I*) of an amino acid such as alanine is the average of pK_{a_1} and pK_{a_2}:

$$pI = \frac{1}{2}(2.3 + 9.7) = 6.0 \quad \text{(isoelectric point of alanine)}$$

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When a base is added to a solution of the net cationic form of alanine (initially at pH 0, for example), the first proton removed is the carboxylic acid proton, as we have said. In the case of alanine, when a pH of 2.3 is reached, the carboxylic acid proton will have been removed from half of the molecules. This pH represents the pK_a of the alanine carboxylic acid proton, as can be demonstrated using the **Henderson–Hasselbalch equation**.

- The **Henderson–Hasselbalch equation** shows that for an acid (HA) and its conjugate base (A^-) when $[HA] = [A^-]$, then $pH = pK_a$.

$$pK_a = pH + \log \frac{[HA]}{[A^-]}$$

Henderson–Hasselbalch equation

Therefore, when the acid is half neutralized,

$$[HA] = [A^-], \log \frac{[HA]}{[A^-]} = 0, \text{ and thus } pH = pK_a$$

As more base is added to this solution, alanine reaches its isoelectric point (pI), the pH at which all of alanine's carboxylic acid protons have been removed but not its aminium protons. The molecules are therefore electrically neutral (in their dipolar ion or zwitter ionic form) because the carboxylate group carries a –1 charge and the aminium group a +1 charge. The pI for alanine is 6.0.

Now, as we continue to add the base, protons from the aminium ions will begin to be removed, until at pH 9.7 half of the aminium groups will have lost a proton. This pH represents the pK_a of the aminium group. Finally, as more base is added, the remaining aminium protons will be lost until all of the alanine molecules have lost their aminium protons. At this point (e.g., pH 14) the molecules carry a net anionic charge from their carboxylate group. The amino groups are now electrically neutral.

Figure 21.1 shows a titration curve for these equilibria. The graph represents the change in pH as a function of the number of molar equivalents of base. Because alanine has two protons to lose in its net cationic form, when one molar equivalent of base has been added, the molecules will have each lost one proton and they will be electrically neutral (the dipolar ion or zwitterionic form).

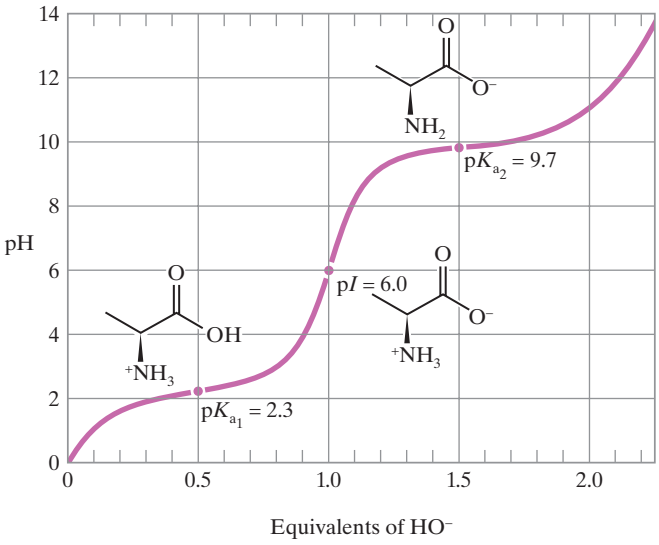

Figure 21.1 A titration curve for alanine.

If an amino acid contains a side chain that has an acidic or basic group, the equilibria become more complex. Consider lysine, for example, an amino acid that has an additional $—NH_2$ group on its ε carbon. In strongly acidic solution, lysine is present as a dication because both amino groups are protonated. The first proton to be lost as the pH is raised is a proton of the carboxyl group ($pK_{a_1} = 2.2$), the next is from the α-aminium group ($pK_{a_2} = 9.0$), and the last is from the ε-aminium group ($pK_{a_3} = 10.5$):

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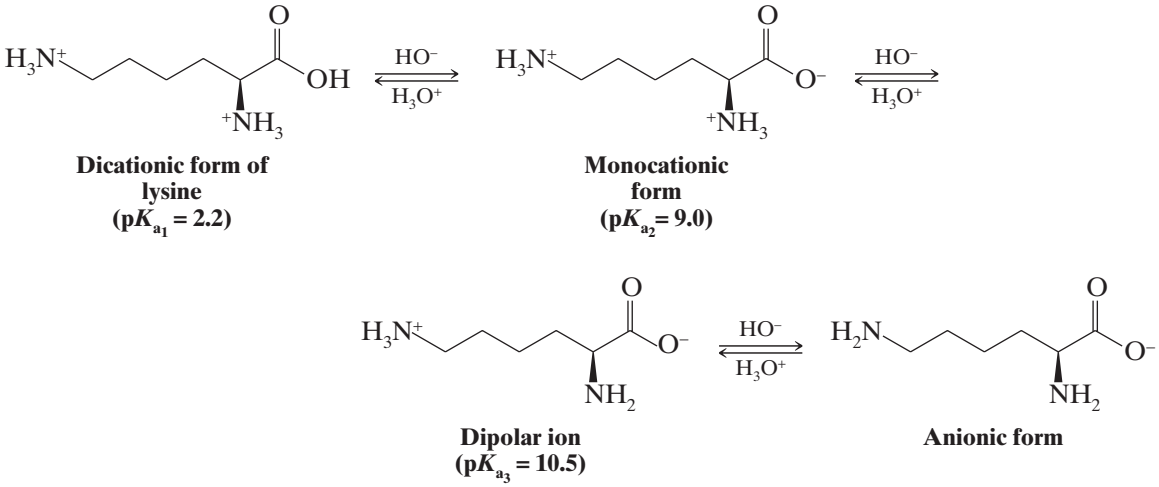


Dicationic form of lysine (pK_{a_1} = 2.2)

Monocationic form (pK_{a_2} = 9.0)

Dipolar ion (pK_{a_3} = 10.5)

Anionic form

The isoelectric point of lysine is the average of pK_{a_2} (the monocation) and pK_{a_3} (the dipolar ion).

$$pI = \frac{1}{2}(9.01 + 0.5) = 9.8 \quad \text{(isoelectric point of lysine)}$$

Practice Problem 21.1

What form of glutamic acid would you expect to predominate in **(a)** strongly acidic solution, **(b)** strongly basic solution, and **(c)** at its isoelectric point (pI = 3.2)? **(d)** The isoelectric point of glutamine (pI = 5.7) is considerably higher than that of glutamic acid. Explain.

Practice Problem 21.2

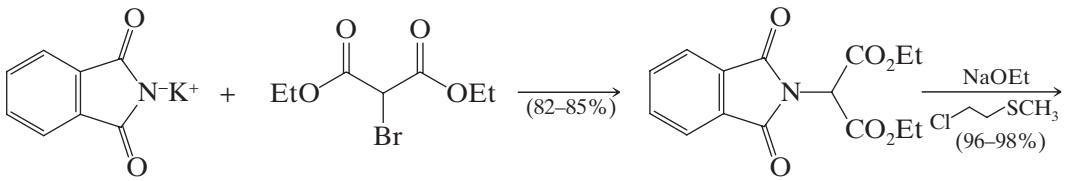
The guanidino group —NH—C(=NH)—NH_2 of arginine is one of the most strongly basic of all organic groups. Explain.

21.3 | SYNTHESIS OF α-AMINO ACIDS

A variety of methods have been developed for the synthesis of α-amino acids. Asymmetric synthesis is an important goal in α-amino acid synthesis due to the biological activity of the natural enantiomeric forms of α-amino acids, and due to the commercial relevance of products made by these routes.

21.3A From Potassium Phthalimide

This method, a modification of the Gabriel synthesis of amines (Section 18.4A), uses potassium phthalimide and diethyl α-bromomalonate to prepare an *imido* malonic ester. The example shown is a synthesis of methionine:



Diethyl α-bromomalonate

Phthalimidomalonic ester

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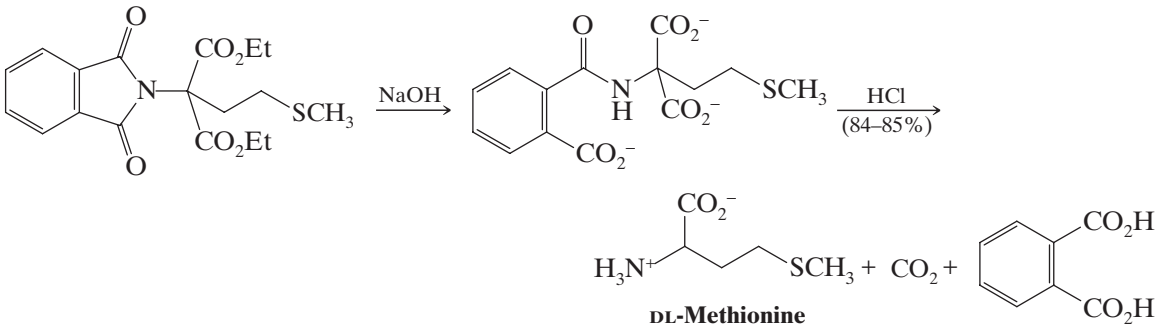


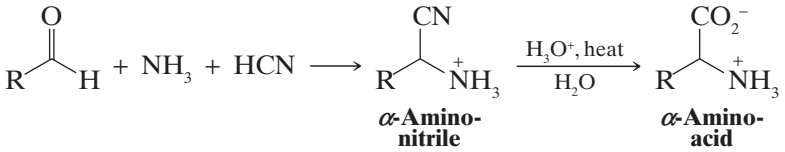
DL-Methionine

Practice Problem 21.3

Starting with diethyl α-bromomalonate and potassium phthalimide and using any other necessary reagents, show how you might synthesize **(a)** DL-leucine, **(b)** DL-alanine, and **(c)** DL-phenylalanine.

21.3B The Strecker Synthesis

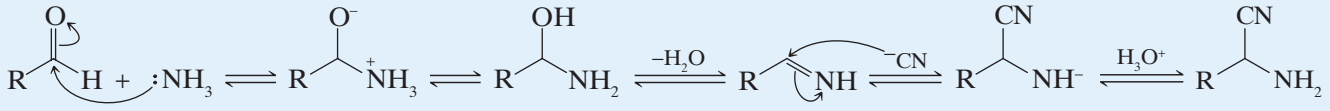
Treating an aldehyde with ammonia and hydrogen cyanide produces an α-aminonitrile. Hydrolysis of the nitrile group (Section 17.3) of the α-aminonitrile converts the latter to an α-amino acid. This synthesis is called the Strecker synthesis:



α-Amino-nitrile — α-Amino-acid

The first step of this synthesis probably involves the initial formation of an imine from the aldehyde and ammonia followed by the addition of hydrogen cyanide.

A MECHANISM FOR THE REACTION — Formation of an α-Aminonitrile during the Strecker Synthesis

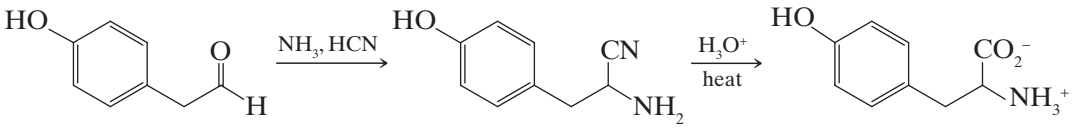


Intermolecular proton transfer — Imine — α-Aminonitrile

Solved Problem 21.1

Outline a Strecker synthesis of DL-tyrosine.

Answer



DL-Tyrosine

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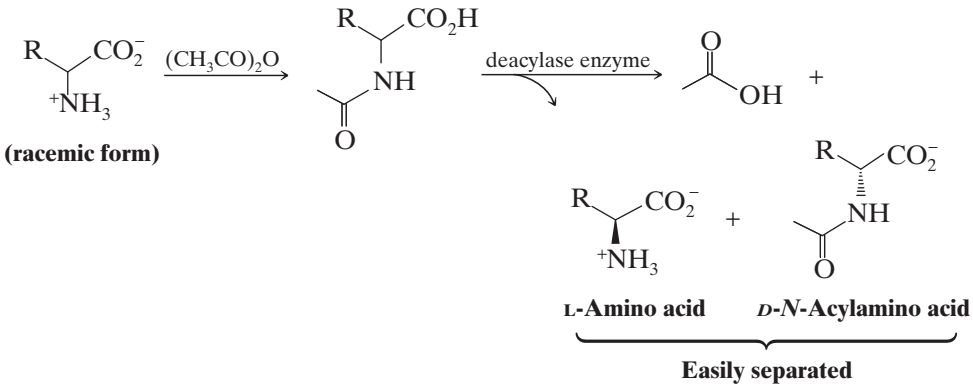
Practice Problem 21.4

(a) Outline a Strecker synthesis of DL-phenylalanine. **(b)** DL-Methionine can also be synthesized by a Strecker synthesis. The required starting aldehyde can be prepared from acrolein (CH_2=CHCHO) and methanethiol (CH_3SH). Outline all steps in this synthesis of DL-methionine.

21.3C Resolution of DL-Amino Acids

With the exception of glycine, which has no chirality center, the amino acids that are produced by the methods we have outlined are all produced as racemic forms. To obtain the naturally occurring L-amino acid, we must, of course, resolve the racemic form. This can be done in a variety of ways, including the methods outlined in Section 18.3F.

One especially interesting method for resolving amino acids is based on the use of enzymes called *deacylases*. These enzymes catalyze the hydrolysis of *N-acylamino acids* in living organisms. Since the active site of the enzyme is chiral, it hydrolyzes only *N*-acylamino acids of the L configuration. When it is exposed to a racemic mixture of *N*-acylamino acids, only the derivative of the L-amino acid is affected and the products, as a result, are separated easily:

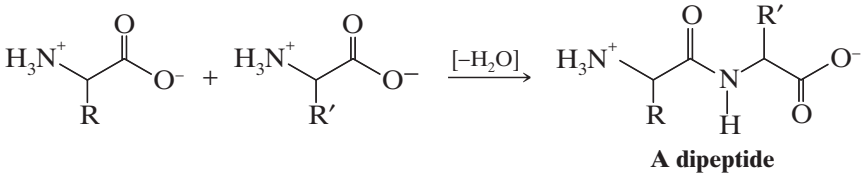


21.4 | POLYPEPTIDES AND PROTEINS

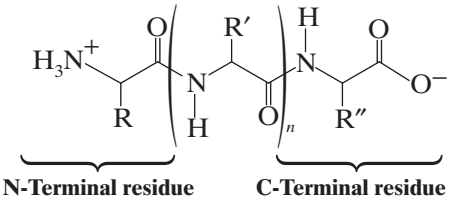
Amino acids are polymerized in living systems by enzymes that form amide linkages from the amino group of one amino acid to the carboxyl group of another.

- A molecule formed by joining amino acids together is called a **peptide**, and the amide linkages in them are called **peptide bonds** or **peptide linkages**. Each amino acid in the peptide is called an **amino acid residue**.

Peptides that contain 2, 3, a few (3–10), or many amino acids are called **dipeptides**, **tripeptides**, **oligopeptides**, and **polypeptides**, respectively. **Proteins** are polypeptides consisting of one or more polypeptide chains.



Polypeptides are **linear polymers**. One end of a polypeptide chain terminates in an amino acid residue that has a free $-NH_3^+$ group; the other terminates in an amino acid residue with a free $-CO_2^-$ group. These two groups are called the **N-terminal** and the **C-terminal residues**, respectively:



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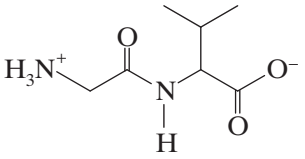
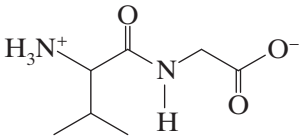
- By convention, we write peptide and protein structures with the N-terminal amino acid residue on the left and the C-terminal residue on the right:

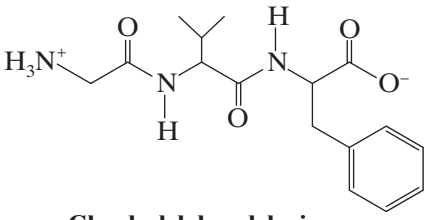


Glycyl valine (GV)



Valyl glycine (VG)

The tripeptide glycylvalylphenylalanine has the following structural formula:



Glycylvalylphenylalanine (GVF)

It becomes a significant task to write a full structural formula for a polypeptide chain that contains any more than a few amino acid residues. In this situation, use of the one-letter abbreviations (Table 21.1) is the norm for showing the sequence of amino acids. Very short peptide sequences are sometimes still represented with the three-letter abbreviations (Table 21.1).

21.4A Hydrolysis

When a protein or polypeptide is refluxed with 6 M hydrochloric acid for 24 h, hydrolysis of all the amide linkages usually takes place, liberating its constitutent amino acids as a mixture. Chromatographic separation and quantitative analysis of the resulting mixture can then be used to determine which amino acids composed the intact polypeptide and their relative amounts.

One chromatographic method for separation of a mixture of amino acids is based on the use of *cation-exchange resins* (Fig. 21.2), which are insoluble polymers containing sulfonate groups. If an acidic solution containing a mixture of amino acids is passed through a column packed with a cation-exchange resin, the amino acids will be adsorbed by the resin because of attractive forces between the negatively charged sulfonate groups and the positively charged amino acids. The strength of the adsorption varies with the basicity of the individual amino acids; those that are most basic are held most strongly. If the column is then washed with a buffered solution at a given pH, the individual amino acids move down the column at different rates and ultimately become separated. In an automated version of this analysis developed at Rockefeller University in 1950, the eluate is allowed to mix with **ninhydrin**, a reagent that reacts with most amino acids to give a derivative with an intense purple color (λ_{max} 570 nm). The amino acid analyzer is designed so that it can measure the absorbance of the eluate (at 570 nm) continuously and record this absorbance as a function of the volume of the effluent.

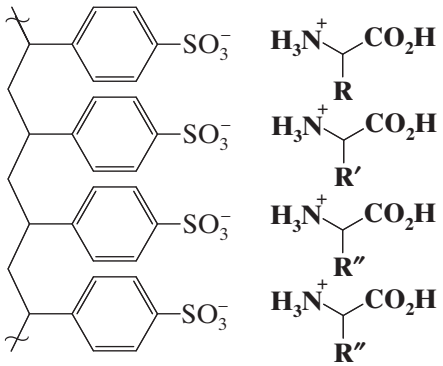


Figure 21.2 A section of a cation-exchange resin with adsorbed amino acids.

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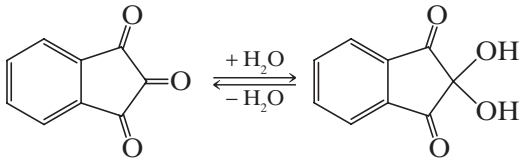
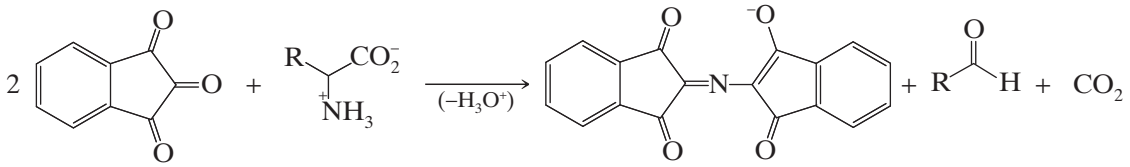


Indane-1,2,3-trione **Ninhydrin**



Purple anion

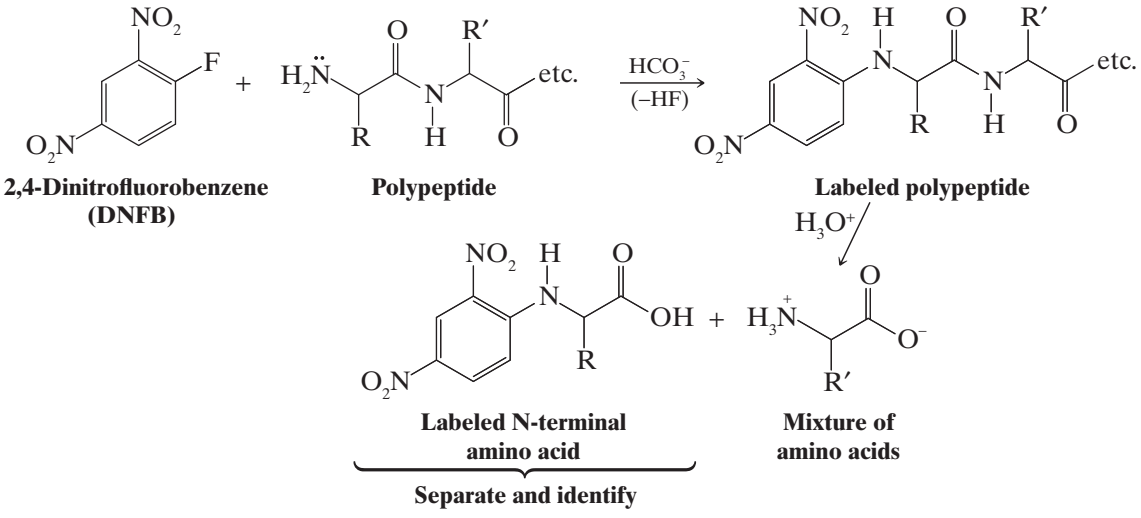
Proline and hydroxyproline do not react with ninhydrin in the same way because their α-amino groups are secondary amines and part of a five-membered ring.

21.5 | PRIMARY STRUCTURE OF POLYPEPTIDES AND PROTEINS

The sequence of amino acid residues in a polypeptide or protein is called its **primary structure**. A simple peptide composed of three amino acids (a tripeptide) can have 6 different amino acid sequences; a tetrapeptide can have as many as 24 different sequences. For a protein composed of 20 different amino acids in a single chain of 100 residues, there are $2^{100} = 1.27 \times 10^{130}$ possible peptide sequences, a number much greater than the number of atoms estimated to be in the universe (9×10^{78})! Clearly, one of the most important things to determine about a protein is the sequence of its amino acids. Fortunately, there are a variety of methods available to determine the sequence of amino acids in a polypeptide. We shall begin with **terminal residue analysis** techniques used to identify the N- and C-terminal amino acids.

21.5A Sanger N-Terminal Analysis

Another method for sequence analysis is the **Sanger N-terminal analysis**, based on the use of 2,4-dinitrofluorobenzene (DNFB). When a polypeptide is treated with DNFB in mildly basic solution, a nucleophilic aromatic substitution reaction (S_NAr) takes place involving the free amino group of the N-terminal residue. Subsequent hydrolysis of the polypeptide gives a mixture of amino acids in which the N-terminal amino acid is labeled with a 2,4-dinitrophenyl group. After separating this amino acid from the mixture, it can be identified by comparison with known standards.



2,4-Dinitrofluorobenzene (DNFB) **Polypeptide** **Labeled polypeptide**

Labeled N-terminal amino acid **Mixture of amino acids**

Separate and identify

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2,4-Dinitrofluorobenzene will react with any free amino group in a polypeptide, including the ε-amino group of lysine, and this fact complicates Sanger analyses. Only the N-terminal amino acid residue of a peptide will bear the 2,4-dinitrophenyl group at its α-amino group, however.

21.6 | SECONDARY, TERTIARY, AND QUATERNARY STRUCTURES OF PROTEINS

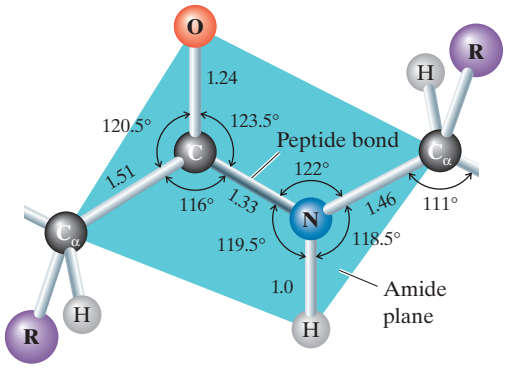
We have seen how amide and disulfide linkages constitute the covalent or *primary structure* of proteins. Of equal importance in understanding how proteins function is knowledge of the way in which the peptide chains are arranged in three dimensions. The secondary and tertiary structures of proteins are involved here.

21.6A Secondary Structure

- The **secondary structure** of a protein is defined by the local conformation of its polypeptide backbone.
- Secondary structures are specified in terms of regular folding patterns called **α helices, β sheets**, and **coil** or **loop conformations**.

To understand how these interactions occur, let us look first at what X-ray crystallographic analysis has revealed about the geometry at the peptide bond itself.

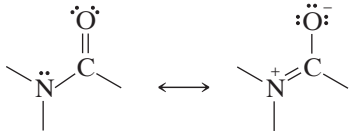
- Peptide bonds tend to assume a geometry such that six atoms of the amide linkage are coplanar (Fig. 21.3).



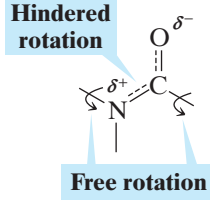
trans-Peptide group

Figure 21.3 The geometry and bond lengths (in angstroms, Å) of the peptide linkage. The six enclosed atoms tend to be coplanar and assume a "transoid" arrangement. (Reprinted with permission of John Wiley & Sons, Inc., from Voet, D. and Voet, J. G., *Biochemistry*, Second Edition. © 1995 Voet, D. and Voet, J. G.)

The carbon–nitrogen bond of the amide linkage is unusually short, indicating that resonance contributions of the type shown here are important:



Contributing resonance structures for an amide



Hybrid resonance structure for an amide

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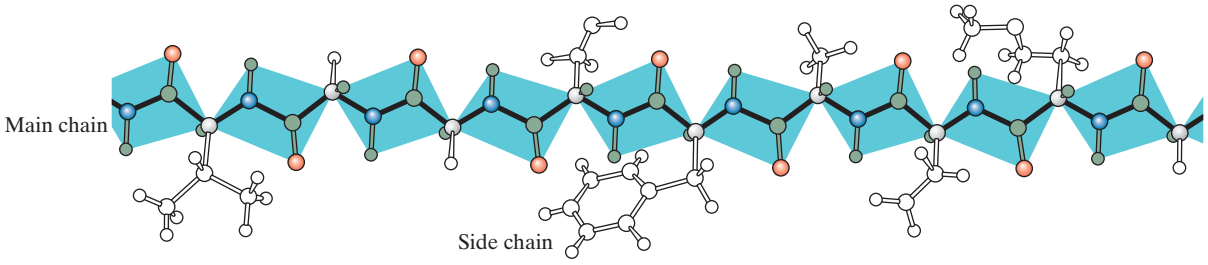
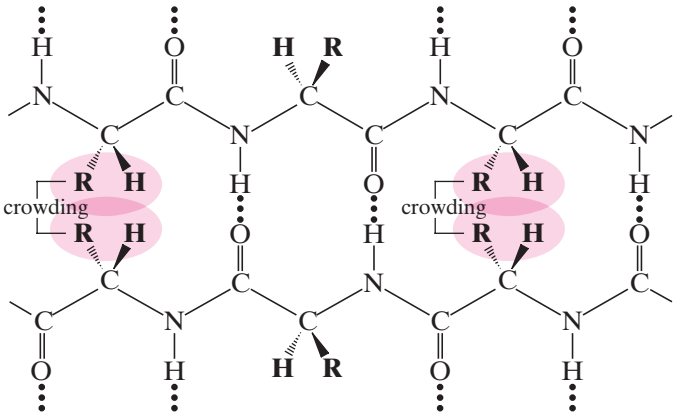
- The amide carbon–nitrogen bond, consequently, has considerable double-bond character (~40%), and rotations of groups about this bond are severely hindered.
- Rotations of groups attached to the amide nitrogen and the carbonyl carbon are relatively free, however, and these rotations allow peptide chains to form different conformations.

A transoid arrangement of groups around the relatively rigid amide bond would cause the side-chain R groups to alternate from side to side of a single fully extended peptide chain:



Calculations show that such a polypeptide chain would have a repeat distance (i.e., distance between alternating units) of 7.2 Å.

Fully extended polypeptide chains could hypothetically form a flat-sheet structure, with each alternating amino acid in each chain forming two hydrogen bonds with an amino acid in the adjacent chain:



Hypothetical flat-sheet structure
(not formed because of steric hindrance)

However, this structure does not exist in naturally occurring proteins because of the crowding that would exist between R groups. If such a structure did exist, it would have the same repeat distance as the fully extended peptide chain, that is, 7.2 Å.

- Many proteins incorporate a **β sheet** or **β configuration** (Fig. 21.4).

In a β sheet structure, slight bond rotations from one planar amide group to the next relieve the steric strain from small- and medium-sized R groups. This allows amide groups on adjacent polypeptide segments to form hydrogen bonds between the chains (see Fig. 21.4). The β sheet structure has a repeat distance of 7.0 Å between amide groups in a chain. The predominant secondary structure in silk fibroin (48% glycine and 38% serine and alanine residues) is the β sheet.

- The **α helix** is also a very important secondary structure in proteins (Fig. 21.5).

The α helix of a polypeptide is right-handed with 3.6 amino acid residues per turn. Each amide group in the chain has a hydrogen bond to an amide group at a distance of three amino acid residues in either direction, and the R groups all extend away from the axis of the helix. The repeat distance of the α helix is 5.4 Å.

The α-helical structure is found in many proteins; it is the predominant structure of the polypeptide chains of fibrous proteins such as *myosin*, the protein of muscle, and of *α-keratin*, the protein of hair, unstretched wool, and nails.

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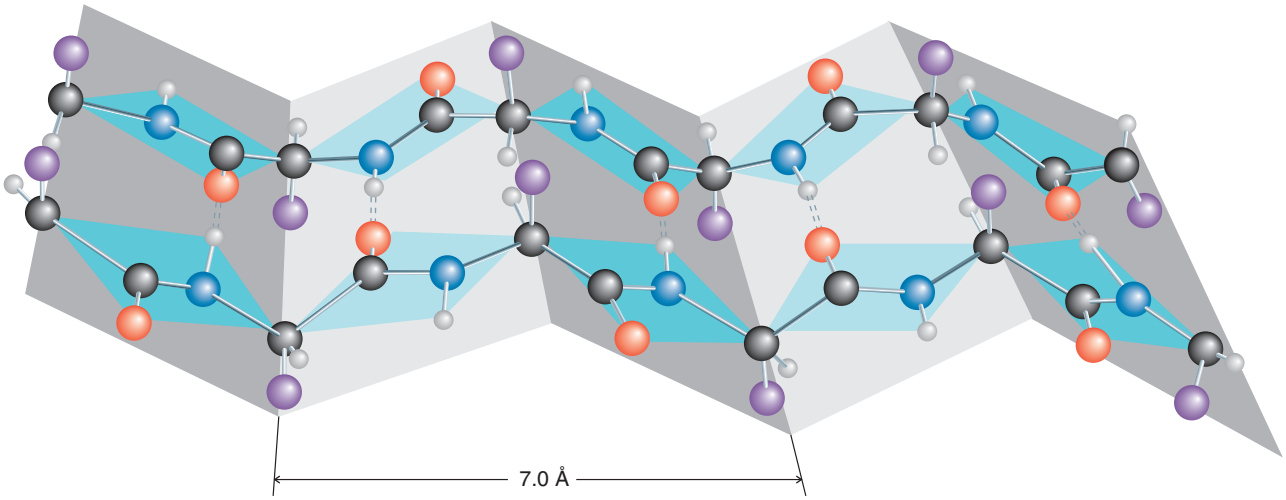

Figure 21.4 The β sheet or β configuration of a protein. (Illustration, Irving Geis. Image from the Irving Geis Collection, HHMI. Rights owned by Howard Hughes Medical Institute. Not to be reproduced without permission.)

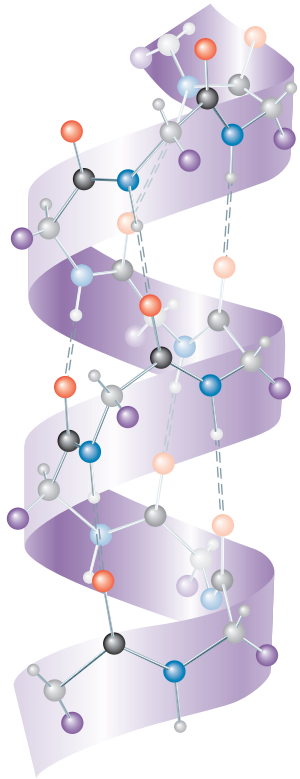

Figure 21.5 A representation of the α-helical structure of a polypeptide. Hydrogen bonds are denoted by dashed lines. (Illustration, Irving Geis. Image from the Irving Geis Collection, HHMI. Rights owned by Howard Hughes Medical Institute. Not to be reproduced without permission.)

Helices and pleated sheets account for only about one-half of the structure of the average globular protein. The remaining polypeptide segments have what is called a **coil** or **loop conformation**. These nonrepetitive structures are not random; they are just more difficult to describe. Globular proteins also have stretches, called **reverse turns** or **β bends**, where the polypeptide chain abruptly changes direction. These often connect successive strands of β sheets and almost always occur at the surface of proteins.

- The locations of the side chains of amino acids of globular proteins are usually those that we would expect from their polarities:

1. Residues with **nonpolar, hydrophobic side chains**, such as *valine, leucine, isoleucine, methionine, and phenylalanine,* are almost always found in the interior of the protein, out of contact with the aqueous solvent. (These hydrophobic interactions are largely responsible for the tertiary structure of proteins that we discuss in Section 21.6B.)
2. Side chains of **polar residues with positive or negative charges**, such as *arginine, lysine, aspartic acid, and glutamic acid,* are usually on the surface of the protein in contact with the aqueous solvent.
3. **Uncharged polar side chains**, such as those of *serine, threonine, asparagine, glutamine, tyrosine, and tryptophan,* are most often found on the surface, but some of these are found in the interior as well. When they are found in the interior, they are virtually all hydrogen bonded to other similar residues. Hydrogen bonding apparently helps neutralize the polarity of these groups.

Certain peptide chains assume what is called a **random coil arrangement**, a structure that is flexible, changing, and statistically random. Synthetic polylysine, for example, exists as a random coil and does not normally form an α helix. At pH 7, the ε-amino groups of the lysine residues are positively charged, and, as a result, repulsive forces between them are so large that they overcome any stabilization that would be gained through hydrogen bond formation of an α helix. At pH 12, however, the ε-amino groups are uncharged and polylysine spontaneously forms an α helix.

The presence of proline or hydroxyproline residues in polypeptide chains produces another striking effect: because the nitrogen atoms of these amino acids are part of five-membered rings, the groups attached by the nitrogen–α

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carbon bond cannot rotate enough to allow an α-helical structure. Wherever proline or hydroxyproline occur in a peptide chain, their presence causes a kink or bend and interrupts the α helix.

21.6B Tertiary Structure

- The **tertiary structure** of a protein is the overall three-dimensional shape that arises from all of the secondary structures of its polypeptide chain.

Proteins typically have either **globular** or **fibrous** tertiary structures. These tertiary structures do not occur randomly. Under the proper environmental conditions the tertiary structure of a protein occurs in one particular way—a way that is characteristic of that particular protein and one that is often highly important to its function.

Various forces are involved in stabilizing tertiary structures, including the disulfide bonds of the primary structure.

- One characteristic of most proteins is that the folding takes place in such a way as to expose the maximum number of polar (hydrophilic) groups to the aqueous environment and enclose a maximum number of nonpolar (hydrophobic) groups within its interior.

The soluble globular proteins tend to be much more highly folded than fibrous proteins. Myoglobin is an example of a globular protein. However, fibrous proteins also have a tertiary structure; the α-helical strands of α-keratin, for example, are wound together into a "superhelix." The superhelix makes one complete turn for each 35 turns of the α helix. The tertiary structure does not end here, however. Even the superhelices can be wound together to give a ropelike structure of seven strands.

21.6C Quaternary Structure

Many proteins exist as stable and ordered noncovalent aggregates of more than one polypeptide chain. The overall structure of a protein having multiple subunits is called its **quaternary structure**. The quaternary structure of hemoglobin, for example, involves four subunits.

REVIEW PROBLEMS

Structure and Reactivity

21.5 **(a)** Which amino acids in Table 21.1 have more than one chirality center?

(b) Write Fischer projections for the isomers of each of these amino acids that would have the L configuration at the α carbon.

(c) What kind of isomers have you drawn in each case?

21.6 **(a)** What product would you expect to obtain from treating tyrosine with excess bromine water?

(b) What product would you expect to be formed in the reaction of phenylalanine with ethanol in the presence of hydrogen chloride?

(c) What product would you expect from the reaction of alanine and benzoyl chloride in aqueous base?

21.7 Synthetic polyglutamic acid exists as an α helix in solution at pH 2–3. When the pH of such a solution is gradually raised through the addition of a base, a dramatic change in optical rotation takes place at pH 5. This change has been associated with the unfolding of the α helix and the formation of a random coil. What structural feature of polyglutamic acid and what chemical change can you suggest as an explanation of this transformation?

21.8 **(a)** On the basis of the following sequence of reactions, Emil Fischer was able to show that L-(−)-serine and L-(+)-alanine have the same configuration. Write Fischer projections for the intermediates **A–C**:

$$\text{(−)-Serine} \xrightarrow[CH_3OH]{HCl} \mathbf{A}\ (C_4H_{10}ClNO_3) \xrightarrow{PCl_5} \mathbf{B}\ (C_4H_9Cl_2NO_2) \xrightarrow[(2)\ HO^-]{(1)\ H_3O^+,\ H_2O,\ \text{heat}} \mathbf{C}\ (C_3H_6ClNO_2) \xrightarrow[\text{dilute } H_3O^+]{\text{Na–Hg}} \text{L-(+)-alanine}$$

(b) The configuration of L-(+)-cysteine can be related to that of L-(−)-serine through the following reactions. Write Fischer projections for **D** and **E**:

$$\mathbf{B}\ \text{(from part a)} \xrightarrow{HO^-} \mathbf{D}\ (C_4H_8ClNO_2) \xrightarrow{NaSH} \mathbf{E}\ (C_4H_9NO_2S) \xrightarrow[(2)\ HO^-]{(1)\ H_3O^+,\ H_2O,\ \text{heat}} \text{L-(+)-cysteine}$$

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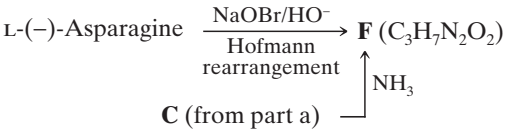
(c) The configuration of L-(−)-asparagine can be related to that of L-(−)-serine in the following way. What is the structure of **F**?



ADDITIONAL OBJECTIVE QUESTIONS

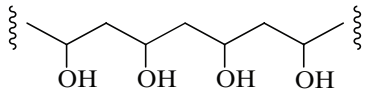
Single Correct Choice Type

1. A peptide bond is formed between two amino acids by
- **(a)** a condensation reaction forming an anhydride.
- **(b)** a condensation reaction forming an ester.
- **(c)** a condensation reaction forming an amine.
- **(d)** a condensation reaction forming an amide.

2. The pentapeptide composed of Val, Ala, Phe and 2 Gly, gives no N_2 with HNO_2. Among its hydrolysis products are Ala, Gly and Gly, Ala. Identify the structure
- **(a)** Gly—Ala—Gly—Phe—Val
- **(b)** Val—Gly—Ala—Gly—Phe
- **(c)** Gly—Ala—Gly (Phe—Val)
- **(d)** Gly—Phe—Gly (Val—Gly)

3. How many different proteins containing 100 amino acids can be made from the 20 naturally occurring amino acids?
- **(a)** 100^{20} **(b)** 20^{100}
- **(c)** 100 – 20 **(d)** None of these

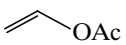
4. The appropriate starting monomer for the following polymer



(a) 

(b) 

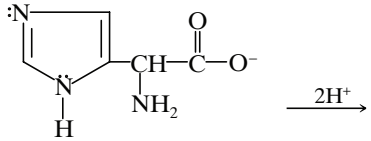
(c) 

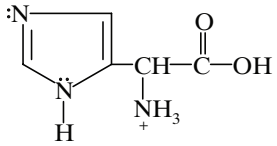
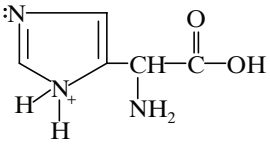
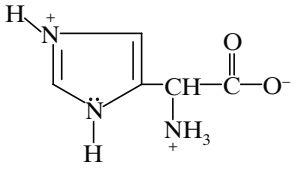
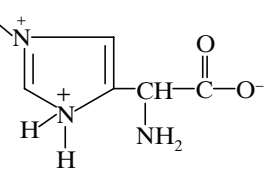
(d) 

5. The majority of amino acids found in proteins are
- **(a)** α-amino acids. **(b)** β-amino acids.
- **(c)** γ-amino acids. **(d)** δ-amino acid.

6. At a pH of 7 amino acids are
- **(a)** neutral.
- **(b)** cationic due to the amino group.
- **(c)** anionic due to the acid group.
- **(d)** zwitter ionic due to both the amino and carboxylic acid groups being charge.

7. Identify the stable conjugate acid that is formed when addition of 2 mol of HCl takes place.



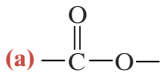
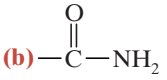
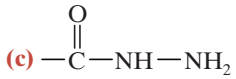
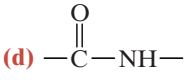
(a) 
(b) 
(c) 
(d) 

8. Protein is a polymer of
- **(a)** amino acid. **(b)** α-amino acid.
- **(c)** γ-amino acid. **(d)** β-amino acid.

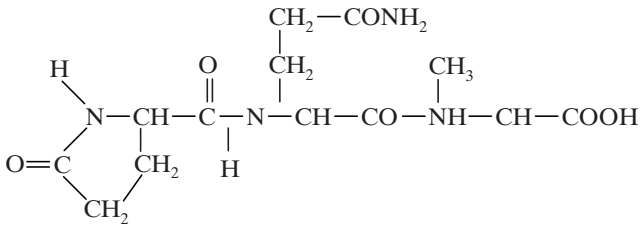
9. With the exception of gly, all amino acids are chiral. Those found in proteins all have which configuration?
- **(a)** D **(b)** L **(c)** Both **(d)** None

10. The isoelectric (or isoionic) point is the pH where the amino acid is
- **(a)** positively charged. **(b)** negatively charged.
- **(c)** neutral. **(d)** can't say.

11. Peptide linkage is

(a) 
(b) 
(c) 
(d) 

12.



Find the correct statement for the above compound
- **(a)** It is a tripeptide.
- **(b)** On complete acidic hydrolysis 3 amino acid of 2 different types obtained.
- **(c)** Does not react with 2,4-dinitrofluorobenzene.
- **(d)** All are correct.

13. Which of the following is the correct representation of L-amino acids?

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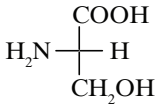
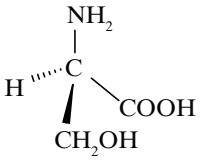
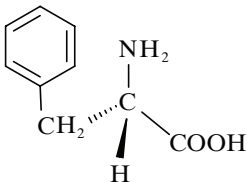
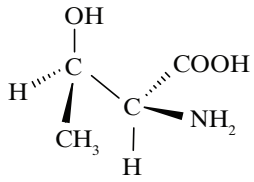
(a) 

(b) 

(c) 

(d) 

14. Which of the following statements regarding the isoelectric point is incorrect?

The isoelectric point is calculated for

(a) amino acids with neutral side chains by taking the average of pK_{a_1} and pK_{a_2}.

(b) amino acids with basic chains by taking the average of pK_{a_1} and pK_{a_2}.

(c) amino acids with acidic side chains by taking the average of pK_{a_1} and pK_{a_2}.

(d) None of these.

15. (At pH = 2) glycine exists as

(a) $H_3N^+—CH_2—COO^-$

(b) $H_3N^+—CH_2—COOH$

(c) $H_2N—CH_2—COOH$

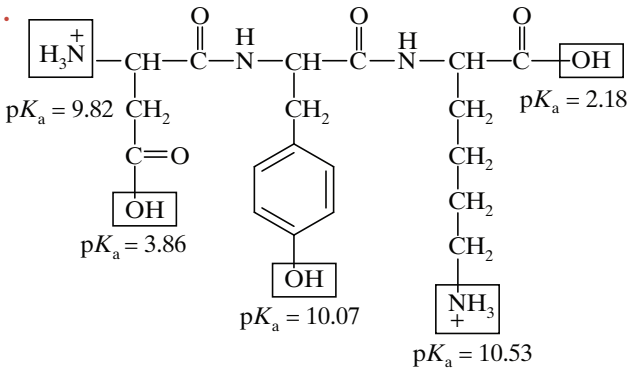
(d) $H_2N—CH_2—COO^-$

16. The pH value of a solution in which a polar amino acids does not migrate under the influence of electric field is called

(a) isoelectric point. **(b)** isoelectronic point.

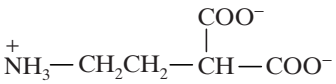
(c) neutralization point. **(d)** none.

Integer Type

1. 

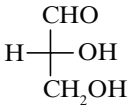
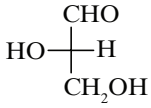
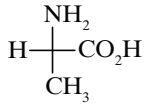
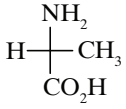
What is the net charge of the above compound at pH = 8?

2. How many acidic groups are present in the given amino acid?



Matrix Match Type

1.

Column I (Molecule)	Column II (Configuration)
(a) 	**(p)** *R*-(Rectus)
(b) 	**(q)** *S*-(Sinister)
(c) 	**(r)** D
(d) 	**(s)** L

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ANSWER KEY

Single Correct Choice Type

1. (d)	**2.** (c)	**3.** (b)	**4.** (d)	**5.** (a)
6. (d)	**7.** (c)	**8.** (b)	**9.** (b)	**10.** (c)
11. (d)	**12.** (d)	**13.** (a)	**14.** (c)	**15.** (b)
16. (a)				

Integer Type

1. (0) **2.** (2)

Matrix Match Type

1. a→(p, r); b→(q, s); c→(q, s); d→(p, r)

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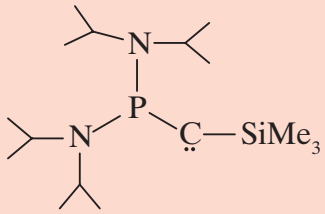
22

Carbene and Carbenoids



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22.2 | Existence of Carbenes
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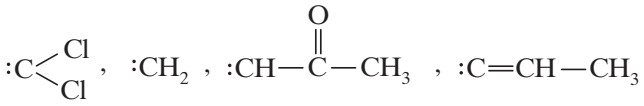
22.5 | Reactions of Carbenes
22.6 | Rearrangement in Carbenes

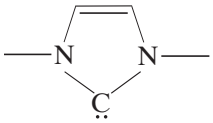
22.1 | INTRODUCTION

Carbenes are divalent carbon compounds. Carbon atoms of carbenes form only two bonds in their molecules with two unshared electrons which may be paired or unpaired. Carbenes are neutral species and not ionic. Some typical examples of carbenes are given below:

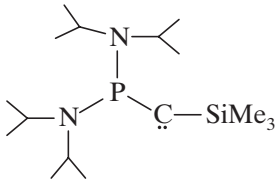


22.2 | EXISTENCE OF CARBENES

The experimental evidence for the existence of carbenes comes from some stable compounds given below.



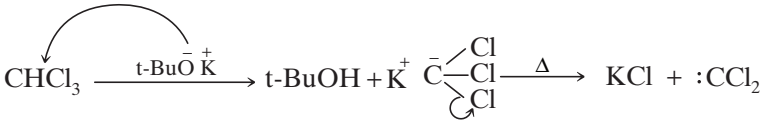
Stable; exists in form of colorless crystals

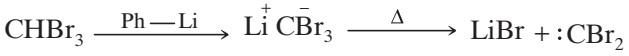


Stable; exists in form of red liquid

22.3 | FORMATION OF CARBENES

1. **By α-elimination or 1,1-elimination or E_α reaction:** α-elimination means removal of two atoms from the same atom. For example,





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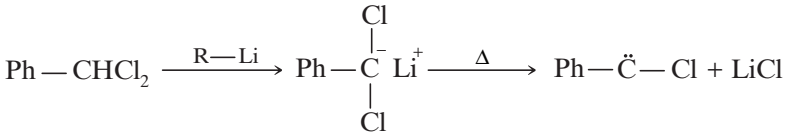
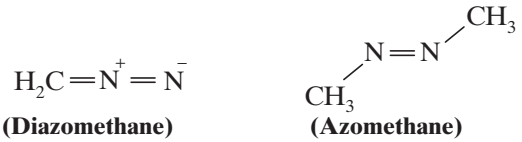
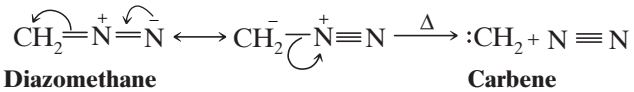


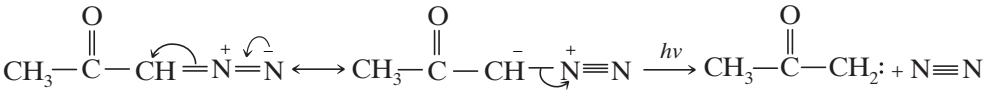
2. **From diazocompounds:** Diazo compounds serve as a good source for obtaining many carbenes. Diazo compounds generate carbene on photolysis or thermolysis. Do not confuse diazo compounds with azo compounds. The two classes of compounds differ in their structural arrangement as illustrated.



(Diazomethane) **(Azomethane)**

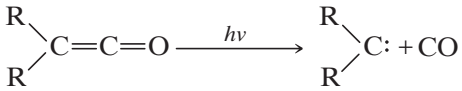


Diazomethane **Carbene**

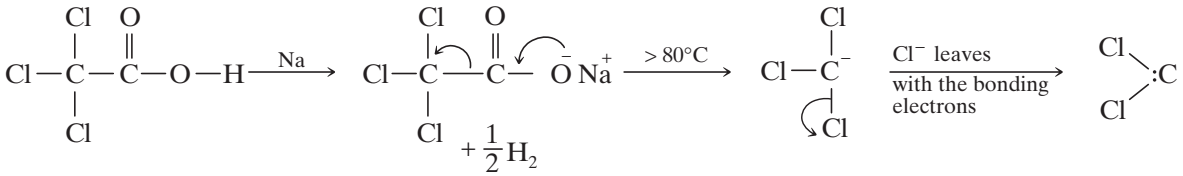


α-Diazoketone **Acetyle carbene**

3. **From ketenes:** Ketenes, which are structurally similar to diazoalkanes, also produce carbenes on photochemical decomposition.



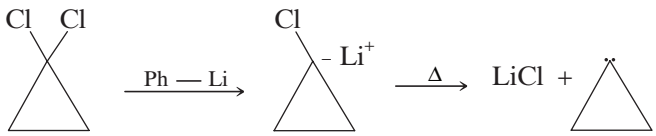
4. **From 1,1,1-trichloroethanoic acid:** This compound gives dichlorocarbene on heating in presence of sodium metal.



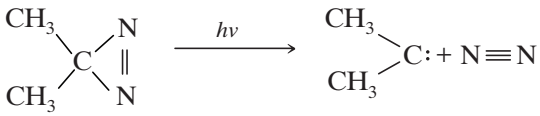
5. **From CBr_4:** CBr_4 generates carbene as follows:



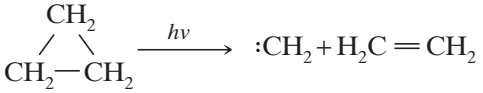
6. **From di-halo cyclopropanes**



7. **From diazirines:**



8. **From cycloeliminations:**



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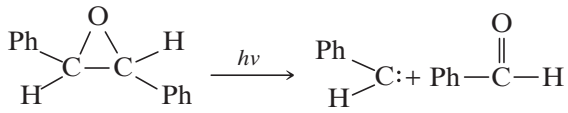
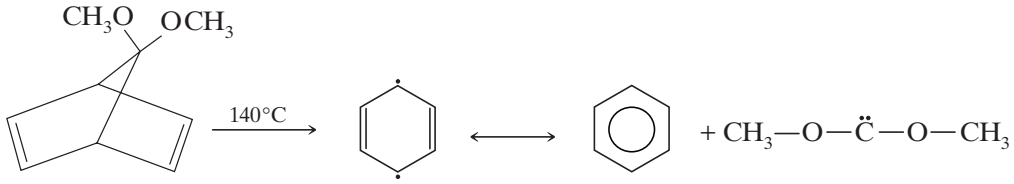
9. From oxiranes:



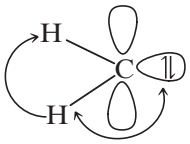
10. From *t*-norbornadienyl ketals: These compounds yield dialkenyl carbene on moderate heating.



22.4 | TYPES OF CARBENES

Carbenes can be classified into two types: Singlet and Triplet. This classification is based on the arrangement of two unshared electrons in the orbitals, as explained below.

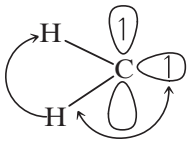
Singlet carbene



Smaller bond angle (100° – 110°)

Two unshared electrons are present in the same orbital, so they experience more repulsion

Triplet carbene



Bond angle (130° – 150°)

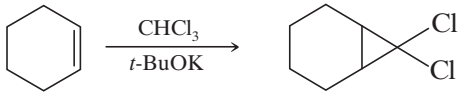
Only one unshared electron is present in each orbital. Therefore, less repulsion is there and bond angle increases

Carbon in sp^2 hybridized state

Most of the carbenes are stable in the triplet state because the energy to be gained by bringing down the electron in the *p* orbital into the sp^2 orbital is insufficient to overcome the increased repulsion existing between the two electrons when present in a single orbital.

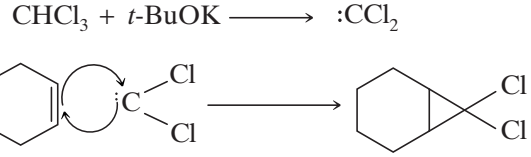
22.5 | REACTIONS OF CARBENES

22.5A Carbenes React with Cycloalkenes to Give Cyclopropanes



(59% yield)

This reaction is an important method of preparing cyclopropanes. The mechanism of the reaction is discussed below:



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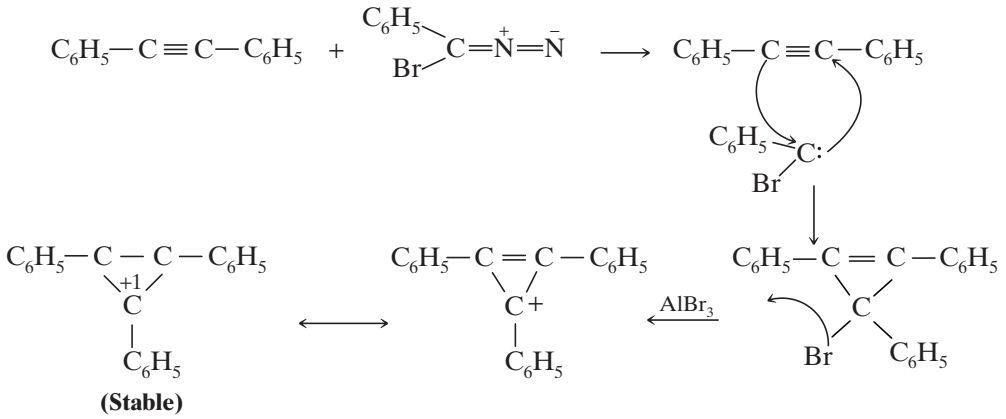
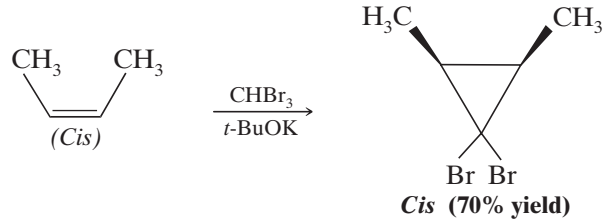
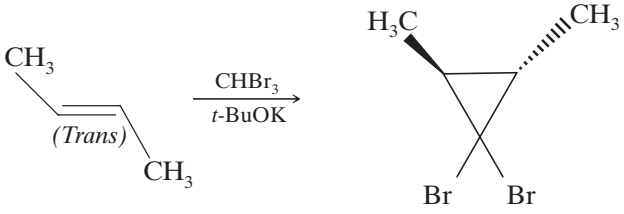
Some other examples:



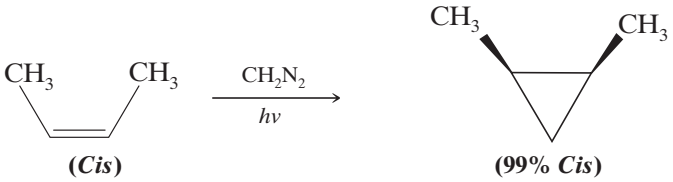
It may be noted that the reactions with alkenes are stereospecific. For example.



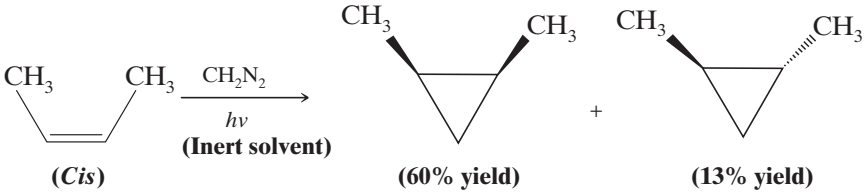
***Cis* (70% yield)**



***Trans* (80% yield)**

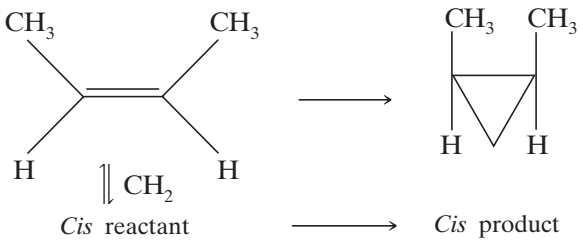


Stereospecific reaction (involves singlet carbene)



Stereoselective reaction (involves triplet carbene)

Mechanism of a reaction involving singlet carbene:



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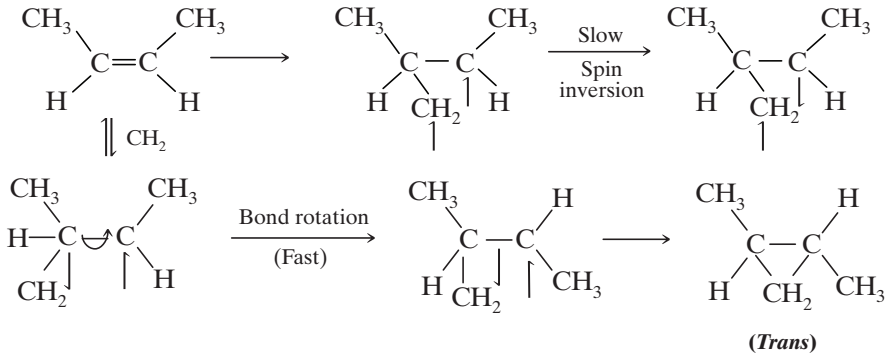
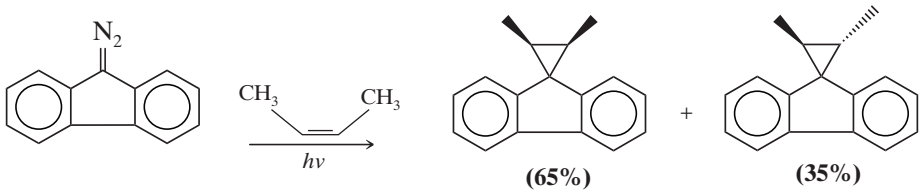
Mechanism of a reaction involving triplet carbene:



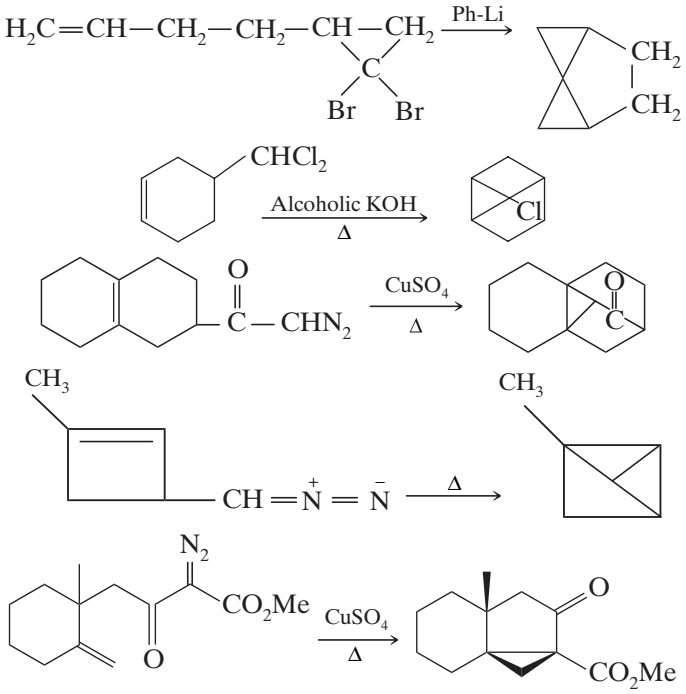
(*Trans*)

An important example involving a triplet carbene is as follows:



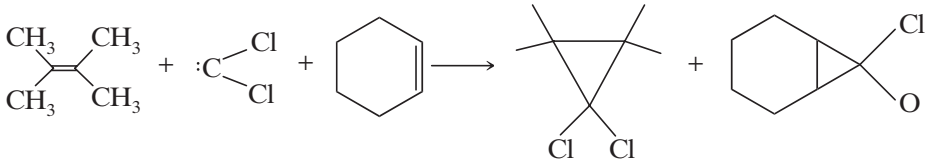
22.5B Intramolecular Addition of Carbenes to Double Bonds

The examples of this type of addition reactions are as follows:



22.5C Reactivities in Addition Reactions

1.



(a) (b) **Product ratio 22:1**

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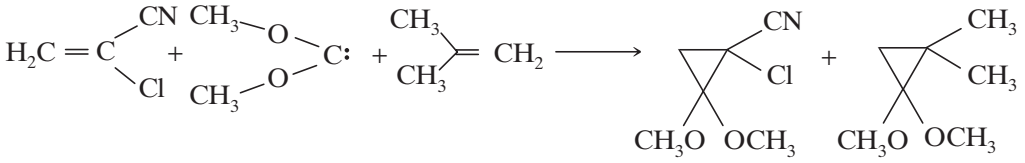
2.



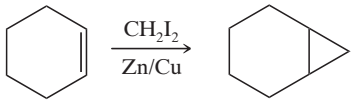
(c) **(d)** **(Product ratio is 44000:1)**

In reaction **(1)** the carbene : CCl_2 is an elcctrophile and it will react with the alkene that is more nucleophilic. Here, the alkene **(a)** is more nucleophilic than **(b)**; this justifies the ratio of the products as shown.

In reaction **(2)**, the carbene is nucleophilic due to the +M effect of $-OCH_3$. Therefore, it will attack the alkene that is more electrophilic. That is why alkene **(c)** is more reactive than **(d)**.

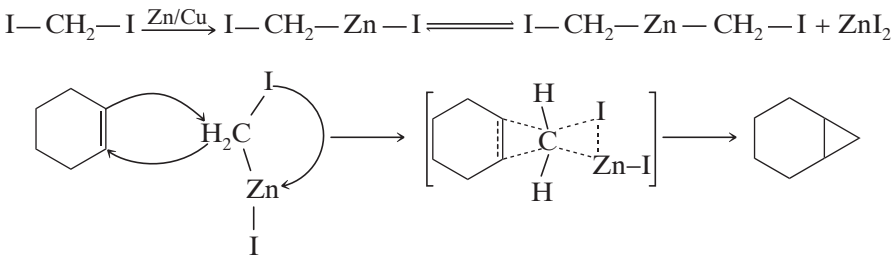
22.5D Simmons–Smith Reaction

This reaction is also used for the preparation of cyclopropane derivatives.

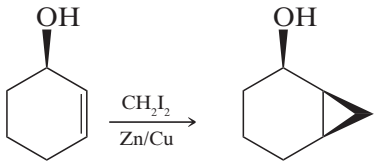


(86–92% yield)

The mechanism of the reaction is as follows:

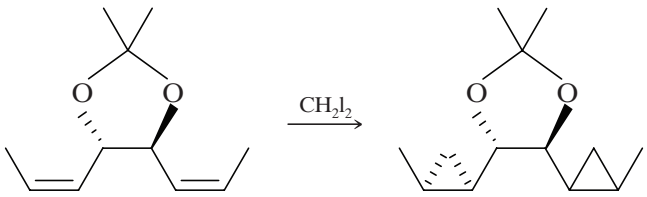


It was observed that reaction with an allylic alcohol is about 100 times faster than that with the unfunctionalized alkene equivalents. For example



(63% yield)

Another interesting example of this reaction is



It may be noted here that this reaction does not involve a free carbene; zinc remains associated with the carbon atom during the reaction.

A rather vague term *carbenoids* is used to refer to the molecules in which all the carbons are tetravalent, but which have properties similar to those of carbenes. Carbenoids have carbon atoms that are simultaneously bonded to metal as well as halogen atoms.

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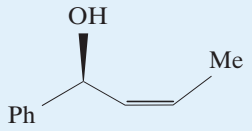
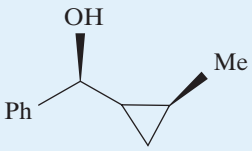
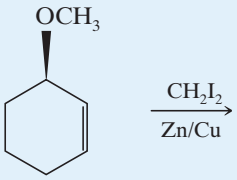
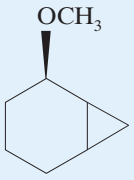
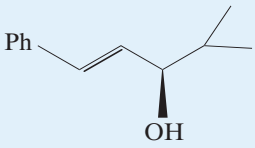
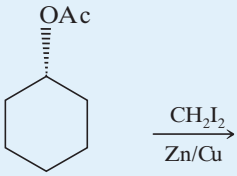
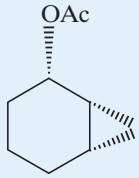
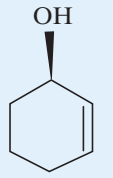
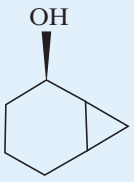
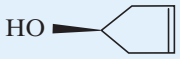
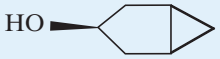
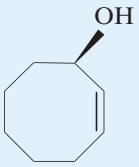
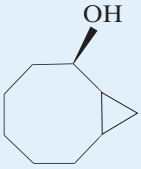
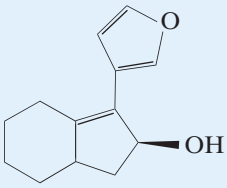
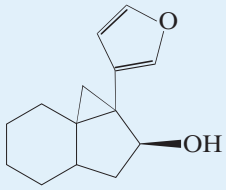
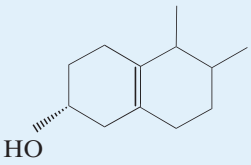
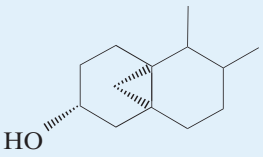
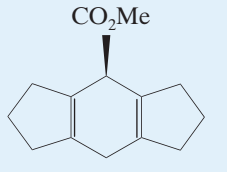
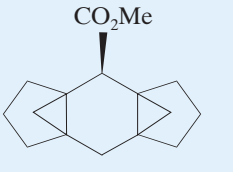
Stereoselective cyclopropanation of a variety of alcohols is summarized in Table 22.1.

Table 22.1 Stereoselective Cyclopropanation of a Variety of Alcohols

Substrate	Major Product	Substrate	Major Product
			
			
			
			
			

22.5E Arndt–Eistert Reaction

Arndt–Eistert reaction is used to increase the number of —CH_2 (i.e., methylene) units in carboxylic acids. For this purpose, first, the carboxylic acid is converted into an aryl chloride derivative and then into a diazomethyl ketone. Methylene group present in diazomethylene acts as the nucleophilic site because of its resonance structure.

Equilibrium mixture of diazonium ketone and HCl is produced by acylation of methylene carbon. If hydrogen chloride is not neutralized by a base, then this mixture reacts further to give chloromethyl ketone and nitrogen. A relatively stable diazoketone is obtained if the HCl is neutralized as it is formed.

Diazomethane itself may function as a base; and the course of a given reaction is established from the manner in which reactants are combined. Evolution of nitrogen is observed when an ethereal solution of diazomethane is slowly added to a warm solution of the acid chloride, chloromethyl ketone being obtained as the chief product. If one equivalent of CH_2N_2 is used then reaction shifts in backward direction so that excess of diazomethane and a cold solution of the acid chloride are added slowly in cold ethereal solution, nitrogen evolution is again observed; however, in that case two equivalents of diazomethane are consumed. In this reaction, the products are methyl chloride [CH_3Cl (g)] and diazoketone which are obtained from the CH_2N_2 and HCl.

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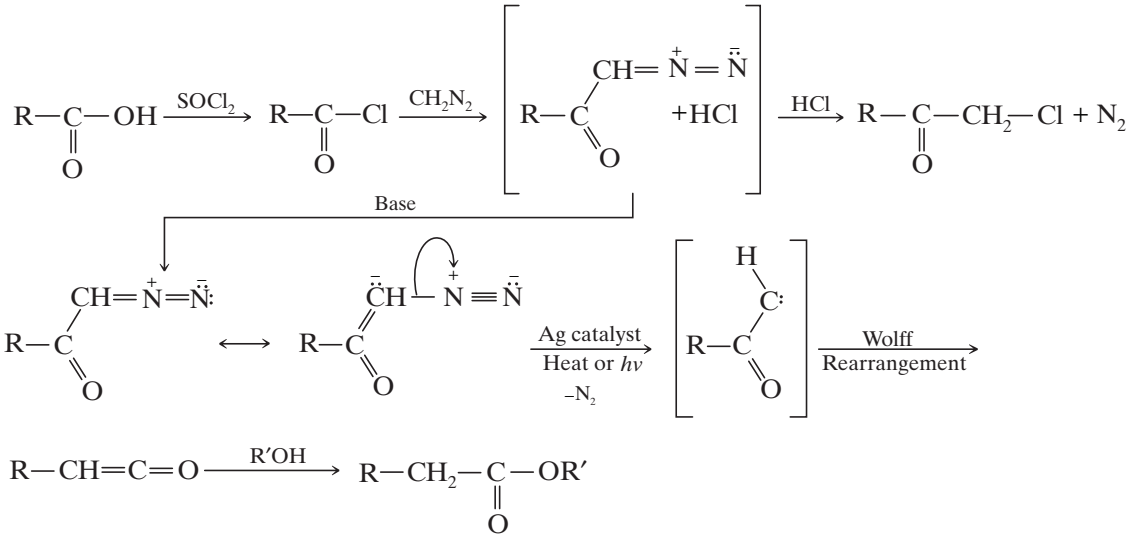
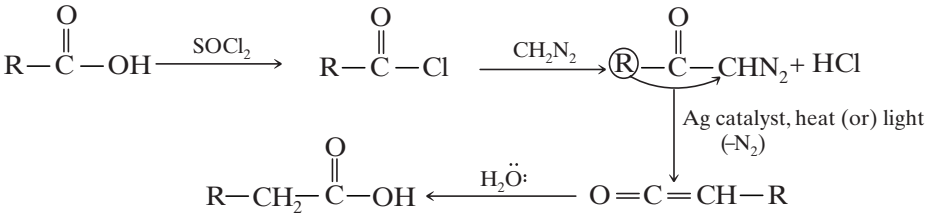
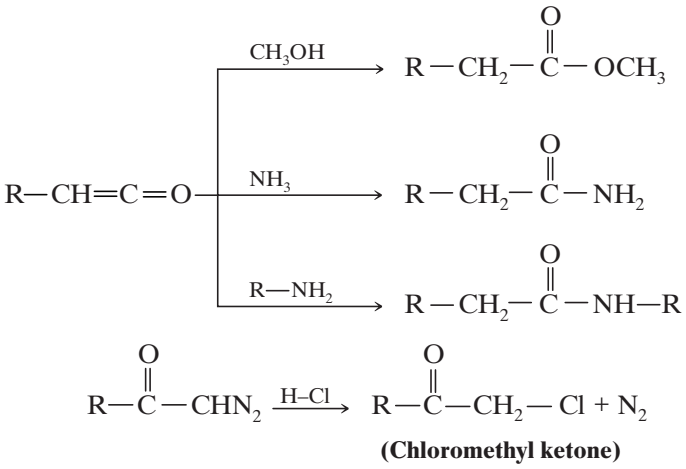
Further, diazoketone is decomposed in the presence of silver oxide or silver nitrate together with heat or light. After rearrangement, the product (i.e., ketone) quickly reacts with any hydroxylic or amine reactant (i.e., HOH, R′OH, R''_2NH, $R'—NH_2$, NH_3, etc.)



Mechanism:



If H_2O is replaced by CH_3OH, NH_3 and $R—NH_2$ the following products will be obtained:



(Chloromethyl ketone)

HCl is neutralized by CH_2N_2 as follows:

$$H—Cl + CH_2N_2 \longrightarrow CH_3—Cl + N_2$$

The resonating structures of diazomethane are as follows:

$$\bar{C}H_2—\overset{+}{N} \equiv N \longleftrightarrow H_2C=\overset{+}{N}=\bar{N}$$

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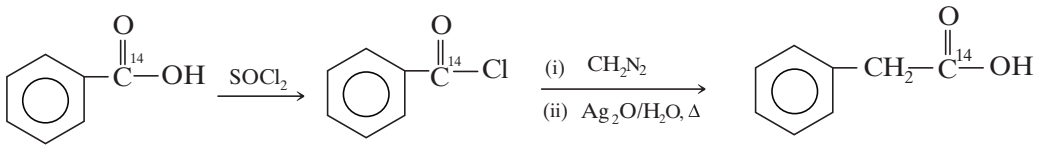
Some other examples of Arndt–Eistert reaction are as follows:

1.



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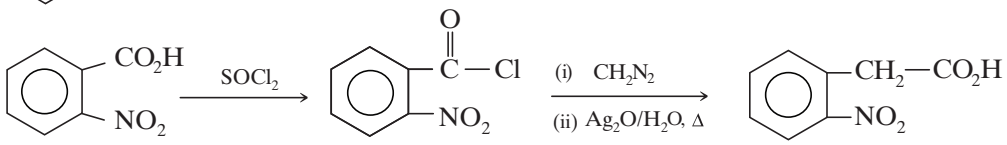

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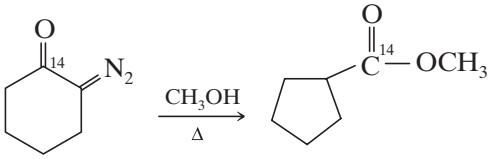

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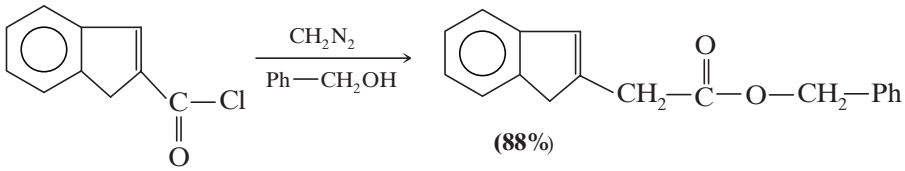
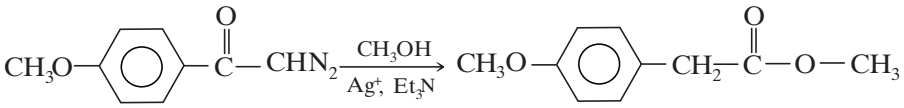


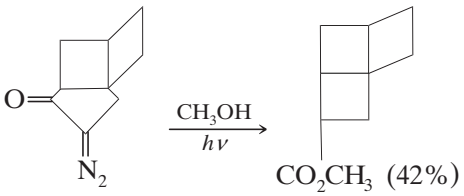
(88%)

5.



(84%)

6.



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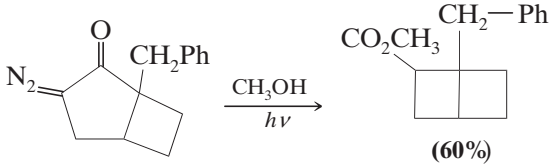
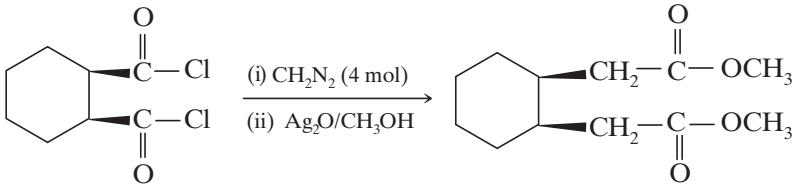


(60%)

8.



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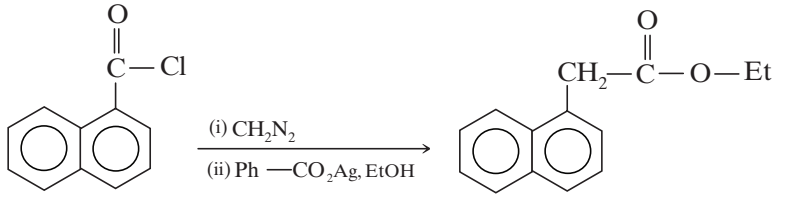
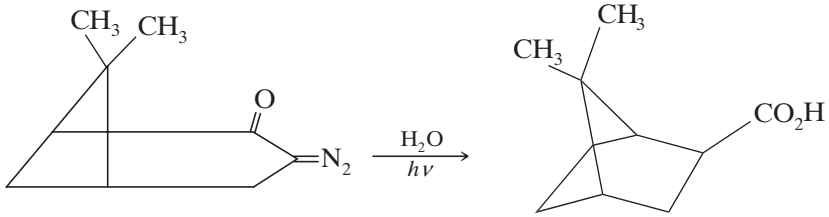


(89–90%)

10.



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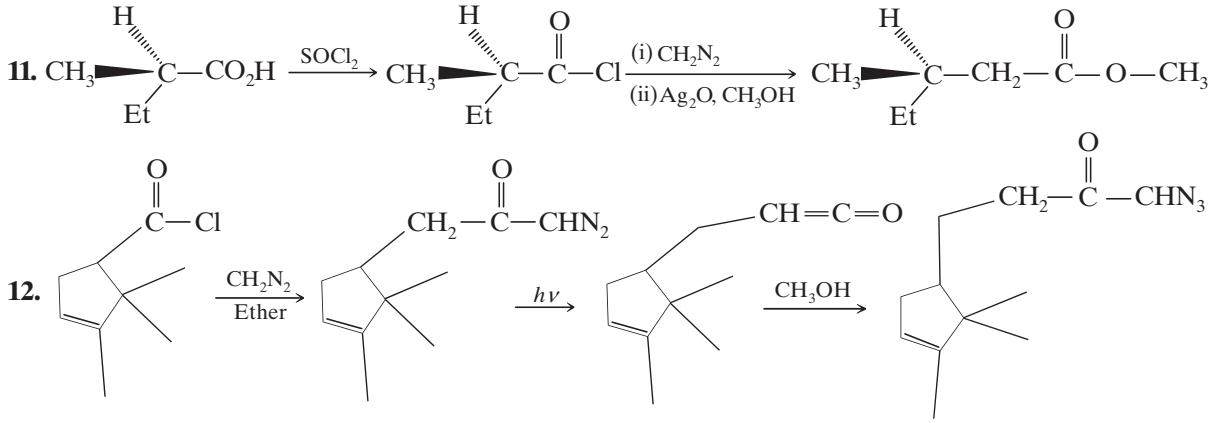
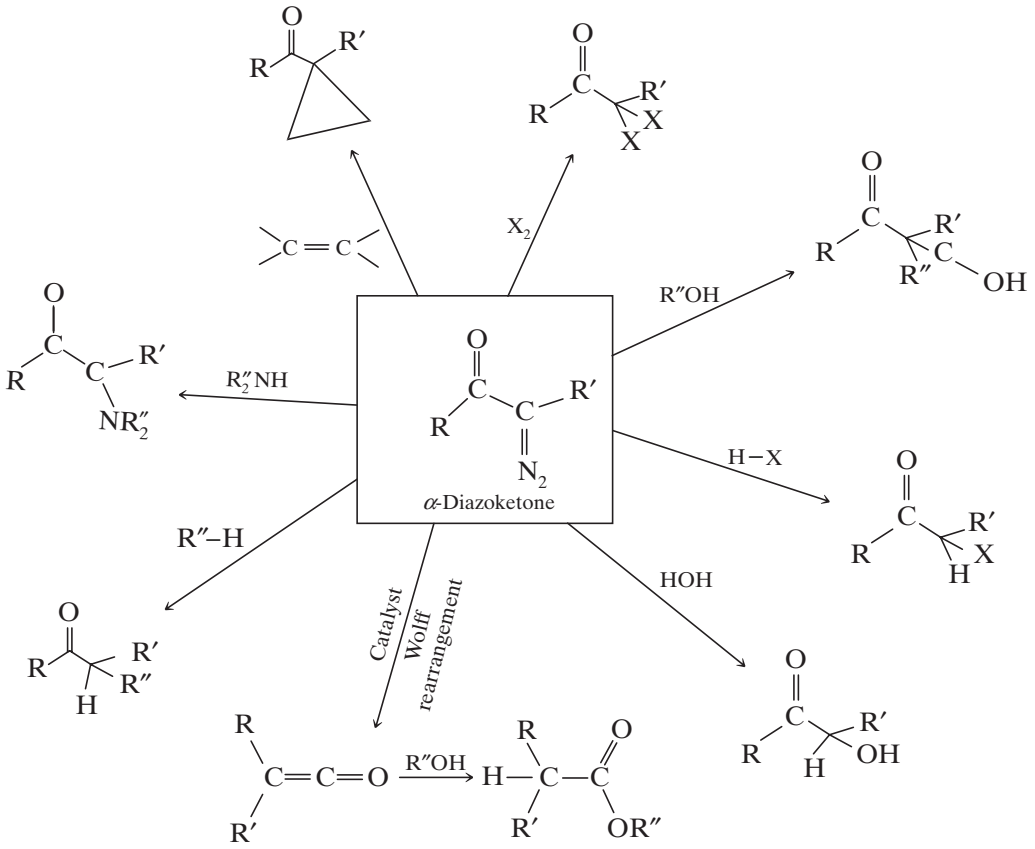


22.5F Reactions of α-Diazoketone

The reactions are shown below:



22.5G Reimer–Tiemann Reaction

The Reimer–Tiemann reaction was found in the year 1876 by two German chemists – Karl Reimer and Ferdinand Tiemann. They isolated and identified hydroxyaldehydes as the chief reaction products of phenol and chloroform in alkaline medium. This reaction was further studied in 1884 by von Auwers, who discovered chlorine-containing cyclohexadienones as byproducts in the formylation of alkylphenols. The ring–expansion products, namely, chloropyridines, were first noted by Ciarnician when he subjected pyrroles to Reimer–Tiemann reaction conditions.

Almost half a century later, Woodward recognized that the conversion of an alkylphenol to a substituted cyclohexadienone led to the synthesis of terpenes and steroids containing an angular methyl group. Although this method

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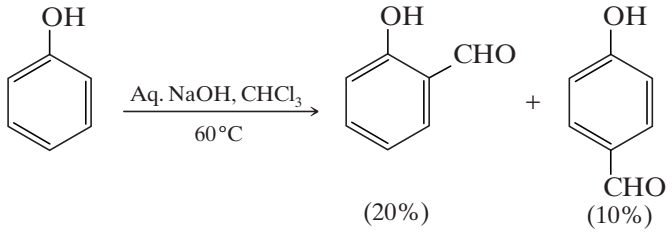
failed as a useful approach for the synthesis of steroids, an A/B *trans*-fused hexahydrophenanthrene was synthesized using Reimer–Tiemann reaction.

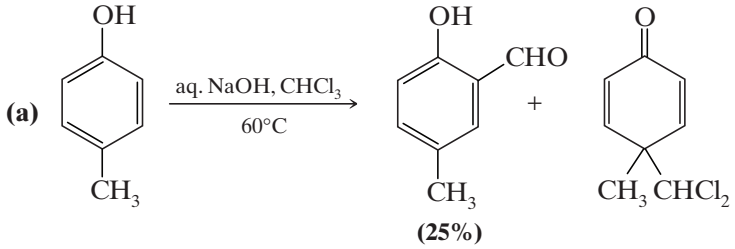
The Reimer–Tiemann reaction can be classified into a normal and an abnormal transformation depending on the reaction products obtained.

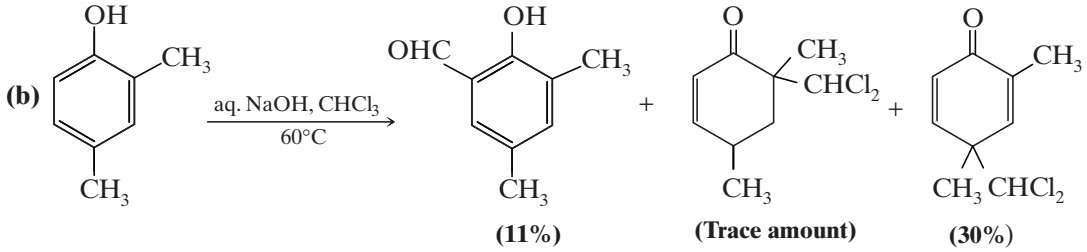
Normal Reimer–Tiemann Reaction: A normal Reimer–Tiemann reaction is the one in which a phenol (or an electron-rich aromatic compound such as pyrrole) yields one or more aldehydes when treated with chloroform and alkali. For example,



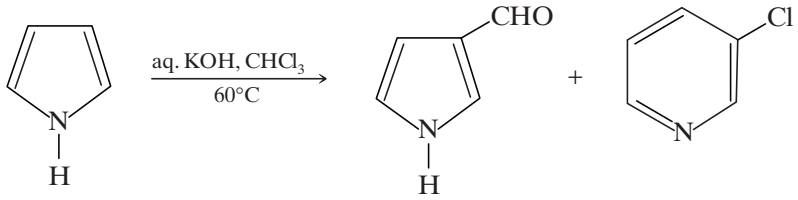
Abnormal Reimer–Tiemann Reaction: In an abnonnal Reimer–Tiemann reaction, the product can further transfonn into cyclohexadienones and ring-expansion products. Thus,

1. When *ortho*- or *para*-substituted phenols undergo Reimer–Tiemann reaction, 2,2- or 4, 4-disubstituted cyclohexadienones may be obtained in addition to the normal products. Various alkylphenols, alkylnaphthols and tetralols are found to be converted into cyclohexadienones, while some alkylpyrroles get converted to pyrrolines in this way, reducing thereby the yield of the normal product.





2. Various five-membered rings yield ring–expansion products in addition to the normal products in Reimer–Tiemann reaction conditions.



In addition to aromatic aldehydes, cyclohexadienones, pyrrolines and ring-expansion products, various other products have also been noted, isolated and identified in a few cases.

Mechanism: Hine, followed by von Doering, Skell. Parham Robinson, and others clearly established that dihalocarbenes were formed when a haloform was treated with an alkali. As such, direct nucleophilic substitution of the phenolate carbanion on chloroform is ruled out. The fact that dichlorocarbene was the reactive intermediate led to the formulation of a rational mechanism. It is convenient to consider the two reactions, namely, the hydrolysis of chloroform and the reaction of a phenol with dichlorocarbene separately.

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$$CHCl_3 + NaOH \underset{}{\overset{\text{Fast}}{\rightleftharpoons}} \overset{+}{N}a\overset{-}{C}Cl_3 + H_2O$$

$$\overset{-}{C}Cl_3 \xrightarrow{\text{Slow}} :CCl_2 + Cl^-$$

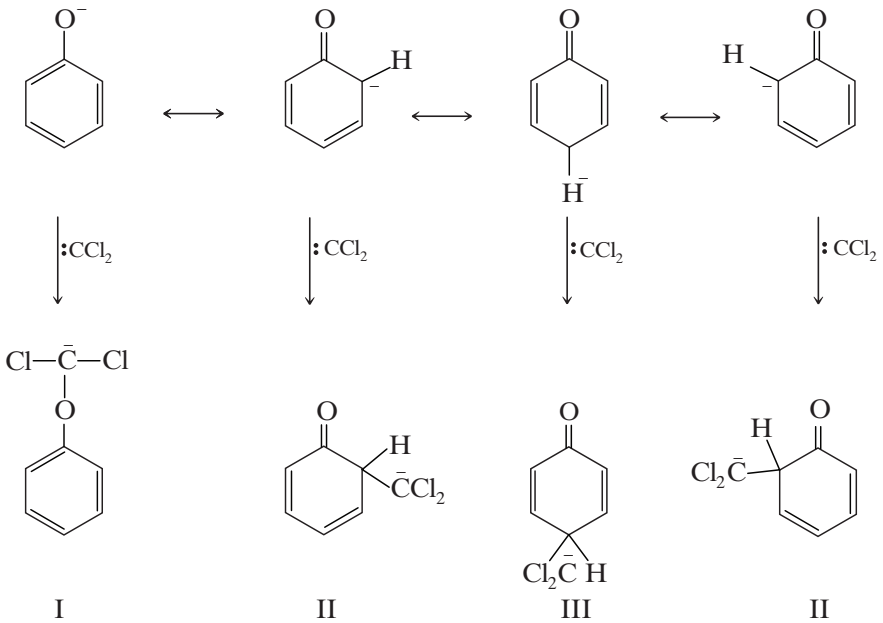
$$:CCl_2 + H_2O \longrightarrow \left[H_2\overset{+}{O}-\overset{-}{C}Cl_2\right] \longrightarrow HOCHCl_2$$

$$HOCHCl_2 + 2NaOH \longrightarrow CO + 2NaCl + 2H_2O$$

$$CO + NaOH \xrightarrow{\text{Slow}} \overset{+}{N}a\overset{-}{O}\overset{O}{\overset{\|}{C}}H_3$$

The first reaction is the rate determining step and involves the generation of carbene by the unimolecular elimination of a chloride ion from the trichloromethyl anion. Dichlorocarbene reacts quickly with water to generate carbon monoxide, which then slowly hydrolyzes into sodium formate in the alkaline medium. It seems that the last two steps appear unimportant to the main reaction, which involves bond formation between the carbene and the phenol. However, the hydrolysis of carbene consumes alkali and competes with the formylation reaction. The low conversion and subsequent recovery of starting phenol was noticed by several investigators; and this is often due to the fact that most, if not all, of the alkali becomes neutralized as the reaction proceeds. Unfortunately, only limited use can be made of the seemingly ideal phase-transfer conditions under which this reaction might proceed, since the phenolic substrate remains in the aqueous alkaline layer while the carbene is largely present in the chloroform layer. The reaction of the dihalocarbene with the phenolate ion comprises the product forming reaction.

Reaction of Dihalocarbene with Phenoxide Anion: The electrophilic attack of dihalocarbene on each of the resonance forms of the phenoxide anion yields the anion having resonance forms I, II and III as shown below:



The O-alkylation product, that is, the anion (I), either decomposes or reacts further to form small amounts of orthoformic esters.

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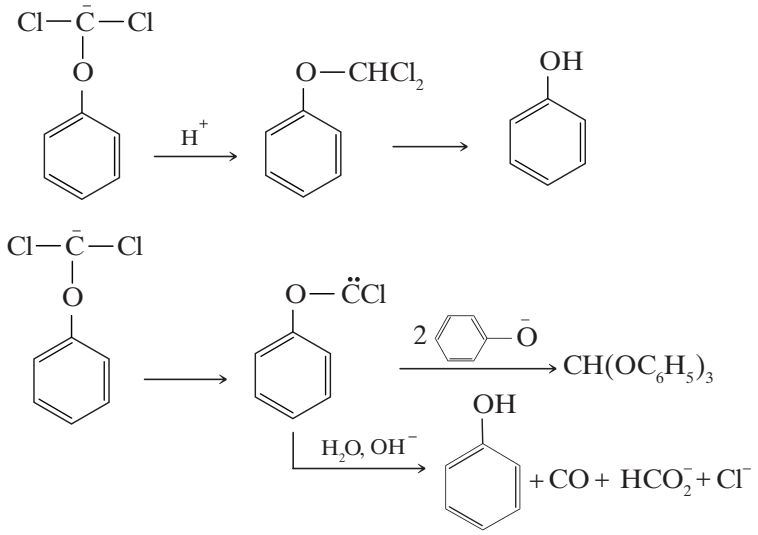
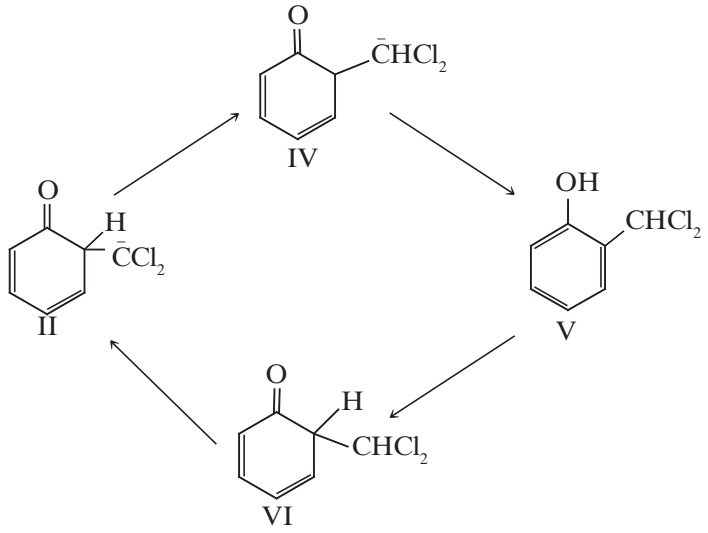
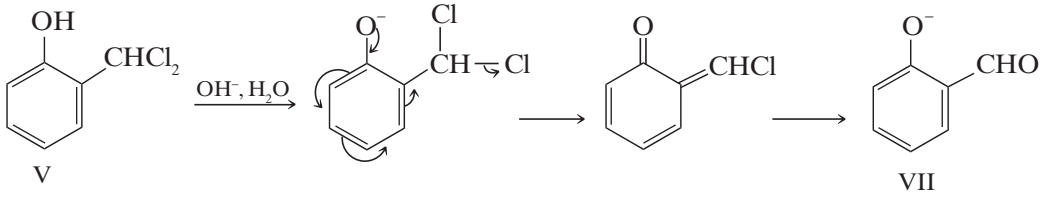


The detailed transformation of the anions (II) and (III) (only for the *ortho*-substituted phenoxide anion) to the corresponding hyroxyaldehydes is still not very clear.



In the above reaction, neither the anion (IV) nor one of the neutral products (V) and (VI) (i.e., 2-dichloromethyl-3,5-cylohexadienone and 2-dichloromethylphenol), have ever been isolated from a Reimer–Tiemann reaction mixture despite claims to the contrary. The 1,2-proton shift of the anion (II) to the anion (IV) appears unlikely considering Hückel and orbital-symmetry calculations. Tritium isotope experiments show complete transfer of the isotope from tritium oxide to the formyl group. There is no proton exchange between water and the aldehydic proton of salicylaldehyde under the reaction conditions. These experiments favor a mechanism involving the neutral intermediate (V). Thus, the elimination sequence suggested below seems more reasonable.



In the above reaction, the neutral intermediate (V) is hydrolyzed to the aldehyde (VII) in alkaline medium. Omitting the details of the intermediate steps, an explanation for the fact that *ortho*- and *para*-hydroxybenzal halides

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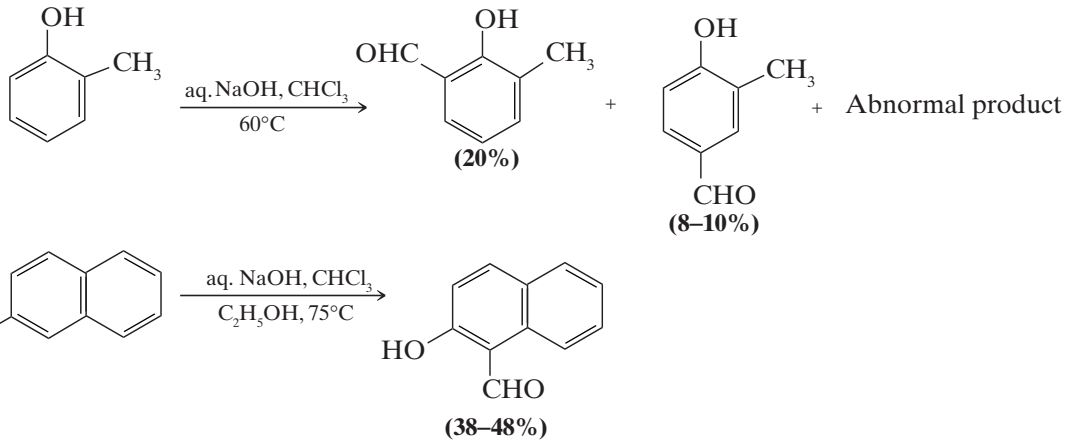
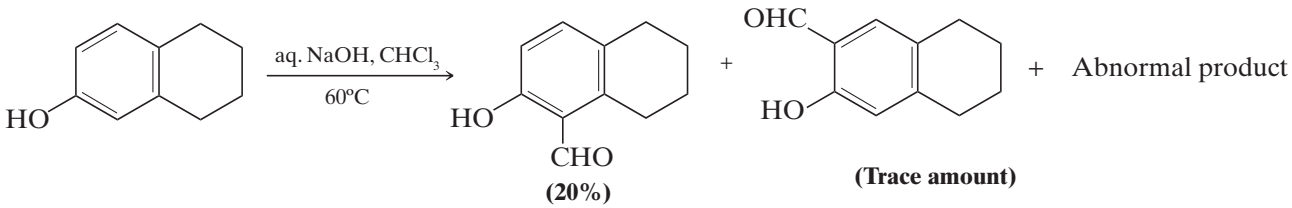
(such as V) have not been isolated, whereas benzal halides without *ortho*- or *para*-hydroxy functions are isolable is as follows. It is easily seen from the above reaction that there exists a driving force which clearly aids the decomposition of (V) into the aldehyde. It is important to note that the abnormal products are not tautomeric with their phenols because they lack the required proton on the α- or γ carbon atom. The scope and limitations of Reimer–Tiemann reaction are as follows:

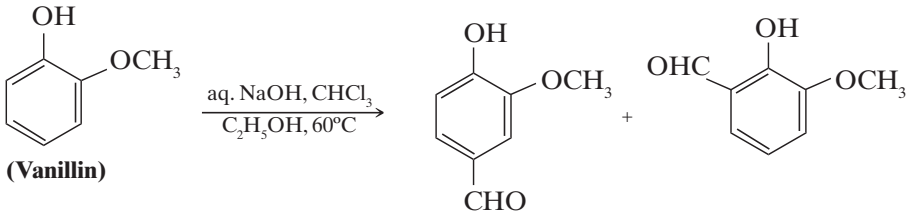
1. **Phenols and alkyl phenols:** Almost all phenols and alkyl phenols on treatment with chloroform and a base give *ortho*- and/or *para*-substituted aldehydes. However, the consistent exceptions are 2,4,6-trialkylphenols, which form alkyl dichloromethylcyclohexadienones.



It has been reported that traces of hydroxyaldehydes are formed when 1-naphthol is treated with chloroform and a base. Earlier studies have also mentioned the failure of this phenol to yield Reimer–Tiemann reaction products. Another report by the same workers said that, a trace (2%) of 2-hydroxy-4-naphthalenecarboxaldehyde, the *meta* product, is formed from 2-naphthol. It has been proven conclusively that the major product from the formylation of 2-hydroxy-5,6,7,8-tetrahydronaphthalene is 2-hydroxy-5,6,7,8-tetrahydro-1-naphthalenecarboxaldehyde and trace amount of 3-naphthalenecarboxaldehyde are also formed.



2. **Hydroxy- and alkoxyphenols:** Catechol, resorcinol and hydroquinone as well as their monomethyl ethers have been formylated successfully. In the reaction of 3-methoxyphenol with chloroform and aqueous alkali, 2-hyroxy-6-methoxybenzaldehyde has never been isolated, although it is one of the possible products. The evidence is still in question for the formation of dialdehydes in the Reimer–Tiemann reaction of resorcinol and resorcinol monomethyl ether. The yield of vanillin from guaiacol is said to be affected favorably on addition of ethanol.



3. **Carboxy and sulfonic acid substituted phenols:** As per the accepted mechanism (electrophilic carbene attack on the phenolate anion) of the Reimer–Tiemann reaction, it is not surprising that phenols containing electron-withdrawing groups furnish hydroxyaldehydes in lower yields. Formylation of salicyclic acid, one of the earliest

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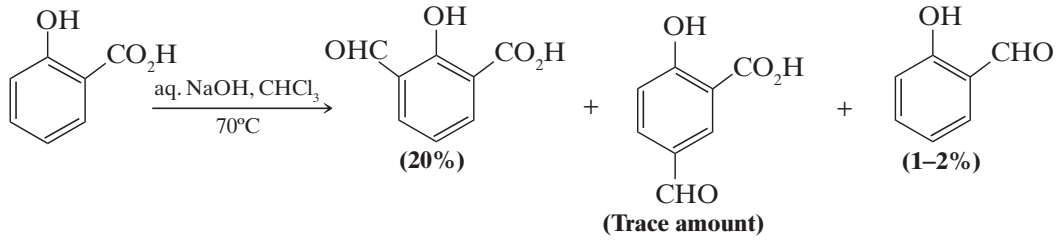
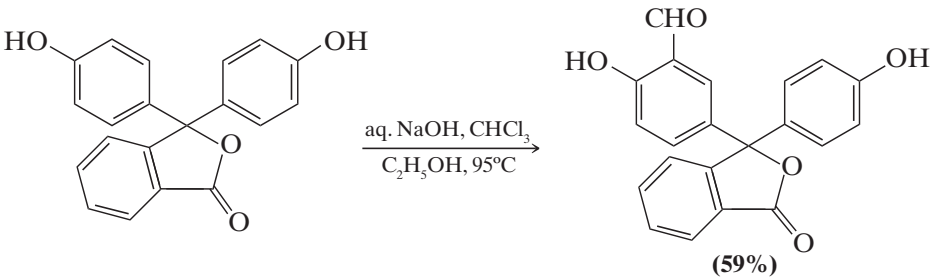
Reimer–Tiemann reactions, yields hydroxyaldehydes lacking the carboxyl group in addition to the expected products.

One possible mechanism for this transformation is by attack of dichlorocarbene at the 1 position of the salicylate dianion followed by decarboxylation of the resulting dienone intermediate. Even two carboxyl groups do not prevent nuclear formylation; both 4- and 5-hydroxyisophthalic acids yield the corresponding aldehydes. In a series of patents, the successful formylation of naphtholmonosulfonic acid and naphtholdisulfonic acid has been reported; however, details of analytical data, yields or structure proofs are not available for these products.

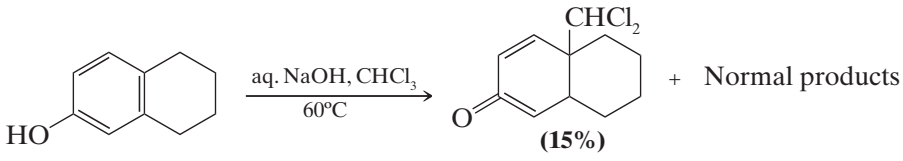


4. **Heterocyclic phenols:** The product from phenolphthalein is obtained in high yields.

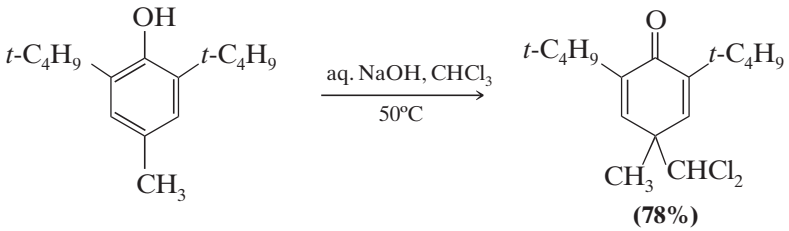


5. **Abnormal products:** Appropriately substituted phenols subjected to Reimer–Tiemann reaction conditions are transformed into cyclohexadienones. The hyroxyaldehydes are called *normal* products, while the dihalomethyl cyclohexadienones and ring–expansion compounds are called *abnormal* products, an increasing number of high-yield abnormal reactions have been reported in the literature. Several aspects of the abnormal reactions have contributed to their present use. The reaction with certain alkylphenols leads to non-aromatic products under alkaline conditions. The introduction of potential *gem*-dialkyl groups or an angular methyl group via the abnormal reaction has attracted interest in steroid and terpene synthesis. Many abnormal products are formed in good to excellent yields, in contrast to the yields of normal products.

6. **Cyclohexadienones and related non-aromatics:** The conversion of appropriately substituted alkyl (or aryl) phenols, pyrroles and indoles into angularly alkylated cyclohexadienones, pyrrolines and indolines is well known. A classic example is the transformation of 2-hydroxy-5,6,7,8-tetrahydronaphthalene, which is of potential use in steroid synthesis.



The examples of the reactions that proceed in high yield with and without regio-selectivity are shown below.



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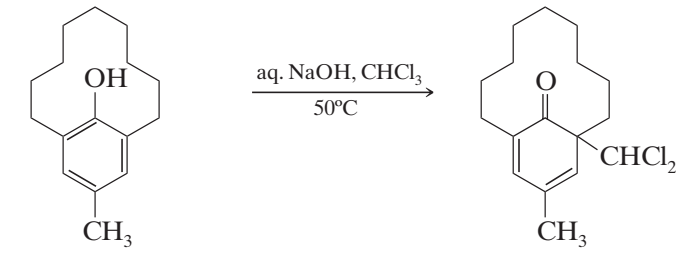
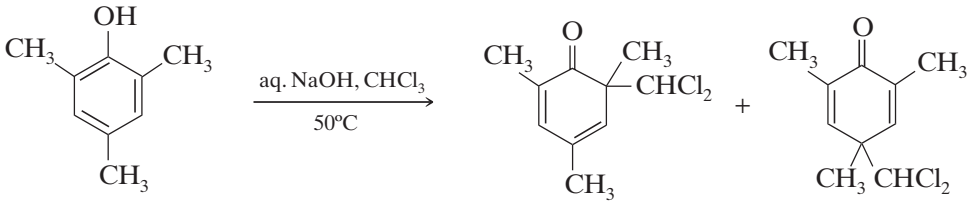
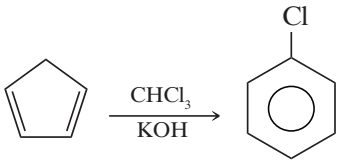


(76%)



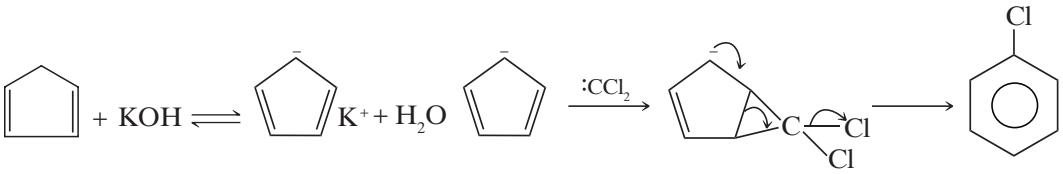
(Total yield is 67–77%)

Another peculiar reaction is



This reaction proceeds as follows:

$$CHCl_3 + KOH \rightleftharpoons :CCl_2 + KCl + H_2O$$



Some more similar examples are given below:

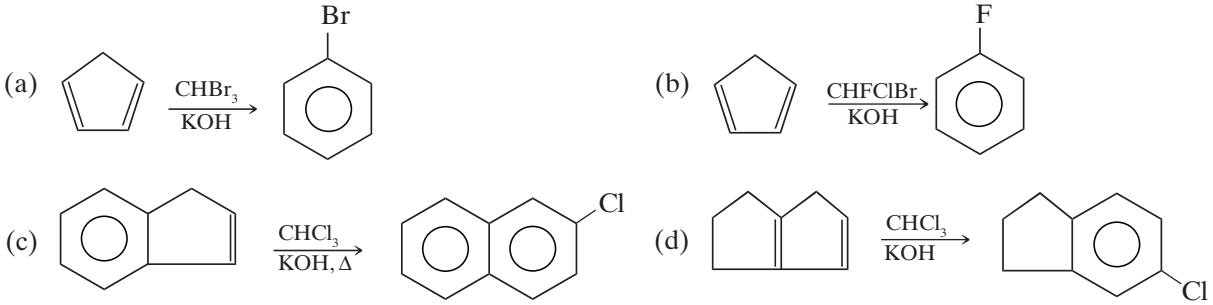


Table 22.2 Summarization of the formylation of phenols and alkylphenols is given in Table 22.2.

Table 22.2 Formylation of Phenols and Alkylphenols

Number of Carbon Atoms	Substrate	Product(s) with Yield(s) (%)
6	Phenol	2-Hydroxybenzaldehyde (20), 4-Hydroxybenzaldehyde (10)
7	2-Methylphenol (*o*-cresol)	2-Hydroxy-3-methylbenzaldehyde (20), 4-Hydroxy-3-methylbenzaldehyde (8)
	3-Methylphenol (*m*-cresol)	2-Hydroxy-4-methylbenzaldehyde (—), 2-Hydroxy-6-methylbenzaldehyde (20), 4-Hydroxy-2-methylbenzaldehyde (8)

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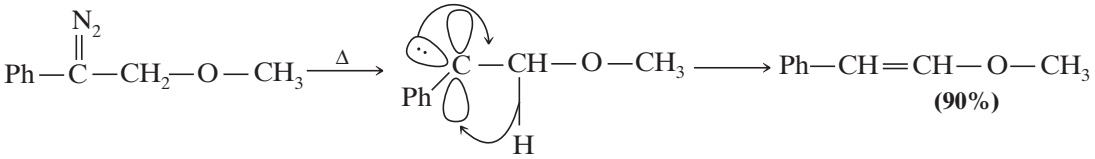
Table 22.2 Continued

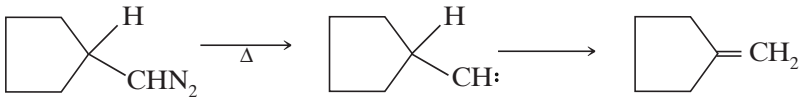
Number of Carbon Atoms	Substrate	Product(s) with Yield(s) (%)
	4-Methylphenol (*p*-cresol)	2-Hydroxy-4-methylbenzaldehyde (25)
8	2,4-Dimethylphenol	3,5-Dimehtyl-2-hydroxybenzaldehyde (11)
	2,5-Dimethylphenol	3,6-Dimethyl-2-hydroxybenzaldehyde (—), 2,5-Dimethyl-4-hydroxybenzaldehyde (—)
	3,4-Dimethylphenol	2,3-Dimethyl-6-hydroxybenzaldehyde (—), 3,4-Dimethyl-6-hydroxybenzaldehyde (—)
	3,5-Dimethylphenol	4,6-Dimethyl-2-hydroxybenzaldehyde (—), 2,6-Dimethyl-4-hydroxybenzaldehyde (—)
9	2,4,5-Trimethylphenol	2-Hydroxy-3,5,6-trimethylbenzaldehyde (5)
10	2-Methyl-5-*i*-propylphenol	2-Hydroxy-3-methyl-6-*i*-propylbenzaldehyde (—), 4-Hydroxy-3-methyl-6-*i*-propylbenzaldehyde (—)
	5-Methyl-2-*i*-propylphenol	2-Hydroxy-6-methyl-3-*i*-propylbenzaldehyde (17), 4-Hydroxy-6-methyl-3-*i*-propylbenzaldehyde (11)
	4-*i*-Butylphenol	5-*i*-Butyl-2-hydroxybenzaldehyde (—)
	4-*t*-Butylphenol	5-*t*-Butyl-2-hydroxybenzaldehyde (—)
11	4-*i*-Amylphenol	5-*i*-Amyl-2-hydroxybenzaldehyde (—)
12	4-Phenylphenol	2-Hydroxy-5-phenylbenzaldehyde (—)
13	4-Benzylphenol	2-Hydroxy-5-benzylbenzaldehyde (—)

22.6 | REARRANGEMENT IN CARBENES

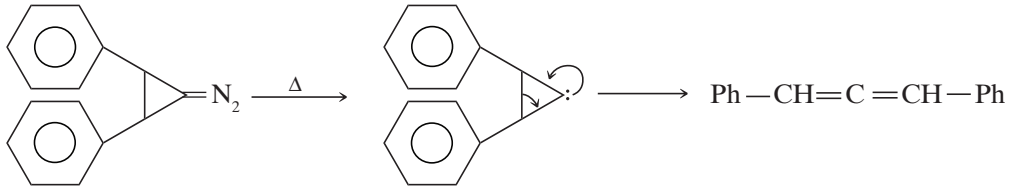
Activation energy for hydrogen migration in alkyl carbene appears to be only about 1 kcal/mol, and 1,2-migration of hydrogen occurs extremely easily in singlet carbene.

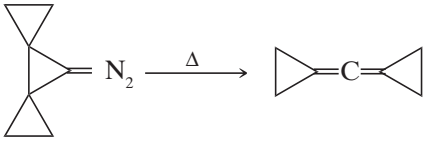






Hydrogen migration in carbene is so rapid that intermolecular reaction of the carbene cannot compete with the rearrangement reaction of carbene into alkene. Hydrogen migration in three-membered ring carbene would yield highly strained double bonds system. Therefore, three-membered ring typically undergoes ring opening reaction to form allenes. For example,





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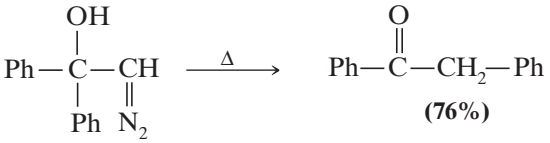
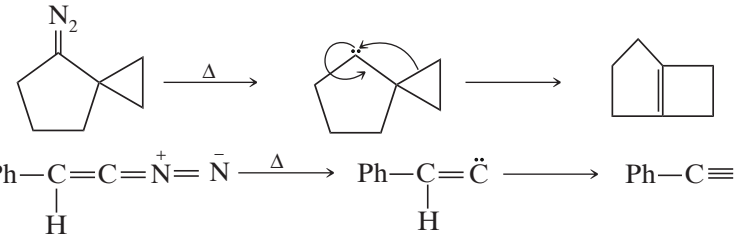
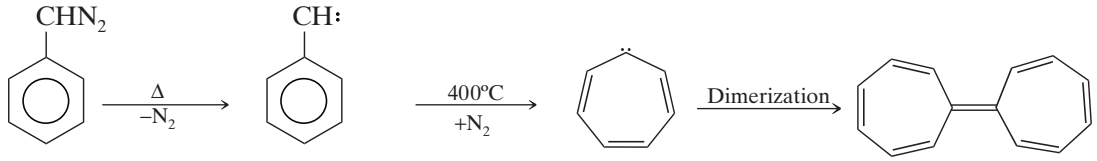
Alkyl group migration takes place when there exists a strained ring or there is formation of a ketone.



(76%)



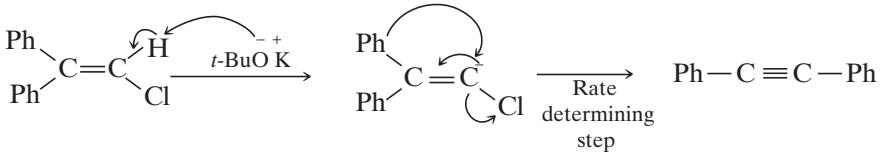
Aryl carbene can undergo rearrangement via a complicated mechanism.



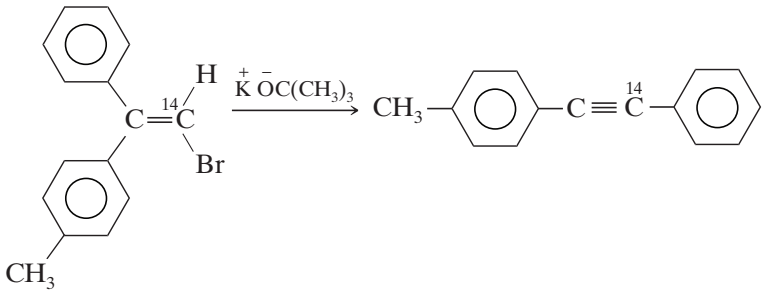
(Aromatic)

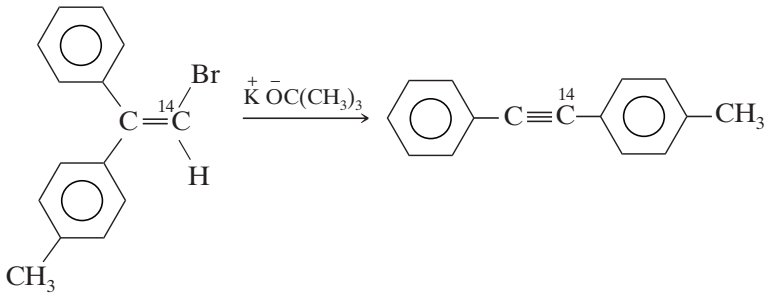
22.6A Fritsch Reaction

The reaction in which 1-halo-2,2-diphenylether reacts with a strong base to form an alkyne is known as Fritsch reaction. For example,



Orientation is important in this reaction, that is, the group opposite to the leaving group will migrate due to less steric hindrance. For example,





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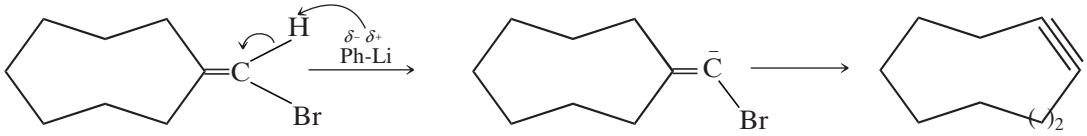
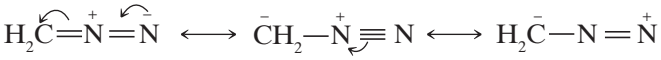
The reaction of 2,2-disubstituted vinylbromide with strong base, such as potassium *t*-butoxide or alkyl lithium, can result in the formation of alkyne.

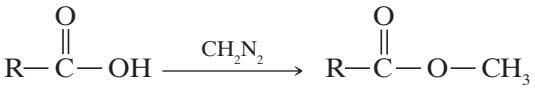


22.6B Reaction of Diazomethane with Carboxylic Acids

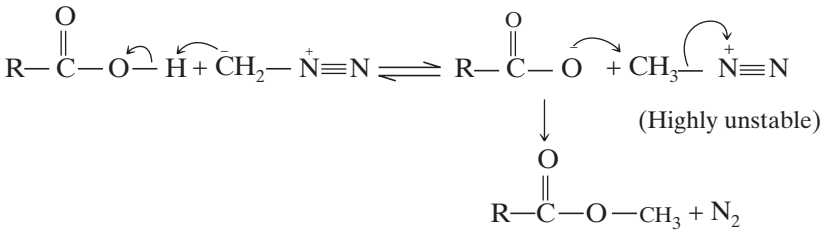
Diazomethane, CH_2N_2, is a rather strange compound that can be represented as a dipole. There are various ways of representing its structure.



Diazomethane methylates carboxylic acids because carboxylic acids readily protonate it giving an extremely unstable diazonium cation. This compound readily loses N_2, the best leaving group, and it does so, with the N_2 being substituted by carboxylate anion.

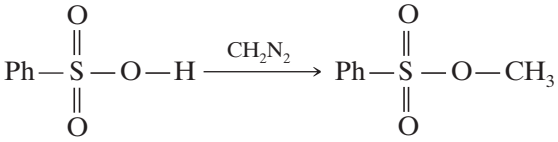


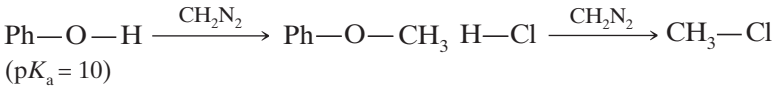
The mechanism of the reaction is as follows

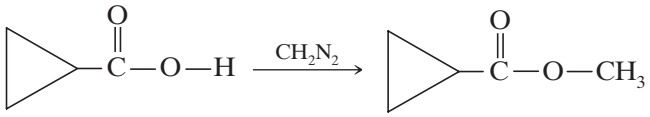


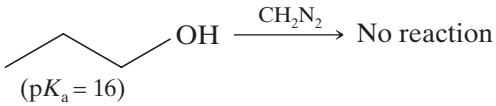
Diazomethane methylation is a good method for preparing methyl ester from carboxylic acids on a small scale because yields are excellent and the only byproduct is nitrogen. However, there is also a drawback; diazomethane has a boiling point of –24°C and it is a toxic and highly explosive gas. Therefore, it has to be used in solution, usually in ether. Moreover, the solution must be dilute, because concentrated solutions of diazomethane are also explosive.

Some other examples of diazomethane reaction are as follows:









Ordinary alcohols are not methylated because of not being strongly acidic to protonate diazomethane. Lewis acid is used to increase the acid nature of alcohol by creating a positive charge on the more electronegative atom to cause the reaction. For example,

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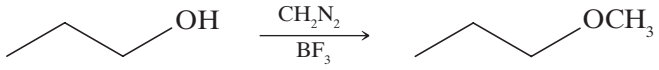
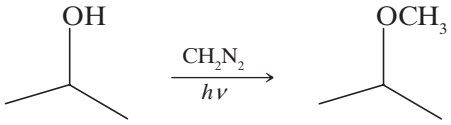


Photolysis of diazomethane produces a carbene and alcohols can be methylated by diazomethane (though in low yield) if the mixture is irradiated with light.

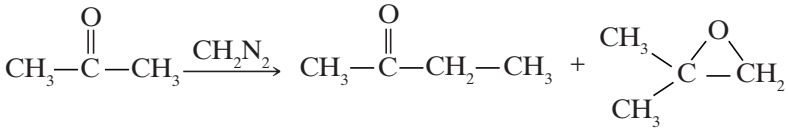


(Low yield)

The mechanism in this case is totally different because the light energy promotes loss of nitrogen (N_2) from the molecule without protonation.

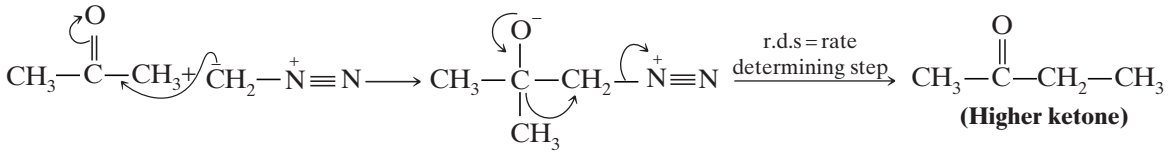
22.6C Reaction of Diazomethane with Aldehydes or Ketones

A ketone reacts with diazomethane to yield a higher ketone and epoxide in a side reaction.

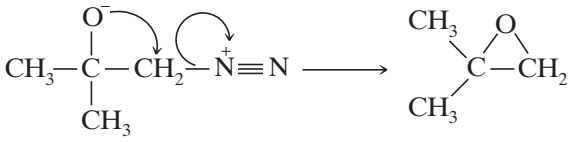


(Major) **(Minor)**

The mechanism of this reaction is as follows:

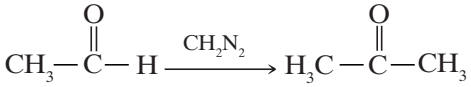


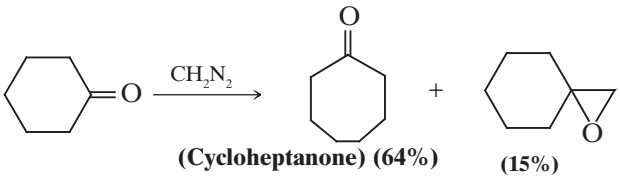
Epoxide will be obtained from intramolecular nucleophilic attack.



Solved Problem 22.1

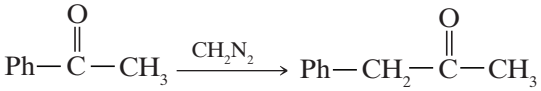
Give the reaction products when acetophenone, acetaldehyde and cyclohexane undergo reaction with diazomethane.





Answer

The products of the given reactions are as follow:



22.6D Reaction of CH_2N_2 with Alkanes

Carbenes react with hydrocarbons by insertion into carbon–hydrogen bond. The reaction is not regioselective and hence not useful for synthesis.

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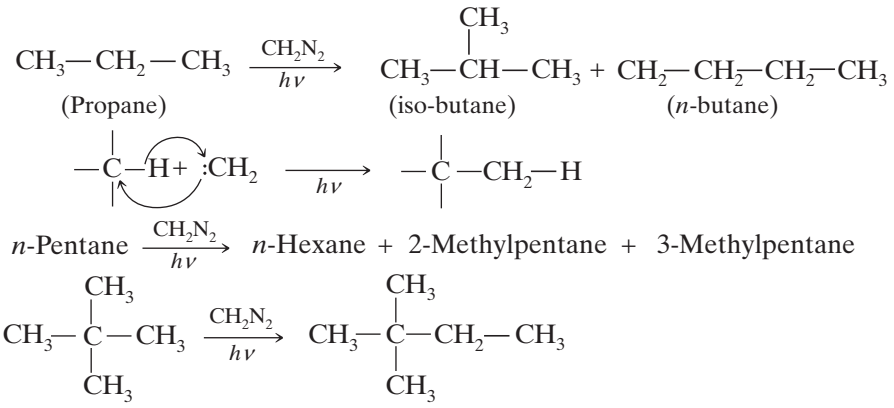
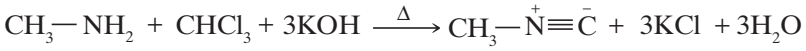
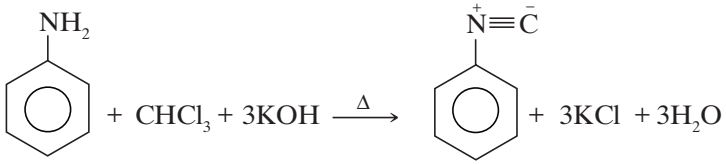


22.6E Isocyanide Test (or) Carbylamine Reaction

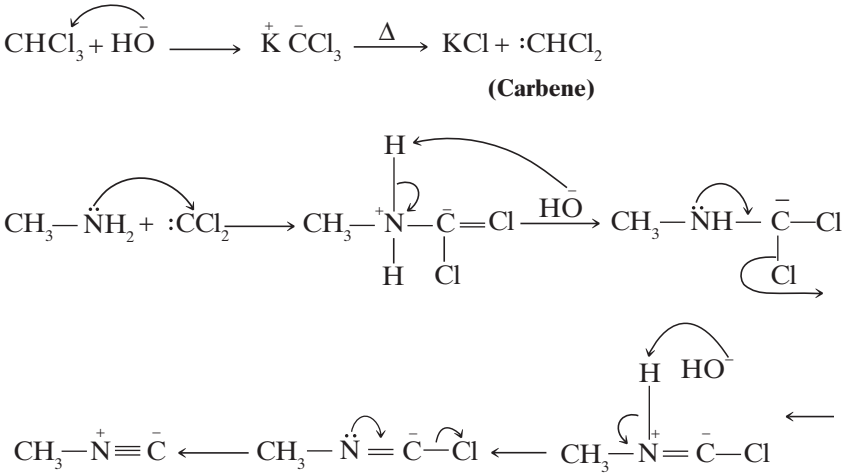
The carbylamine reaction is a chemical test for the detection of primary amines. In this reaction, when a primary amine is heated with alcoholic potassium hydroxide and chloroform, an isocyanide is formed. Carbylamine reaction with methylamine is given below:



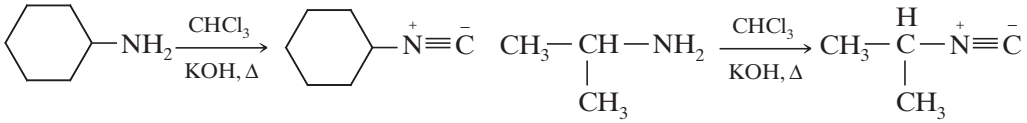
The reaction with aniline is as follows:



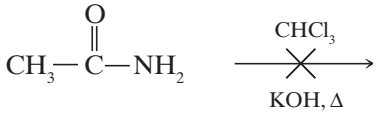
The mechanism of the reaction is explained as follows:



The carbylamine test is not positive in case of secondary and tertiary amines because there is no possibility of isocyanide formation.



Amides do not give isocyanide test.



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Solved Problem 22.2

Give the products in the carbylamine reaction of ethylamine.

$$CH_3—CH_2—NH_2 \xrightarrow[KOH,\,\Delta]{CHCl_3} (A) \xrightarrow{H_3O^+} (B) + (C)$$

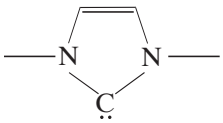
Answer

The reaction is as follows:

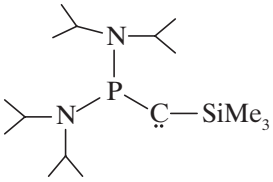
$$A = CH_3—CH_2—\overset{+}{N}\equiv\overset{-}{C} \quad B = CH_3—CH_2—NH_2 \quad C = HCO_2H$$

SUMMARY OF THE METHODS OF FORMATION AND REACTIONS OF CARBENES

1. The experimental evidence for the existence of carbenes comes from the examples of some stable compounds given below:



Stable; exists in form of colorless crystals

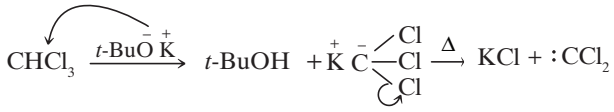


Stable; exists in form of red liquid

2. **Formation of carbene:** Some of the reactions involving formation of carbenes are as follows

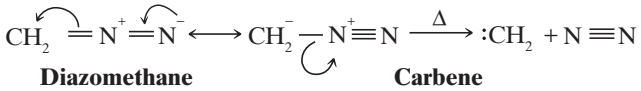
By α-elimination or 1,1-elimination or E_α reaction

Elimination means removal of two atoms from the same atom.



From diazocompounds

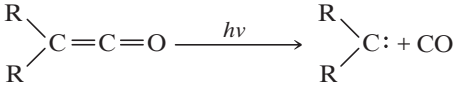
Diazo compounds serve as a good source for obtaining many carbenes.



Diazomethane **Carbene**

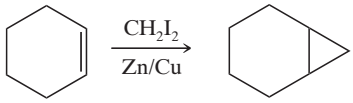
From ketenes

Ketenes which are structurally similar to diazoalkane also produce carbenes on photochemical decomposition.



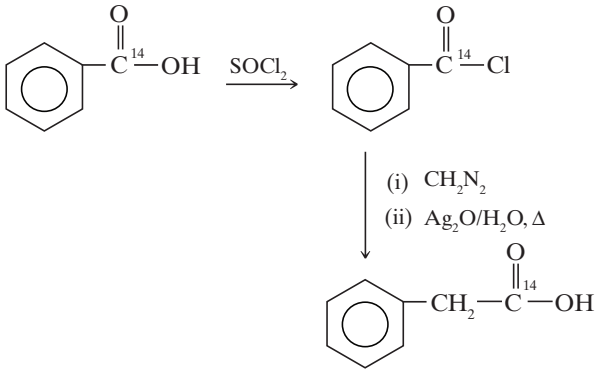
3. **Classification of carbenes:** Carbenes can be classified into two types: singlet and triplet. Most types of carbenes are stable in the triplets state because the energy to be gained by bringing down the electron in the *p* orbital into the sp^2 orbital is insufficient to overcome the increased repulsion existing between the two electrons when present in a single orbital.

4. **Simmons–Smith reaction:** This reaction is also used for the preparation of cyclopropane derivatives.



(86–92% yield)

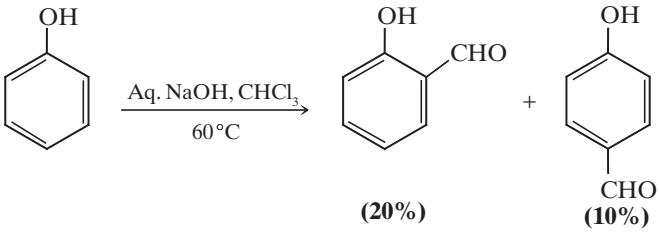
5. **Arndt–Eistert reaction:** This reaction is used to increase the number of $—CH_2$ (i.e., methylene) units in carboxylic acids.



6. **Reimer–Tiemann reaction:** This reaction can be divided into a normal and an abnormal transformation depending on the reaction products obtained.

Normal Reimer–Tiemann reaction

A normal Reimer–Tiemann reaction is the one in which a phenol (or an electron-rich aromatic compound such as pyrrole) yields one or more aldehydes when treated with chloroform and alkali.



(20%) **(10%)**

Abnormal Reimer–Tiemann reaction

In an abnormal Reimer–Tiemann reaction, the product can further transfotm into cyclohexadienones and ring-expansion products.

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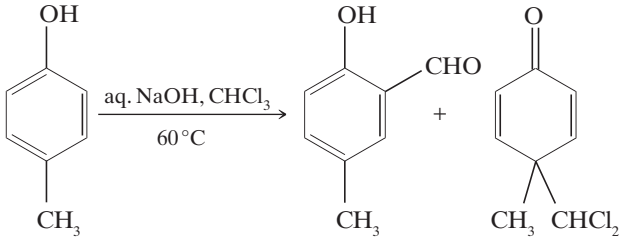
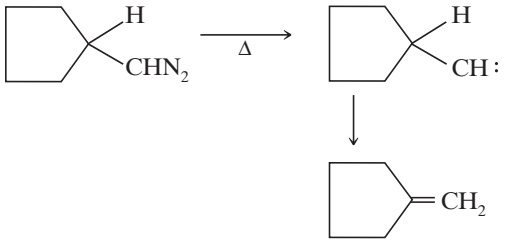
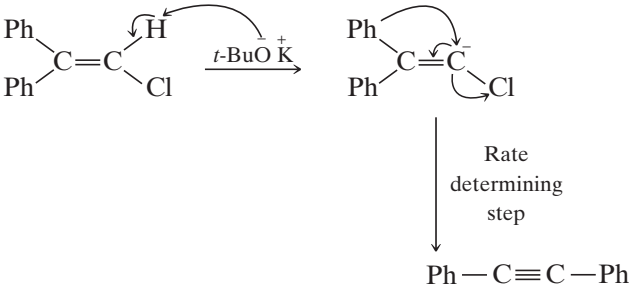


7. **Rearrangement in carbene:** Activation energy for hydrogen migration in alkyl carbene appears to be only about 1 kcal/mol, and 1,2-migration of hydrogen occurs extremely easily in singlet carbene.



8. **Frisch reaction:** The reaction in which 1-halo-2,2-diphenyl-ether reacts with a strong base to form alkyne is known as Fritsch reaction.



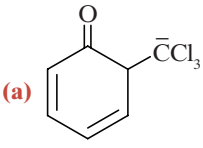
9. **Carbylamine reaction:** This reaction is a chemical test for the detection of primary amines. In this reaction, when a primary amine is heated with alcoholic potassium hydroxide and chloroform, an isocyanide is formed.

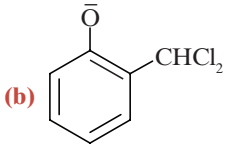
$$CH_3—NH_2 + CHCl_3 + 3KOH \xrightarrow{\Delta} CH_3—\overset{+}{N}\equiv\overset{-}{C} + 3KCl + 3H_2O$$

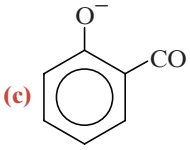
ADDITIONAL OBJECTIVE QUESTIONS

Single Correct Choice Type

1. In Reimer–Tiemann reaction, the medium of reaction is
   (a) acidic. **(b)** basic. **(c)** neutral. **(d)** gas-phase.
2. Carbylamine forms from aliphatic or aromatic primary amines via which of the following intermediates?
   (a) Carbene **(b)** Carbon radical
   (c) Carbocation **(d)** Carbanion
3. A compound X on reaction with chloroform and NaOH gives a compound with a very unpleasant odor. X is
   (a) $C_6H_5CONH_2$ **(b)** $C_6H_5NH_2$
   (c) $C_6H_5CH_2NHCH_3$ **(d)** $C_6H_5NHCH_3$
4. In Reimer–Tiemann formylation reaction, molecular weight of phenol increases by
   (a) 27 **(b)** 28 **(c)** 29 **(d)** 30
5. When chloroform is treated with amine and KOH, we get
   (a) rose like odor.
   (b) bitter almond like smell.
   (c) offensive odor.
   (d) sour oil of winter green like smell.
6. If we use pyrene (CCl_4) in the Reimer–Tiemann reaction in place of chloroform, the product formed is
   (a) salicylaldehyde. **(b)** phenolphthalein.
   (c) salicylic acid. **(d)** cyclohexanol.
7. When phenol is reacted with $CHCl_3$ and NaOH followed by acidification, salicyldehyde is obtained. Which of the following species are involved in the above mentioned reaction as intermediate?

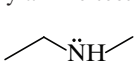


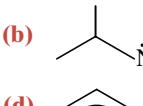


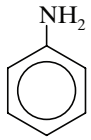


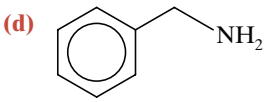
(d) All of these

8. Which of following compound gives positive isocyanide test?
   (a) $CH_3—NH—CH_3$ **(b)** $CH_3—CH_2—NH_2$
   (c) $CH_3—NH—Ph$ **(d)** $CH_3—N(CH_3)—CH_3$
9. Phenol $\xrightarrow[H^+]{CHCl_3/NaOH}$ Salicyldehyde.
   The above reaction is known as
   (a) Rimer–Tiemann reaction. **(b)** Bucherer reaction.
   (c) Gattermann synthesis. **(d)** Perkin reaction.
10. Which of the following compound does not give Hoffman's carbylamine test?









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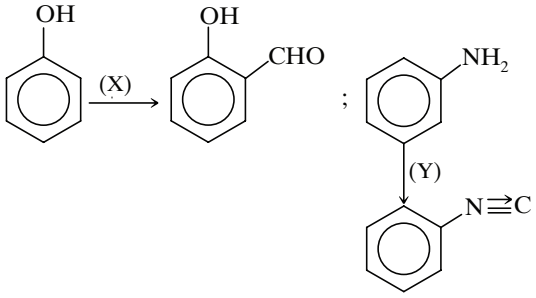
11. $R—NH_2 + xKOH + CHCl_3 \longrightarrow R—N\equiv C$ where x is moles of KOH consumed, and is equal to

(a) 1 **(b)** 2 **(c)** 3 **(d)** 4

12.



Reagent (X) and (Y) respectively are

(a) CH_3Cl, KOH and $CHCl_3$, KOH

(b) $CHCl_3$, KOH and $CHCl_3$, KOH

(c) CCl_4, KOH and $CHCl_3$, KOH

(d) $CHCl_3$, KOH and CCl_4, KOH

13. Salicylic acid can be prepared using Reimer–Tiemann's reaction by treating phenol with

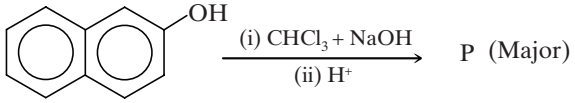
(a) methyl chloride in the presence of anhydrous aluminium chloride.

(b) carbon dioxide under pressure in sodium hydroxide solution.

(c) carbon tetrachloride and concentrated sodium hydroxide.

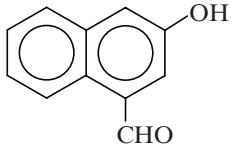
(d) sodium nitrite and a few drops of concentrated sulphuric acid.

14.

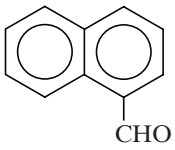


Identify the structure of P

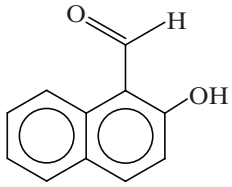
(a)



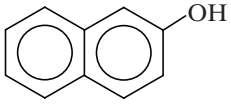
(b)



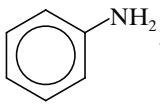
(c)



(d)



15.



$+ KOH + CHCl_3 \longrightarrow (A)$

The product A is

(a) $Ph—N\equiv C$ **(b)** $Ph—NH=CH_2$

(c) $Ph—C\equiv N$ **(d)** $Ph—NH_2$

16. Reaction of phenol with chloroform/sodium hydroxide to give *o*-hydroxy benzaldehyde involves the formation of

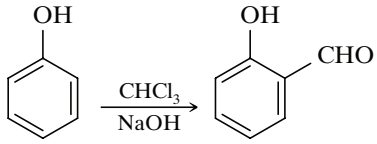
(a) dichloro carbine. **(b)** trichloro carbine.

(c) chlorine atoms. **(d)** chlorine molecules.

Linked Comprehension Type

Paragraph for Question 1 to 3

Reimer–Tiemann reaction is carried out by refluxing an alkaline solution of phenol with chloroform at 60°C, distilling off the excess of chloroform, acidifying the residual liquid with sulphuric acid, and then steam-distilling it. Unchanged phenol and *o*-hydroxy benzaldehyde distil over leaving behind *p*-hydroxy benzaldehyde.



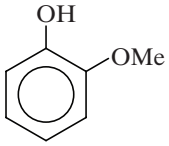
77% yield

1. Which of the following compounds give Reimer–Tiemann reaction?

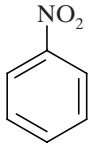
(a)



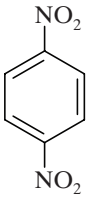
(b)



(c)

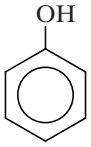


(d)



2. Electrophile in the above reaction is/are

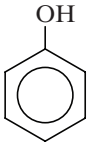
(a)



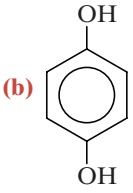
(b) $\ddot{C}HCl_2$ **(c)** $:CCl_2$ **(d)** $ArCHCl_2$

3. Which is more reactive towards Reimer–Tiemann reaction?

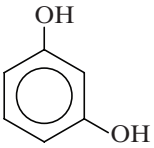
(a)



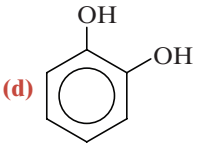
(b)



(c)



(d)



Paragraph for Question 4 to 6

Reimer–Tiemann reaction introduces an aldehyde group on to the aromatic ring of phenol, *ortho* to the hydroxyl group. This reaction involves electrophilic aromatic substitution. This is a general method for the synthesis of substituted salicylaldeydes as depicted:

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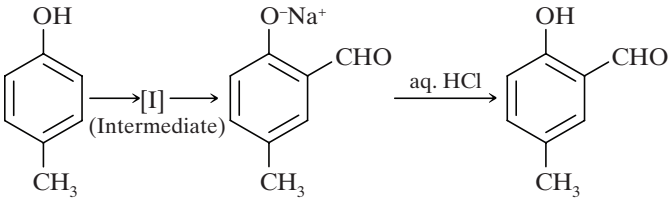


(I) **(II)** **(III)**

4. Which one of the following reagents is used in the above reaction?

(a) aq. NaOH + CH_3Cl

(b) aq. NaOH + CH_2Cl_2

(c) aq. NaOH + $CHCl_3$

(d) aq. NaOH + CCl_4

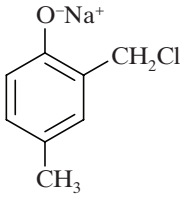
5. The electrophile in this reaction is

(a) :CHCl **(b)** $^+CHCl_2$

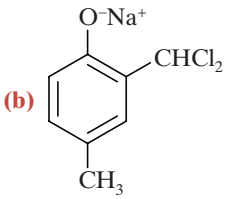
(c) $:CCl_2$ **(d)** $\cdot CCl_2$

6. The structure of the intermediate I is

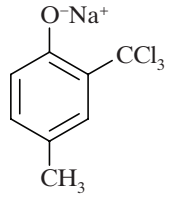
(a)



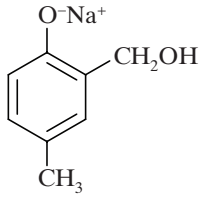
(b)



(c)

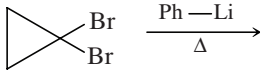
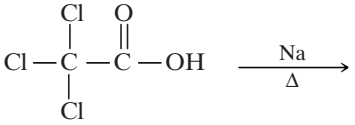
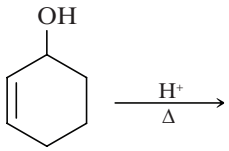


(d)



Matrix Match Type

1.

Column I (Reaction)	Column II (Intermediate)
(a) $CHCl_3 + KOH \xrightarrow[\Delta]{}$	**(p)** Carbocation
(b) 	**(q)** Carbanion
(c) 	**(r)** Free radical
(d) 	**(s)** Carbene

ANSWER KEY

Single Correct Choice Type

1. (b)	**2.** (a)	**3.** (b)	**4.** (b)	**5.** (c)
6. (c)	**7.** (a)	**8.** (b)	**9.** (a)	**10.** (a)
11. (c)	**12.** (b)	**13.** (c)	**14.** (c)	**15.** (a)
16. (a)				

Linked Comprehension Type

1. (b)	**2.** (c)	**3.** (c)	**4.** (c)	**5.** (c)
6. (b)				

Matrix Match Type

1. a→(q, s); b→(q, s); c→(q, s); d→(p)

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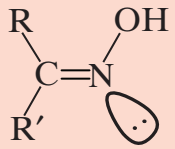

Reactions of Nitrene and Electron Deficient Oxygen

Contents

23.1 | Migration to Electron Deficient Nitrogen
23.2 | Nitrene Formation
23.3 | Hofmann—Curtius—Lossen—Schmidt Group of Rearrangements
23.4 | Curtius Reaction
23.5 | Schmidt Reaction
23.6 | Hofmann-Bromamide Reaction or Hofman Rearrangement
23.7 | Beckmann Rearrangement
23.8 | Stieglitz Rearrangement

23.1 | MIGRATION TO ELECTRON DEFICIENT NITROGEN

It is expected that alkyl or aryl migration can take place from carbon to the following species:

$R_3\overset{+}{C}$; $\begin{matrix} R \\ R \end{matrix}\!\!>\!C\!:$ (Carbene); $R_2\overset{+}{\underset{\cdot\cdot}{N}}$ and $R-\ddot{N}$ (Nitrene)

We have discussed the chemistry of carbenes and carbenoids in the previous chapter. We will now study preparation and reactions of nitrenes.

23.2 | NITRENE FORMATION

23.2A By Photolysis

Organic azides are unstable substances, frequently explosive. The aryl sulphenyl azides are among the more tractable examples, but will decompose on heating with loss of nitrogen. A wide variety of azides can be decomposed to yield nitrenes.

$$R-\ddot{N}=\overset{+}{N}=\overset{-}{N} \xrightarrow[\text{or } \Delta]{h\nu} R-\ddot{N} + N_2\uparrow$$

(R = alkyl, aryl, H)

$$R-\overset{O}{\overset{\|}{S}}(=O)-N=\overset{+}{N}=\overset{-}{N} \xrightarrow[\text{or } \Delta]{h\nu} R-SO_2-\ddot{N} + N_2$$

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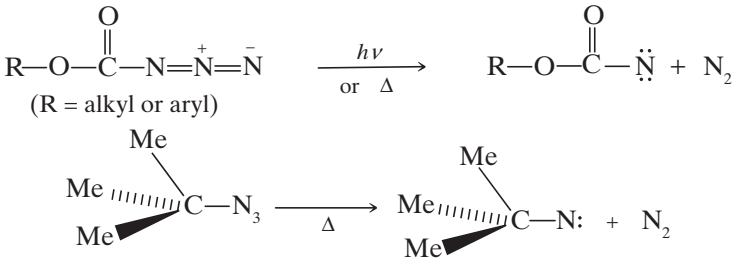
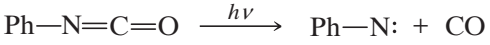


The thermal decomposition of azide shows a large positive entropy of activation. For example, the following decomposition has $\Delta G^{\ddagger}$ = 160 kJ/mol and $\Delta S^{\ddagger}$ = + 80 kJ/mol.

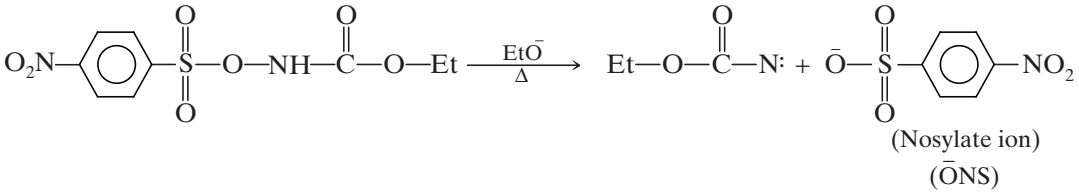


Isocyanate can also be photolyzed to nitrene.

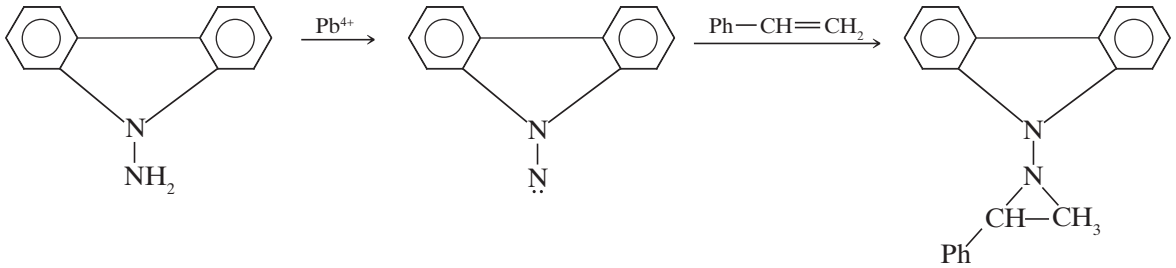


23.2B By α-Elimination

These are relatively rare – one probable example is as follows.

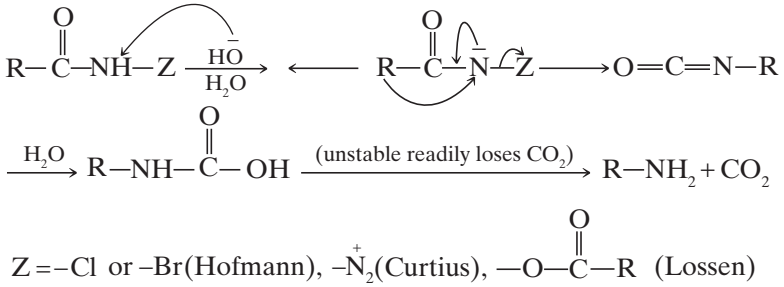


23.2C By Oxidation of Primary Amino Groups



23.3 | HOFMANN—CURTIUS—LOSSEN—SCHMIDT GROUP OF REARRANGEMENTS

This group of reactions is important preparatively for the conversion of a carbonyl function into a primary amine with the loss of carbonyl carbon. All these reactions involve migration from carbon to electron deficient nitrogen. The following steps are common in all these reactions:



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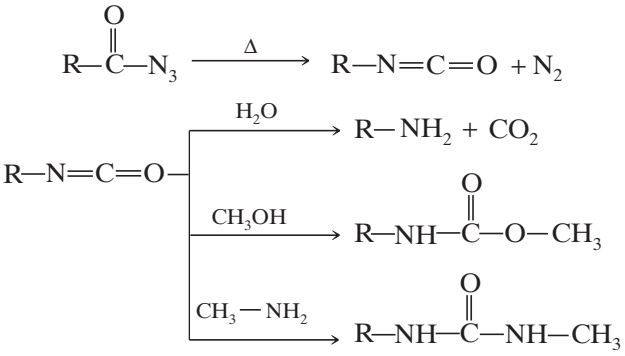
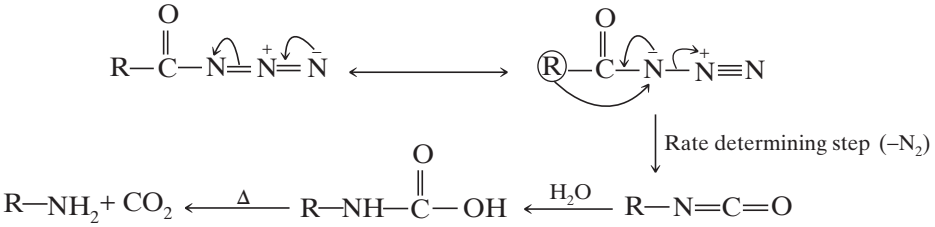
23.4 | CURTIUS REACTION

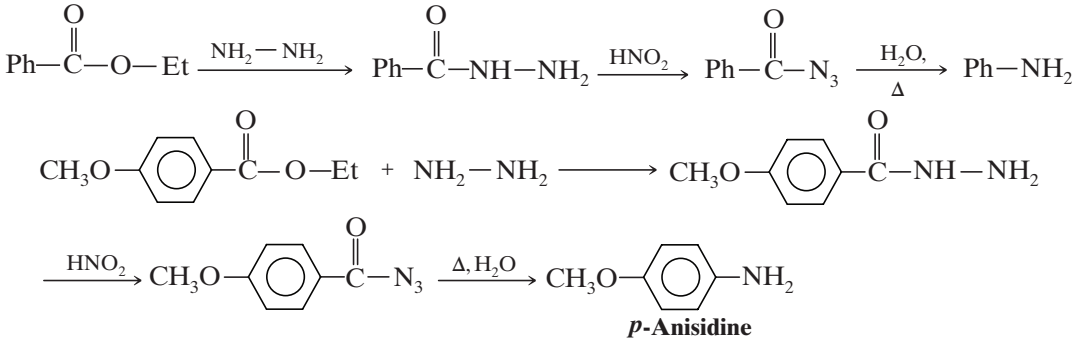
Curtius rearrangement involves the decomposition of acyl azides in an inert solvent by gentle heating to form isocyanate in good yield.



The mechanism of the reaction is as follows:



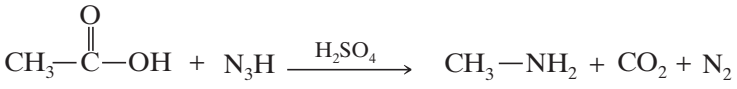
This reaction finds application in preparation of primary amines, aminoacids and aldehydes.



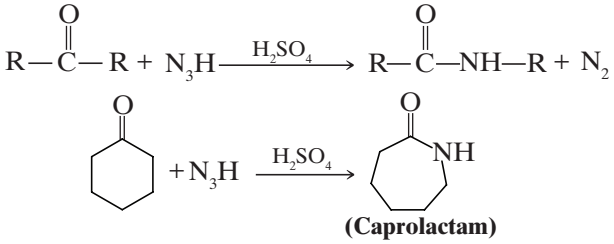
***p*-Anisidine**

23.5 | SCHMIDT REACTION

The reaction in which carboxylic acids give amines is known as Schmidt reaction. For example,



Free hydrazoic acid is highly toxic, and hence sodium azide is slowly added to the solution of the carboxylic acid in sulfuric acid when hydrazoic acid is liberated. Schmidt reaction also takes place with ketones or aldehydes. For example,



(Caprolactam)

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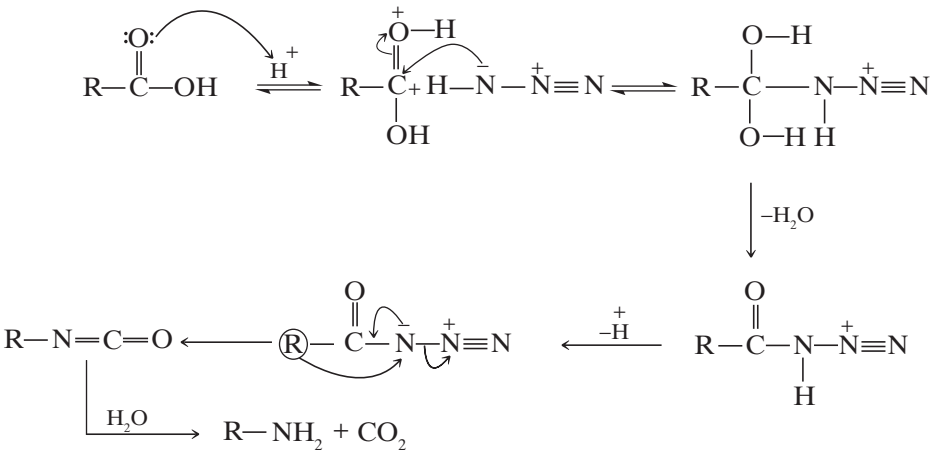
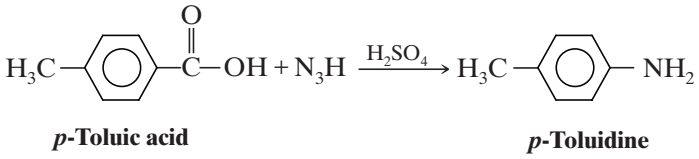
The mechanism of the reaction is as follows:

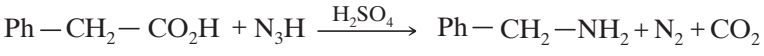


23.5A Application of Schmidt Reaction

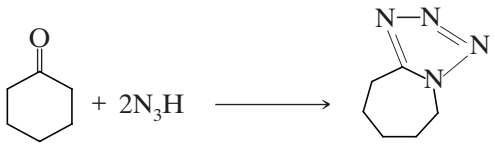
Primary amine will be obtained in good yield by this reaction, provided the acid does not contain a group sensitive to the concentrated sulfuric acid. For example,



***p*-Toluic acid** ***p*-Toluidine**



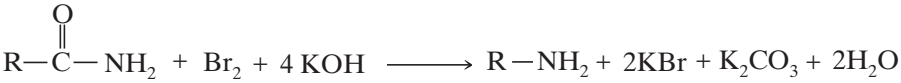
Phenylacetic acid **Benzylamine**



Cardiazole (a stimulant)

23.6 | HOFMANN-BROMAMIDE REACTION OR HOFMAN REARRANGEMENT

This reaction is used for the conversion of an amide into a primary amine with one carbon less. The overall reaction is as follows:



In the above reaction. R may be aliphatic, aromatic or heterocyclic. Other reagents used in this reaction are KOBr, $Br_2 + Ca(OH)_2$, $Cl_2 + Ca(OH)_2$, NaOCl.

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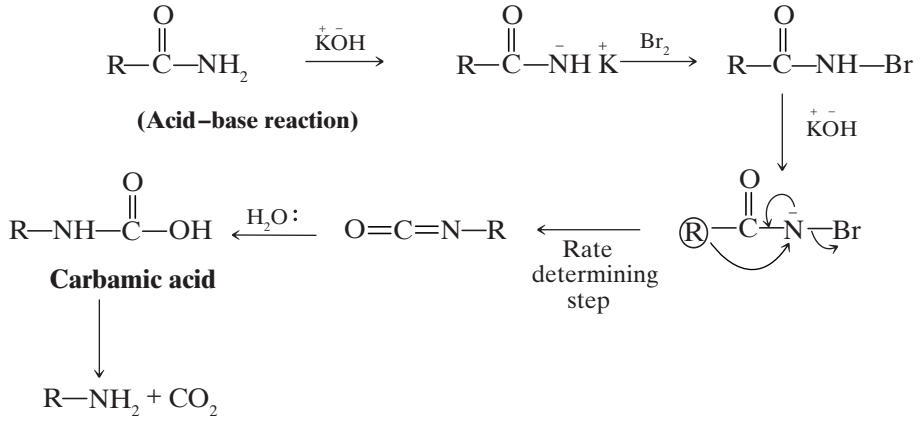
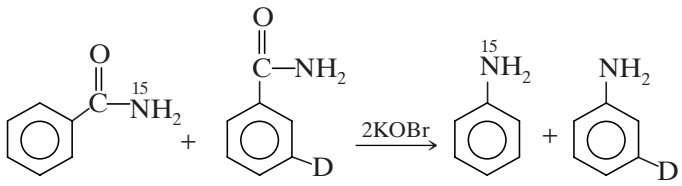
The mechanism of the reaction is as follows:

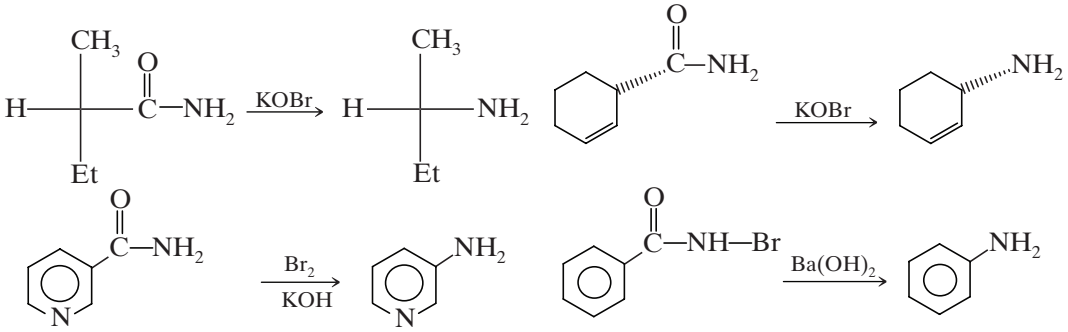


Since the intermediate is an *N*-bromamide, the reaction is also known as bromamide reaction. As no crossover products are obtained when two different amides are rearranged, it is assumed that the rearrangement is intramolecular and the migrating group never completely separates during the migration.



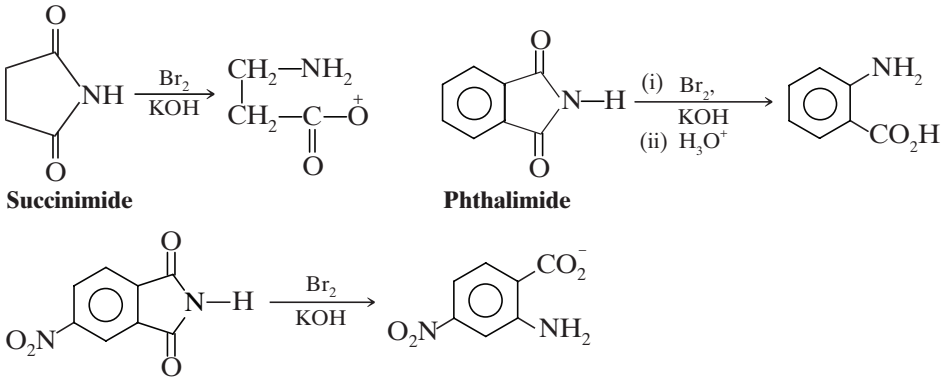
The reaction is completed with retention of configuration.

Some other examples are:



N-substituted amide ($CH_3—CO—NH—CH_3$) will not undergo Hofmann rearrangement because formation of isocyanate is not possible in this case.

1. **Synthesis of amino acids:**



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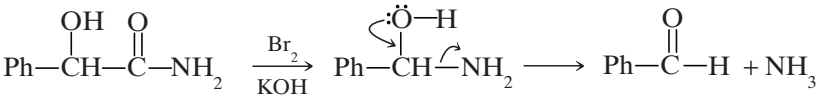
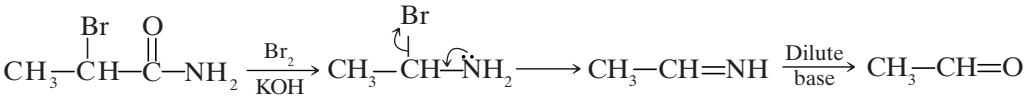
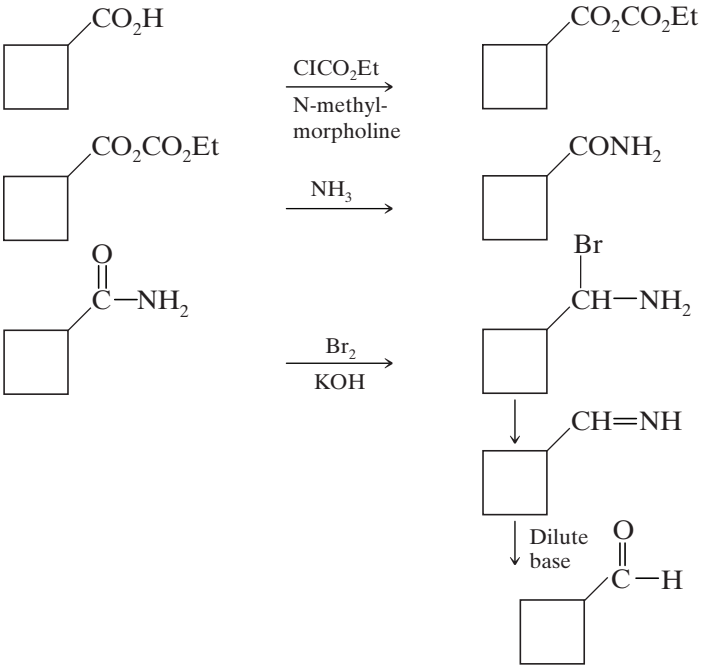
2. Prepartion of aldehydes/ketones



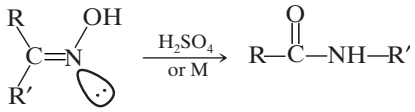
Mandelic acid amide



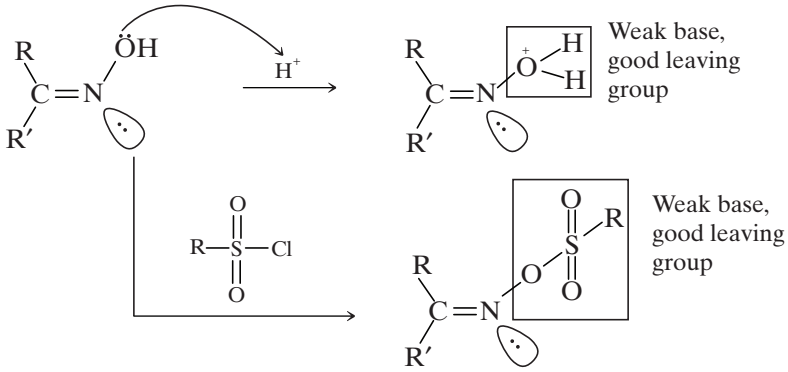


23.7 | BECKMANN REARRANGEMENT

Conversion of ketoximes to *N*-substituted amides is known as Beckmann rearrangement. In this rearrangement, the migration takes place from carbon to nitrogen. The reaction is catalyzed by various acidic reagents.



where M = RSO_2Cl, PCl_5, BF_3, TsCl, SO_3 or P_2O_5. The main function of the acidic catalyst is to convert —OH of the oxime into a better leaving group by protonation, esterification, etc.



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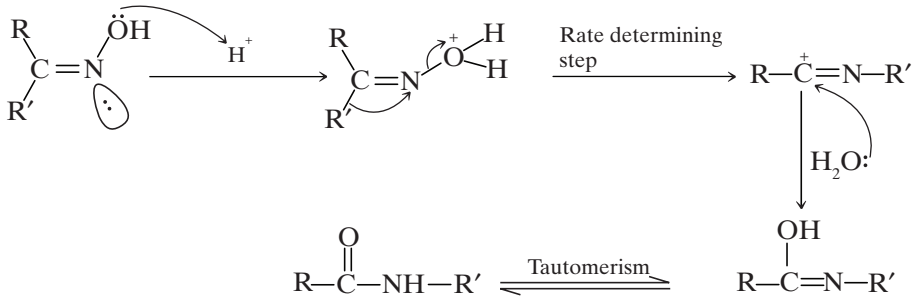
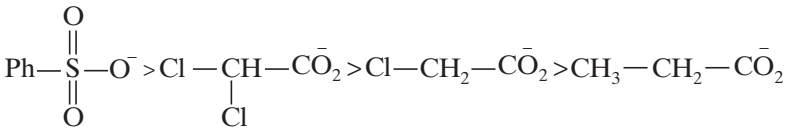
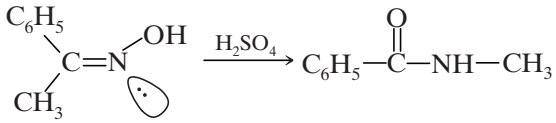
The mechanism of this reaction is as follows:

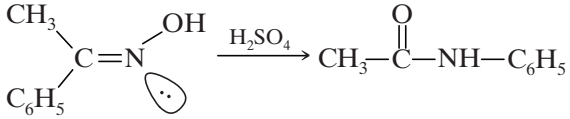


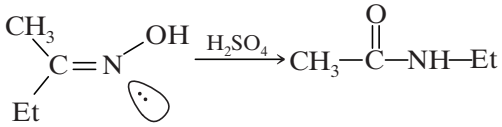
Interesting feature of this reaction is that the migratory aptitude will not decide the major product. Stereochemical arrangement of the R and R′ groups determines which of them migrates. Almost without exception it is found that it is the group anti to —OH group that migrates. Since the rate limiting step involves removal of leaving group, the rate of Beckmann rearrangement is affected by the leaving group tendency, as follows:

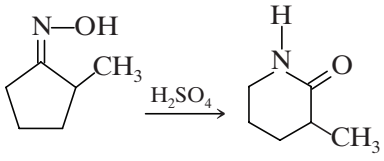


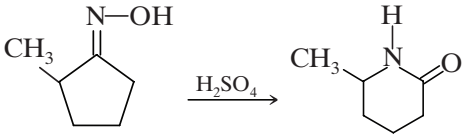
Some examples of Beckmann rearrangement are as follows:

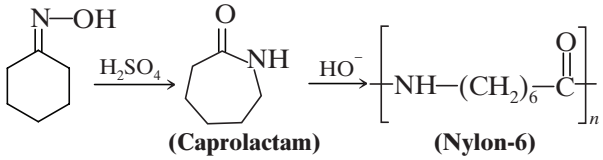
1. 

2. 

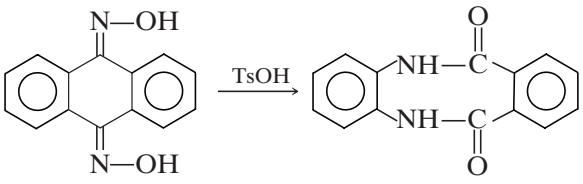
3. 

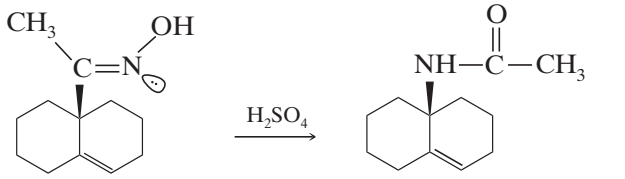
4. 

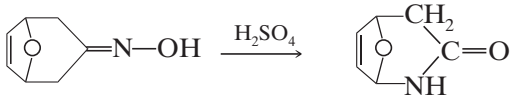
5. 

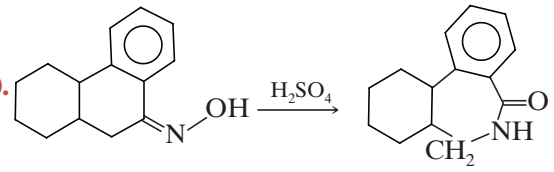
6. 

Large-scale application of Beckmann rearrangement is in the synthesis of the textile polymers. Nylon-6 is prepared from cyclohexanone oxime as shown above.

7. 

8. 

9. 

10. 

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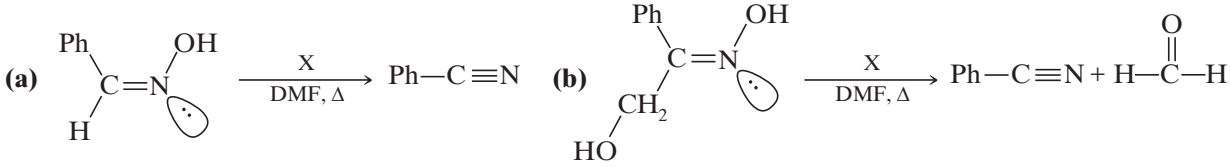
23.7A Abnormal Beckmann Rearrangement

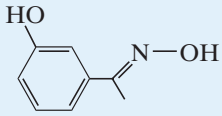
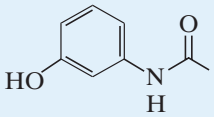
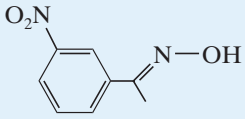
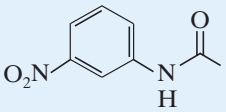
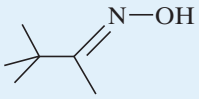
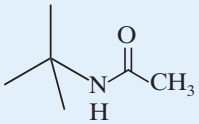
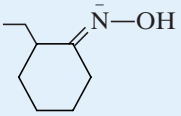
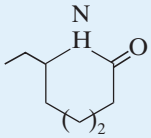
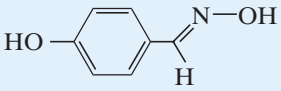
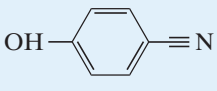
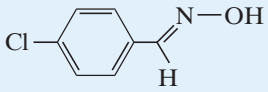
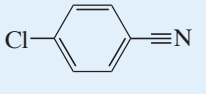
Some examples are as follows:



where X = 2,4,6-trichloro [1,3,5] triazine

Different ketoximes prepared from the corresponding ketones, undergo Beckmann rearrangement at room temperature (Table 23.1) and give excellent yields of nitriles upon treatment with 2,4,6-trichloro[1,3,5]triazine in *N*,*N*-dimethylformamide. Nitriles are obtained from aldoximes in the same way.

Table 23.1 Backmann Rearrangement of Ketoximes

Oxime	Product	t(h)	
		6	100
		12	80
		24	92
		8	100
		4	100
		4	100

23.8 | STIEGLITZ REARRANGEMENT

The examples of rearrangements to sp^2 hybridized azacations are rare as compared to their carbon analogs. The starting materials for generating such azacations are usually chloramines or hydroxyl amines. Some examples of these transformations called Stieglitz rearrangements are discussed as follows. The first example is similar to Wagner–Meerwein rearrangement, and the second is similar to pinacol rearrangement. Competitive shifts of *para*-substituted phenyl groups in reactions are similar to the third example, and demonstrate that a methoxy substituent facilitates rearrangement, whereas a nitro substituent retards it. In the last example, a conjugated azacation activates the benzene ring to nucleophilic substitution, in contrast to the usual role played by amine substituents.

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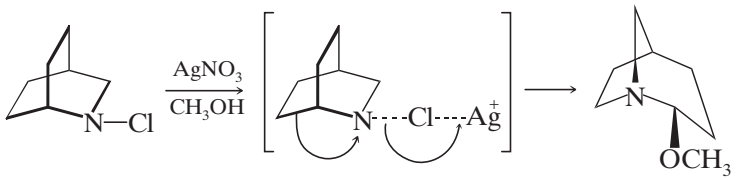
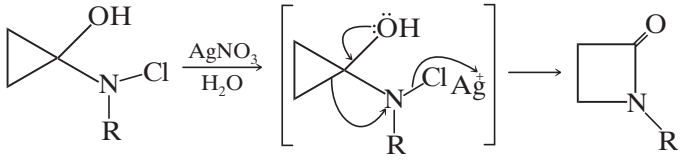
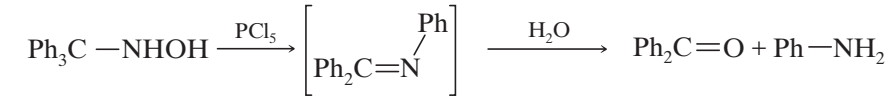
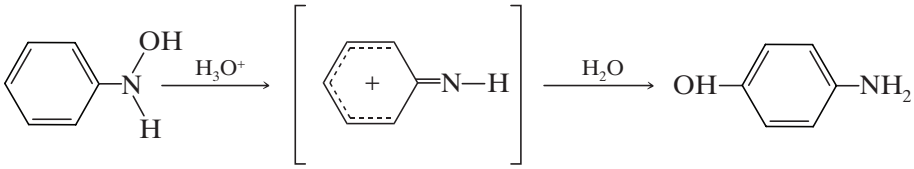
1. 

2. 

3. 

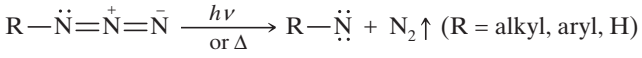
4. 

SUMMARY OF FORMATION AND REACTIONS OF NITRENES

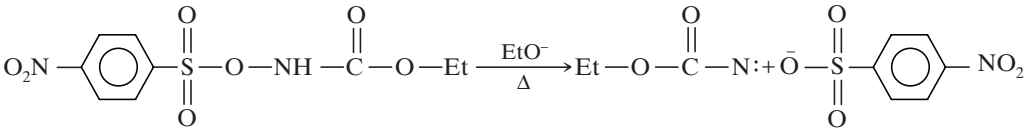
In this chapter, we described the reactions of nitrenes and electron deficient oxygen.

1. **Formation of nitrenes:** Nitrenes can be formed by the following methods.

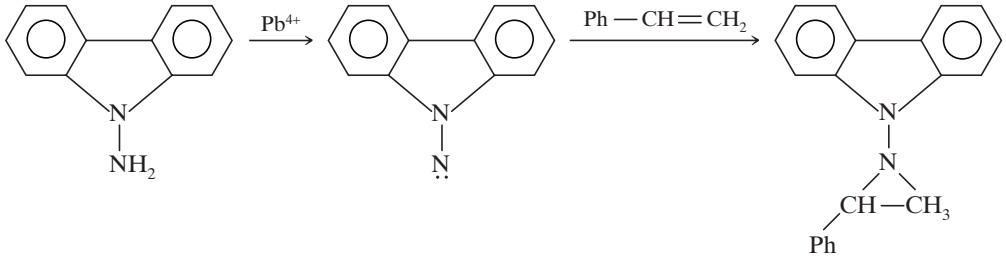
By thermal decomposition



By α-elimination



By oxidation of primary amino groups



2. **Hofmann–Curtius–Lossen–Schmidt group of rearrangements:** This group of reactions is important preparatively for the conversion of a carbonyl function into a primary amine with loss of the carbonyl carbon.

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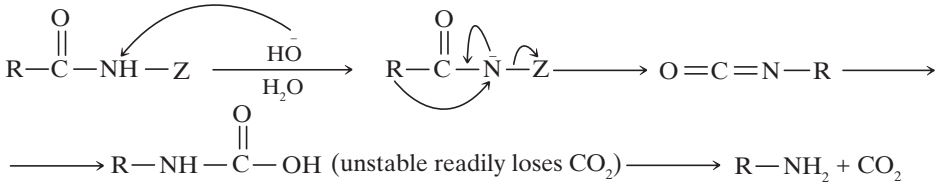
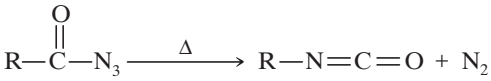
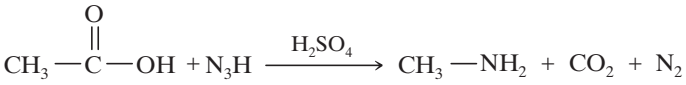


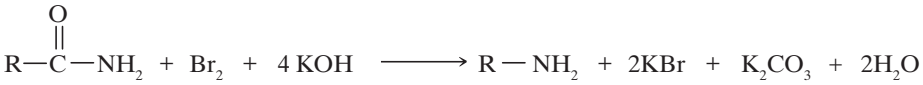
3. **Curtius rearrangement:** This rearrangement involves the decomposition of acyl azides in an inert solvent by gentle heating to form isocyanate.



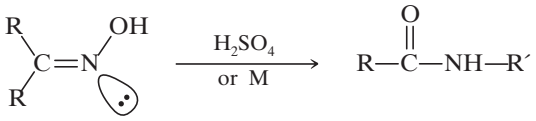
4. **Schmidt reaction:** This reaction is used for the conversion of carboxylic acids to amines.



5. **Hofmann–bromamide reaction:** This reaction is used for the conversion of an amide into a primary amine with one carbon less.

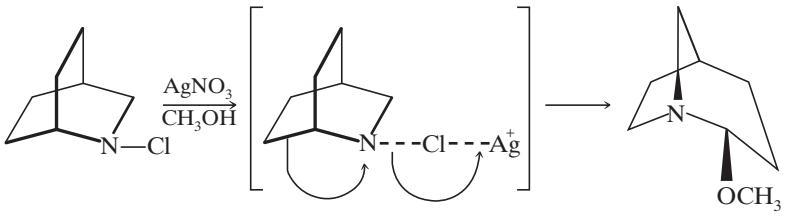


6. **Beckmann rearrangement:** Conversion of ketoxime to *N*-substituted amide is known as Beckmann rearrangement. In this rearrangement, the migration takes place from carbon to nitrogen.



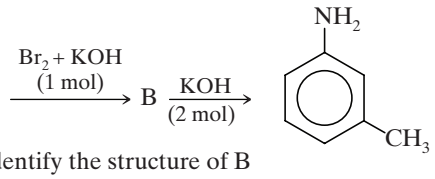
where $M = RSO_2Cl, PCl_5, BF_3, SO_3$ or P_2O_5

7. **Stieglitz rearrangement:** The transformation of chloramines or hydroxyl amines leading to the formation of sp^2 hybridized azacations is called Stieglitz rearrangement.

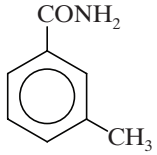


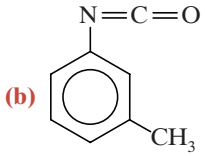
ADDITIONAL OBJECTIVE QUESTIONS

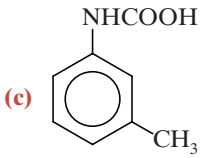
Single Correct Choice Type

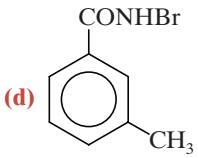
1. 

Identify the structure of B

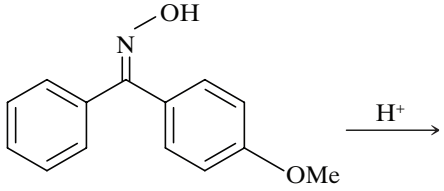
(a) 

(b) 

(c) 

(d) 

2. The major product obtained in the following reaction is



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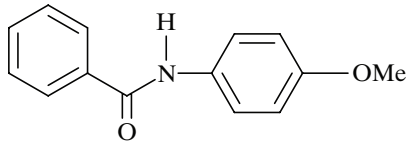
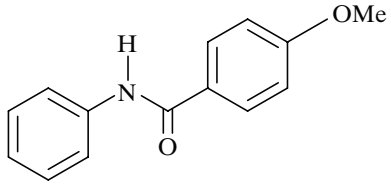
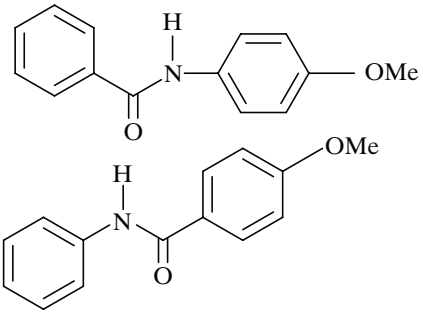
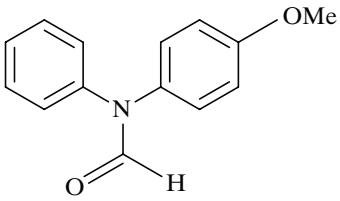
(a) 

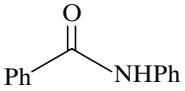
(b) 

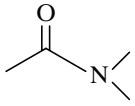
(c) An equimolar mixture of

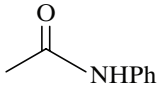


(d) 

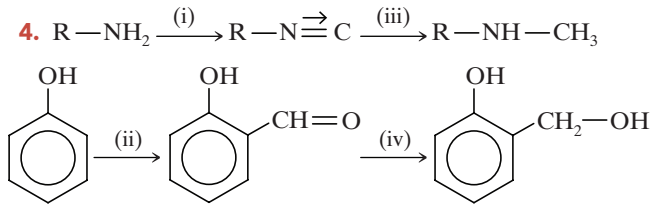
3. Which of the following will not undergo Hoffmann Bromamide reaction?

(a) 

(b) 

(c) 

(d) All

4. 

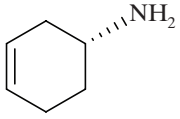
Missing reagent is

(a) i and ii = $CHCl_3$/NaOH; iii and iv = H_2/Ni

(b) i and ii = $CHCl_3$/R – Li; iii and iv = $CHCl_3$/NaOH

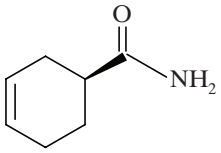
(c) i and ii = H_2/Ni; iii and iv = $LiAlH_4$

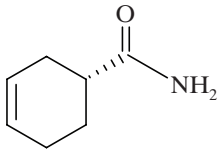
(d) i and ii = $LiAlH_4$; iii and iv = $CHCl_3$/NaOH

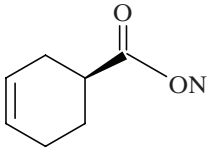
5. A $\xrightarrow{NaOI}$ 

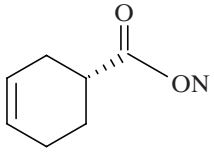
(Major)

In the above reaction, A is

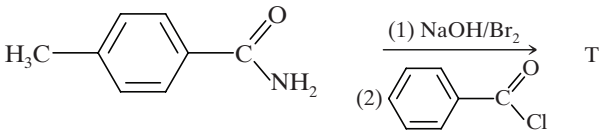
(a) 

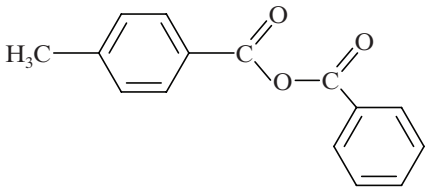
(b) 

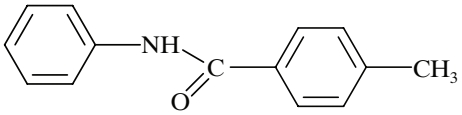
(c) 

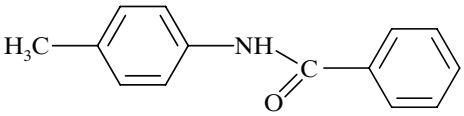
(d) 

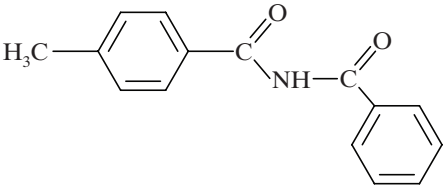
6. In the reaction, product T is

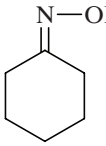


(a) 

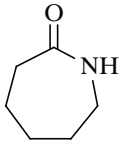
(b) 

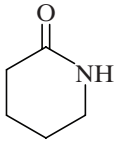
(c) 

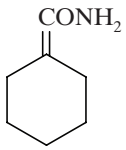
(d) 

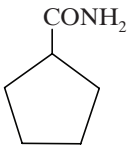
7. 

Identify structure of A.

(a) 

(b) 

(c) 

(d) 

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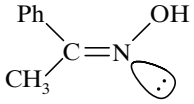
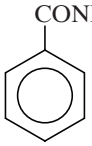
8.  $\xrightarrow{H^+}$ P Major .

Identify the structure of P.

(a) $CH_3-\underset{\underset{O}{\|}}{C}-NHC_6H_5$ **(b)** $C_6H_5-\underset{\underset{O}{\|}}{C}-NH-CH_3$

(a) Both (a) and (b) **(d)** $C_6H_5-\underset{\underset{O}{\|}}{C}-NH_2$

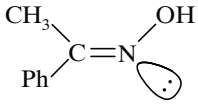
9.  $\xrightarrow{KOBr}$ A $\xrightarrow[\Delta]{(CH_3CO)_2O}$ B, Product B is

(a) $PhNHCOCH_3$ **(b)** $PhCONHCH_3$
(c) $PhNH_2$ **(d)** $PhNHCH_3$

10. $CH_3NH_2 + CHCl_3 + KOH \longrightarrow$ Nitrogen containing compound + KCl + H_2O.
The nitrogen containing compound is

(a) $CH_3-C\equiv N$ **(b)** $CH_3-NH-NH_3$

(c) $CH_3-\bar{N}=\bar{C}$ **(d)** $CH_3-N\rightleftarrows C$

11.  $\xrightarrow{H^+}$ P (Major)

Identify the structure of P.

(a) $CH_3-\underset{\underset{O}{\|}}{C}-NHC_6H_5$ **(b)** $C_6H_5-\underset{\underset{O}{\|}}{C}-NH-CH_3$

(c) Both (a) and (b) **(d)** $C_6H_5-\underset{\underset{O}{\|}}{C}-NH_2$

12. In the reaction sequence:

$$C_6H_5CHO \xrightarrow[\Delta]{NH_2OH/H^+} [X] \xrightarrow[(Beckmann)]{P_2O_5/\Delta} [Y] \xrightarrow{H_2O/H^+} [Z]$$

[X], [Y] and [Z] respectively be:

(a) $C_6H_5CH=N-OH$, C_6H_5CN, C_6H_5COOH
(b) $C_6H_5CH=NOH$, $C_6H_5CONH_2$, C_6H_5COOH
(c) $C_6H_5-CH=NOH$, C_6H_5COOH, $C_6H_5CONH_2$
(d) $C_6H_5-CH=NOH$, C_6H_5COOH, C_6H_5CN

13. $Ph-\underset{\underset{14}{}}{\overset{\overset{O}{\|}}{C}}-CHN_2 \xrightarrow[H_2O]{Ag_2O}$ (P). Product (P) is

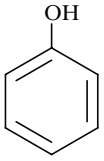
(a) $Ph-{}^{14}CH_2-CO_2H$ **(b)** $Ph-CH_2-{}^{14}CO_2H$

(c) $Ph-{}^{14}CO_2H$ **(d)** $Ph-CO_2H$

14. $CH_3-\overset{\overset{O}{\|}}{C}-NH_2 \xrightarrow{KOBr}$ (A)
$\xrightarrow{LiAlH_4}$ (B)

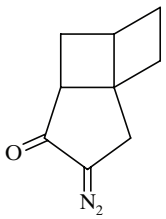
Relation between (A) and (B) is

(a) identical. **(b)** functional isomer.
(c) homologous. **(d)** positional isomers.

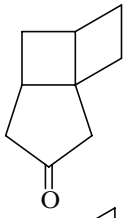
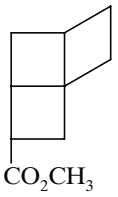
15.  $\xrightarrow[(ii)\ H^+]{(i)\ CO_2, NaOH}$ (A) $\xrightarrow{CH_3-\overset{\overset{O}{\|}}{C}-Cl}$ (B)

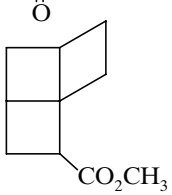
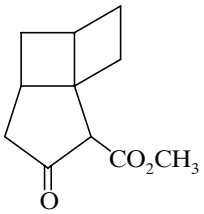
The product (B) is

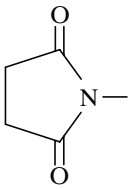
(a) aspirin. **(b)** oil of winter green.
(c) salol. **(d)** salicylic acid.

16.  $\xrightarrow[CH_3OH]{h\nu}$ (P).

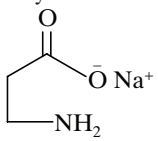
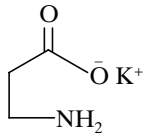
The product (P) is

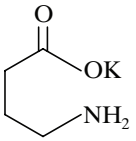
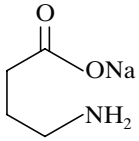
(a)  **(b)** 

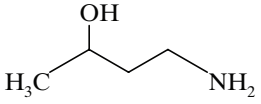
(c)  **(d)** 

17.  $\xrightarrow{KOBr}$ P (Major)

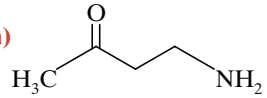
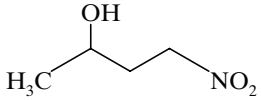
Identify the structure of P.

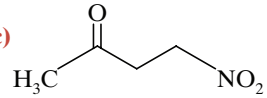
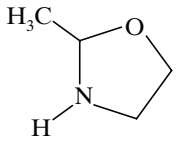
(a)  **(b)** 

(c)  **(d)** 

18.  $\xrightarrow[H^+\ cold]{KMnO_4}$

The product formed is

(a)  **(b)** 

(c)  **(d)** 

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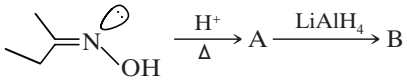
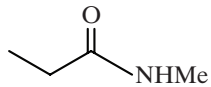
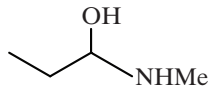
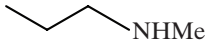
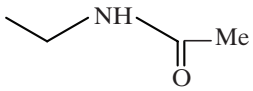
19. 

The product (B) is

(a) 

(b) 

(c) 

(d) 

20. Which one of the following is called a carbylamine?

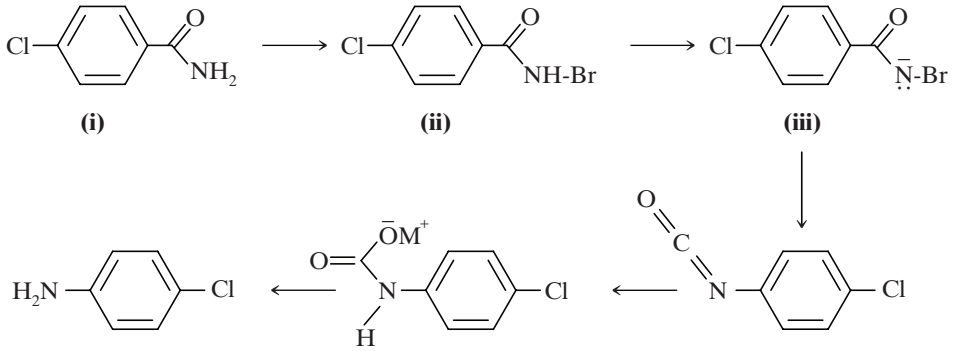
(a) RCN **(b)** $RCONH_2$

(c) RCH=NH **(d)** RNC

Linked Comprehension Type

Paragraph for Questions 1 to 3

$RCONH_2$ is converted into RNH_2 by means of Hofmann bromamide degradation.



(i) **(ii)** **(iii)** **(iv)** **(v)** **(vi)**

In this reaction, RCONHBr is formed from which this reaction has derived its name. Electron-donating group at phenyl activates the reaction. Hofmann degradation reaction is an intramolecular reaction.

1. How can the conversion of (i) to (ii) be brought about?

(a) KBr **(b)** KBr + CH_3ONa

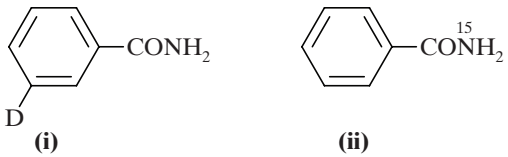
(c) KBr + KOH **(d)** Br_2 + KOH

2. Which is the rate-determining step in Hofmann bromamide degradation?

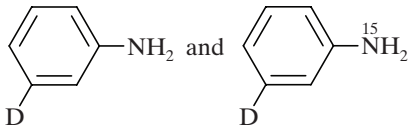
(a) Formation of (i) **(b)** Formation of (ii)

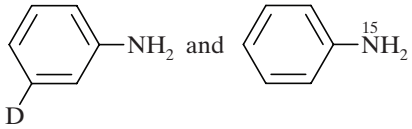
(c) Formation of (iii) **(d)** Formation of (iv)

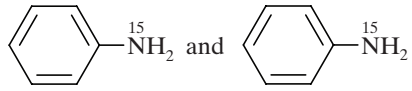
3. What are the constituent amines formed when the mixture of (i) and (ii) undergoes Hofmann bromamide degradation?

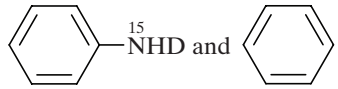


(i) **(ii)**

(a) 

(b) 

(c) 

(d) 

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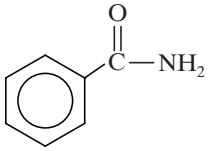
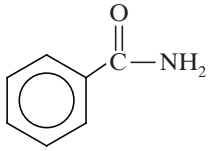
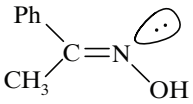
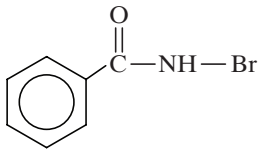
Matrix Match Type

1.

Column-I	Column-II
(a)  $\xrightarrow[KOH]{Br_2}$ (A)	(p) One of the last product of reaction is $PhNH_2$
(b)  $\xrightarrow{LiAlH_4}$ (A)	(q) One of the last product of reaction $PhCH_2NH_2$
(c)  $\xrightarrow[\Delta]{H_2SO_4}$ (A) $\xrightarrow{H_3O^+}$ (B)+(C)	(r) Last product gives positive isocyanide test.
(d)  $\xrightarrow{Ba(OH)_2}$ (A)	(s) Migration of phenyl group is rate determining step

ANSWER KEY

Single Correct Choice Type

1. (d)	2. (b)	3. (d)	4. (a)	5. (b)
6. (c)	7. (a)	8. (b)	9. (a)	10. (d)
11. (a)	12. (b)	13. (b)	14. (c)	15. (a)
16. (b)	17. (b)	18. (c)	19. (c)	20. (d)

Linked Comprehension Type

1. (d) 2. (d) 3. (b)

Matrix Match Type

1. a→(p, r); b→(q, r); c→(p, r, s); d→(p, r)

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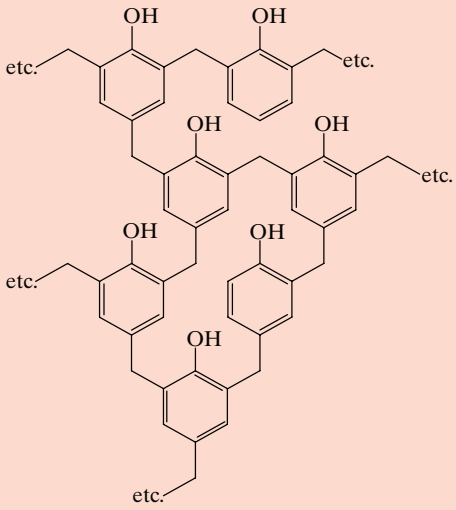
24

Polymers



Bakelite

Contents

24.1 | Some Terms Related to Polymers
24.2 | Classification of Polymers
24.3 | Types of Polymerization Reactions
24.4 | Natural Rubber
24.5 | Synthetic Rubbers
24.6 | Molecular Mass of Polymers
24.7 | Biodegradable Polymers
24.8 | Polymers of Commercial Importance

Natural fibers such as silk, wool and cotton are polymers and have been used for thousands of years. However, in the past few years synthetic polymers such as polyolefins, polyesters, acrylics, nylons, etc., have replaced them extensively as clothing and protective materials. It may be added that biological materials such as proteins, deoxyribonucleic acid (DNA) and polysaccharides are also polymers. Many synthetic polymeric materials, known as biomaterials, are increasingly being employed within the human body either as artificial organs, bone cements, dental cements, ligaments, pacemakers or contact lenses because they are inert and accepted by the body. These include natural polymeric materials, which are derived from animals or plants such as cellulosics, chitin (or chitosan), dextran, agarose and collagen and synthetic polymeric materials such as polysiloxane, polyurethane, polymethyl methacrylate, polyacrylamide, polyester and polyethene oxides. It is being predicted that within a few years, polymers may replace many more conventional materials for various applications.

The term **polymer** is derived from the Greek word *polumerés*, meaning "having many parts". Polymer is a macromolecule with high molecular mass, formed by the repeated unit of several simple molecules called monomers. The process of linking the repeating units is called *polymerization*. The repeating units in a polymer are linked through covalent bonds. For example, polyethene (PE), polymethylmethacrylate (PMMA), polyvinyl chloride (PVC), etc.

$$[-CH_2-CH_2-]_n \quad [-CH_2-\underset{\displaystyle COOCH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}-]_n \quad [-CH_2-\underset{\displaystyle Cl}{\underset{|}{CH}}-]_n$$

Here, n represents the chain length of the polymer.

24.1 | SOME TERMS RELATED TO POLYMERS

1. **Monomers** are simple molecules, which combine with each other to form polymers. Monomers are also called "building blocks" of polymers. To qualify as a monomer, a molecule should have at least two bonding sites (in the form of double or triple bonds or functional groups, such as —OH, —COOH, —NH_2, —NCO, etc.).

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2. **Functionality** is the total number of bonding sites or functional groups present in a monomer molecule. For example, ethene (bifunctional), methylmethacrylate (bifunctional), adipic acid (bifunctional), phenol (trifunctional), glycerol (trifunctional), etc.
3. **Polymerization** is the process of conversion of substances having low molecular weight (monomers) into substances having high molecular weight (polymers) with or without the elimination of byproducts such as HCl, H_2O, NH_3, etc. Polymerization reaction usually takes place in the presence of initiators. The following are the two kinds of polymerization reactions:

(a) $n CH_2{=}CH_2 \longrightarrow [-CH_2-CH_2-]_n$

Ethene **Polyethene**

(b) $n NH_2(CH_2)_6NH_2 + n HOOC(CH_2)_4COOH \xrightarrow{\text{Polymerization}} [-NH-(CH_2)_6-NH-CO-(CH_2)_4-CO-]_n$

Hexamethylene diamine **Adipic acid** **Nylon-6,6**

4. **Degree of polymerization (DP)** is the number of repeating units present in a polymer. Here n is the degree of polymerization. When the value of n is very large, that is, in the range of hundreds or thousands, the polymers are called *high polymers*. For low values of n, that is, less than 10, the polymers are called *oligomers* in general; and more specifically as *dimers* ($n = 2$), *trimers* ($n = 3$), *tetramers* ($n = 4$), and so on.

24.2 | CLASSIFICATION OF POLYMERS

On the basis of their source, structure, mode of polymerization and molecular forces, the polymers are classified as follows:

24.2A Classification Based on Source

1. **Natural polymers:** The polymers obtained from natural sources such as plants and animals are called natural polymers. For example, wood, cellulose, jute, cotton, wool, silk, proteins, natural rubber, etc.
2. **Semisynthetic polymers:** These are polymers obtained from natural polymers by subjecting them to some chemical processes. For example, rubber is subjected to process of vulcanization to get vulcanized rubber. A large number of polymers derived from cellulose such as cellulose acetate and cellulose nitrate are also semisynthetic polymers.
3. **Synthetic polymers:** The polymers synthesized from simple molecules (monomers), are called synthetic polymers. These include plastics, synthetic fibers and synthetic rubbers. Some examples are PE, PVC, PMMA, polytetrafluoro ethene (PTFE), polycarbonate (PC), polyurethane, nylon, Buna-S rubber, etc.

24.2B Classification Based on Structure of Polymers

1. **Linear polymers:** These are polymers in which the molecules form long chains without branches or cross-linked structures. These linear chains may be held together by physical forces but no chemical interactions occur across the chains. For example, bifunctional ethene monomer polymerizes to yield linear structure of high-density polyethene.
2. **Branched chain polymers:** These polymers contain molecules having a linear backbone with branches arising randomly from it. Branched chain polymer is formed when a bifunctional monomer is mixed and polymerized with a little amount of trifunctional monomer. For example, low-density polyethene (LDPE), polystyrene, PMMA, etc.
3. **Cross-linked or network polymers:** When the functionality of monomer is 3 and above, cross-linked three-dimensional network of polymer is formed. They are linked by strong covalent bonds. In fact, whenever a multifunctional monomer is polymerized, the polymer ultimately forms a network polymer. For example, bakelite, urea–formaldehyde, etc.

The structures of linear, branched chain and cross-linked polymers are shown in Fig. 24.1.

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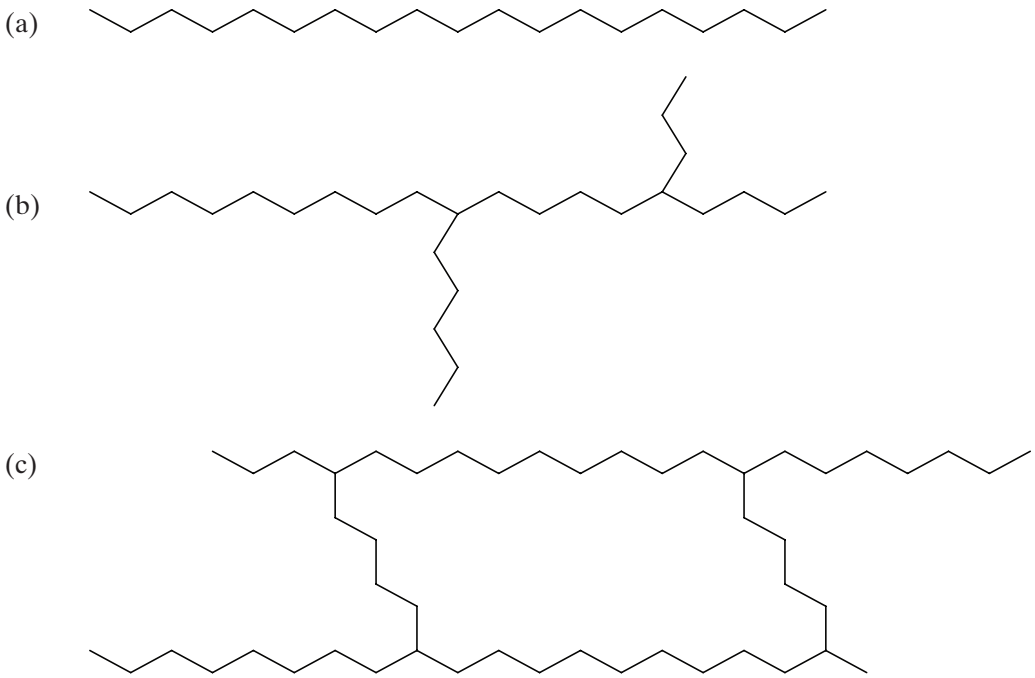
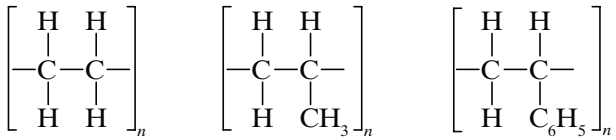


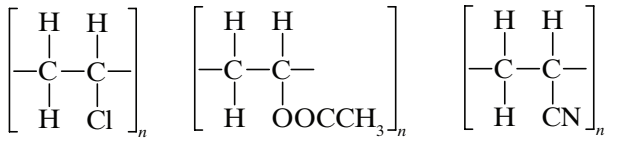
Figure 24.1 (a) Linear, (b) branched chain and (c) cross-linked polymers.

24.2C Classification Based on Mode of Polymerization

1. **Addition polymers:** The polymers formed by self-addition of several monomers having double and triple bonds without elimination of byproducts are called addition polymers. Examples of addition polymers are PE, PVC, PMMA, etc.

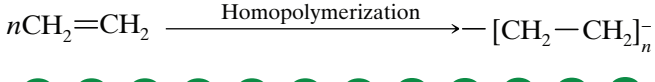


Polyethene **Polypropene** **Polystyrene**



Polyvinyl chloride **Polyvinyl acetate** **Polyacrylonitrile**

Polymers formed from the same type of monomers are called **homopolymers**; for example, polyethene formed by ethene monomers.





Homopolymer

If two or more different repeating units (monomers) make up the polymer, it is known as a copolymer, for example, Buna-S.

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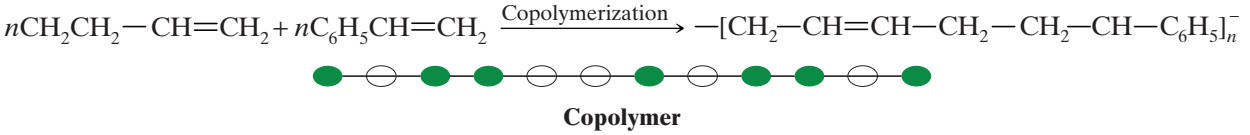


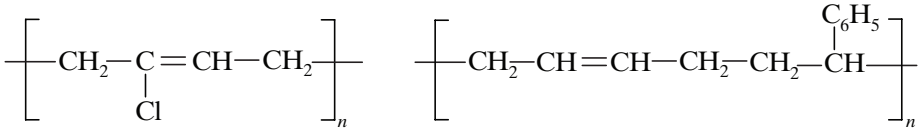
2. **Condensation polymers:** The polymers formed by intermolecular condensation reaction by the functional groups of monomers with continuous elimination of byproducts are called condensation polymers. For example, phenol–formaldehyde resin, polyester, epoxy resin, nylon-6,6, etc.



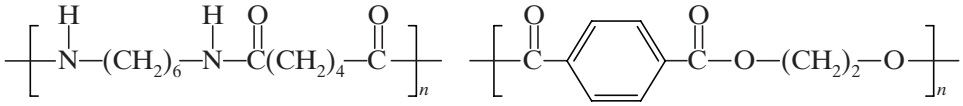
24.2D Classification Based on Molecular Forces

The polymeric chains are held together by intermolecular forces such as van der Waals forces. These forces determine the mechanical properties of a polymer. Further, the different uses and applications of polymers are based on mechanical properties such elasticity, toughness, tensile strength, etc. Based on the nature of intermolecular forces present, polymers may be classified into the following four categories.

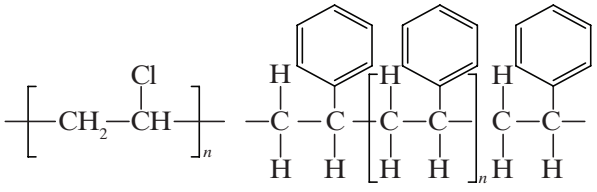
1. **Elastomers:** The polymers which undergo very long elongation when pulled apart, and return to their original length on release are called **elastomers**. These are mainly coiled and long-chain polymers with no intermolecular forces except weak van der Waals forces which allow the polymer to be stretched. Sometimes a few cross-links are introduced between the chains, as in the case of vulcanized rubber, which help the polymer to retract to its original position. Some examples of elastomers are natural rubber, neoprene, Buna-S, butyl rubber, silicone rubber, etc.



2. **Fibers:** These are long, thin and thread-like polymers, whose length is at least 100 times their diameter. They do not undergo stretching and deformation like elastomers but have high tensile strength and modulus. They are linked to each other by strong intermolecular forces like hydrogen bonding, which hold the polymer chains together and make the structure of these polymers crystalline. For example, natural fibers such as jute, wood, silk, etc., and synthetic fibers such as nylon-6,6 and terylene.



3. **Thermoplastic polymers:** The polymers that soften on heating and which can be converted into any shape on cooling are called thermoplastics. The process of heating, reshaping and retaining the shape on cooling can be repeated several times without affecting their properties much. They are either linear or slightly branched long-chain molecules. Their intermolecular forces of attraction are intermediate between elastomers and fibers. For example, polythene, polystyrene, polyvinyls, etc.



4. **Thermosetting polymers:** Some cross-linked or heavily branched polymers undergo chemical changes and cross-linking on heating and become permanently hard, rigid and infusible on cooling. These are called thermosetting

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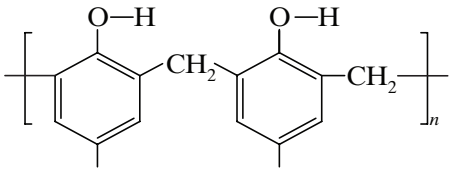
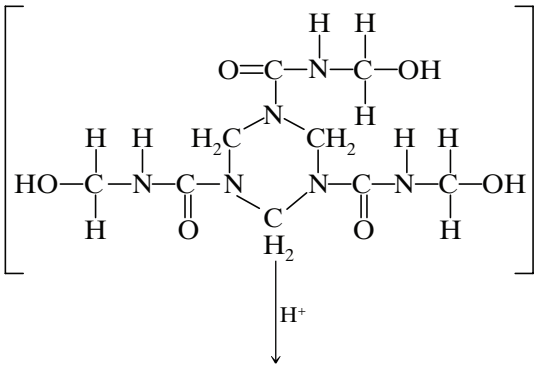
polymers and they do not soften on reheating; instead they undergo degradation. These are not reusable. For example, phenol–formaldehyde (bake-lite), urea–formaldehyde, epoxy resin, etc.



Bakelite



Urea-formaldehyde resin

The structures of thermoplastic and thermosetting polymers are illustrated in Fig. 24.2.

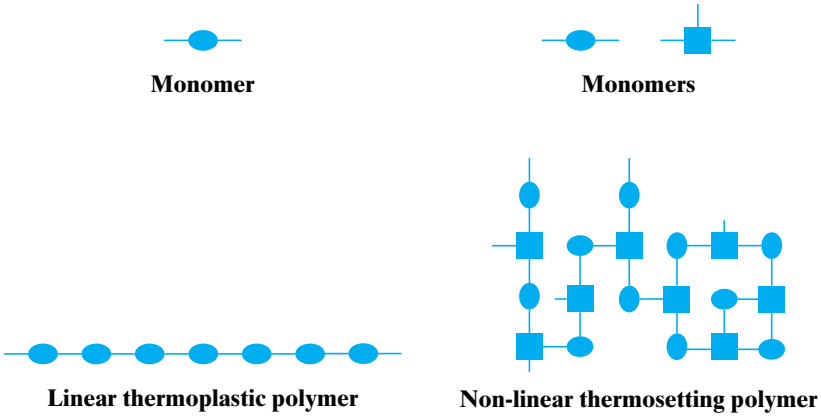


Figure 24.2 Diagrams of thermoplastic and thermosetting polymer structures.

24.3 | TYPES OF POLYMERIZATION REACTIONS

The polymerization reactions can be classified into two broad categories: (a) addition polymerization or chain growth polymerization and (b) condensation polymerization or step growth polymerization.

24.3A Addition Polymerization or Chain Growth Polymerization

A polymerization reaction in which monomers containing one or more double bonds are linked to each other without the elimination of any byproducts, usually in the presence of free radical initiator, is called addition polymerization. Polymerization may also take place in the presence of ionic species. The monomers used in this reaction are unsaturated compounds such as alkenes, alkadienes, etc. Since in this polymerization the monomers are linked by a chain reaction, it is also called **chain growth polymerization** and the polymers formed are called **chain growth polymers**. For example, the formation of polyethene

$$n\mathrm{CH_2{=}CH_2} \xrightarrow{\text{Initiator}} [-\mathrm{CH_2{-}CH_2}-]_n$$

Ethene **Polyethene**

The main features of addition (chain) polymerization are as follows:

1. Only olefinic or vinyl compounds can undergo addition polymerization.
2. There is no elimination of byproducts.
3. Double bond provides required bonding sites.

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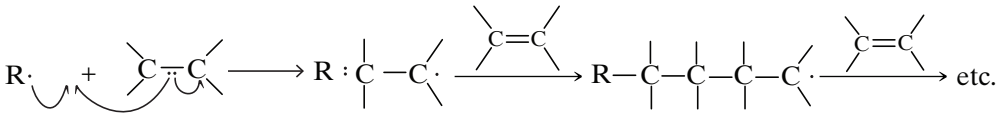
4. The addition of monomers takes place rapidly.
5. The elemental composition of the polymer is the same as that of the monomer.

The formation of chain growth polymers is initiated either in the presence of free radicals or ions. However, mostly chain growth polymerization proceeds through free radical mechanism.

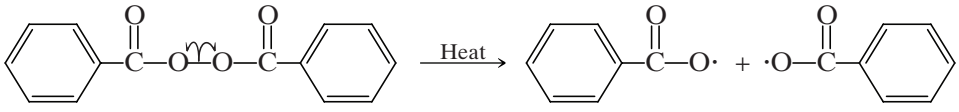
Free Radical Mechanism

The general reaction of free radical mechanism is as follows:

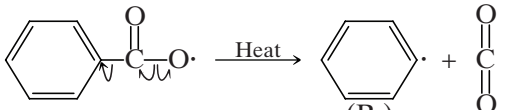


Addition polymerization that takes place through free radical mechanism involves three distinct stages: initiation, propagation and termination. The three stages are described as follows for the polymerization of ethane to polyethene.

1. **Chain initiation:** This process involves two reactions. The first reaction involves the production of free radicals by the homolytic dissociation of an initiator, such as dibenzoyl peroxide (other examples are acetyl peroxide, *tert*-butyl peroxide, etc.) to yield a pair of radicals. A free radical is an atomic or molecular species having an odd or unpaired electron. They are highly active species.



Dibenzoyl peroxide



Benzoyl free radical **Phenyl free radical**

In the second reaction, the process of polymerization begins by the addition of benzoyl or phenyl free radical to the double bond of ethene and is called the chain initiating step. The addition of this radical to the first monomer molecule produces the chain initiating species.

$$\dot{R} + CH_2{=}CH_2 \longrightarrow R{-}CH_2{-}\dot{C}H_2$$

2. **Chain propagation:** In this step, the radical attacks another monomer to produce yet another free radical and the process continues to build new and bigger radicals that carry the reaction forward until termination occurs.

$$R{-}CH_2{-}\dot{C}H_2 + CH_2{=}CH_2 \longrightarrow R{-}CH_2{-}CH_2{-}CH_2{-}\dot{C}H_2 \xrightarrow{n CH_2=CH_2} R{-}(CH_2{-}CH_2)_n{-}CH_2{-}\dot{C}H_2$$

In general

3. **Chain termination:** At some point, the propagating polymer chain stops growing and terminates. Termination can happen by many methods, one of which is coupling or combination of two growing chains.

$$R{-}(CH_2{-}CH_2)_n{-}CH_2{-}\dot{C}H_2 + \dot{C}H_2{-}CH_2{-}(CH_2{-}CH_2)_n{-}R \longrightarrow R{-}(CH_2{-}CH_2)_n{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}(CH_2)_n{-}R$$

Preparation of Some Important Addition Polymers

1. **Polythene:** The two types of polyethenes are prepared as follows:

   (a) Low density polythene (LDP): Ethene is polymerized under high pressure (1000–2000 atm) and temperature (350–570 K) in the presence of dioxygen or the catalyst peroxide initiator. Free radical addition and H atom abstraction take place leading to a highly branched structure of LDP.

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LDP is tough, chemically inert, flexible and a poor conductor of electricity. It is used in electric wire insulation, toys, squeeze bottles, pipes, etc.

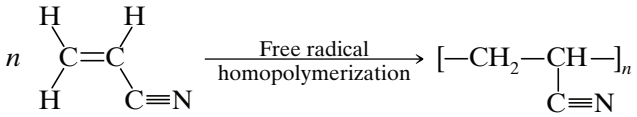
(b) High density polythene (HDP): Ethene is polymerized in a hydrocarbon solvent in the presence of triethyl aluminium and titanium chloride (**Ziegler–Natta catalyst**) as catalysts and at 6–7 atm pressure and 333–343 K temperature. The linear molecules are closely packed. Pipes, bottles, buckets, etc. are manufactured from HDP. It is chemically inert and also more tough and hard.

2. **Polytetrafluoroethene (Teflon):** Tetrafluoroethene (TFE) is heated with a free radical peroxide or ammonium persulphate catalyst at high pressure to give polytetrafluoroethene (PTFE). It is a highly crystalline polymer (93–98%). It has high melting temperature (T_m = 327°C), high temperature stability and low temperature flexibility. It has low coefficient of friction and remains slippery over a wide range of temperature (–40°C to 300°C). It is practically insoluble in any solvent and is not wetted by either oil or water. It has excellent electrical insulating properties.

$$n\underset{\textbf{TFE}}{CF_2{=}CF_2} \xrightarrow[\text{Peroxide as initiator}]{\text{Emulsion polymerization}} \underset{\textbf{PTFE}}{[-CF_2-\dot{C}F_2-]_n}$$

Teflon is used for insulation of motors, generators, transformers, coils, capacitors, wires and cables. It is used as coating on food processing equipments such as bakery trays, frying pans because it is not wetted by oil or water. It is also used for coating on army weapons as an anticorrosive coat. It is also used as a dry lubricant since it remains slippery over a wide range of temperatures.

3. **Polyacrylonitrile:** Acrylonitrile in the presence of a peroxide catalyst forms polyacrylonitrile.

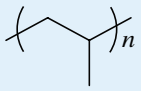
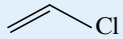
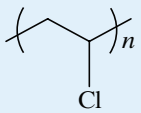
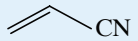
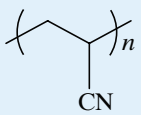
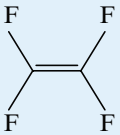
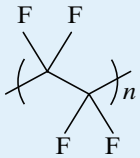
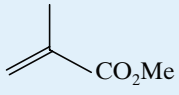
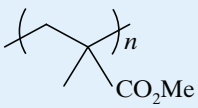


Acrylonitrile **Polyacrylonitrile**

It is used in the manufacture of fibres such as orlon and acrilan and is used as a substitute of wool. Fiber obtained by homopolymerization of acrylonitrile is used for making hot gas filtration systems, outdoor awnings and sails for yachts. These fibers also find use in fiber reinforced concrete.

Table 24.1 lists several other common chain-growth polymers.

Table 24.1 Other Common Chain-Growth Polymers

Monomer	Polymer	Names
		Polypropylene
		Poly(vinyl chloride), PVC
		Polyacrylonitrile, Orlon
		Poly(tetrafluoroethene), Teflon
		Poly(methyl methacrylate), Lucite, Plexiglas, Perspex

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24.3B Condensation Polymerization or Step Growth Polymerization

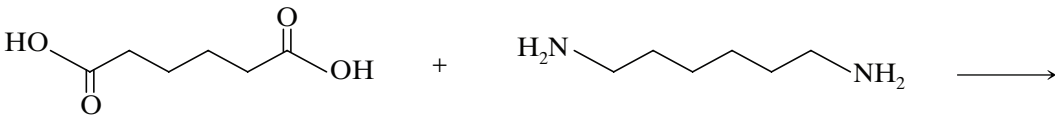
A polymerization reaction in which bifunctional or polyfunctional monomers undergo intermolecular condensation leading to the formation of high molecular mass polymers with continuous elimination of byproducts, such as H_2O, HCl, NH_3, etc., is called **condensation polymerization**.

Condensation polymerization reaction occurs in steps. In each step, a bifunctional species is formed which undergoes further condensation to produce a new functionalized species and the polymer chain grows with each step. Hence, it is also called *step polymerization* and the polymers formed are called *step growth polymers*. The reaction is normally catalyzed by acids or bases.

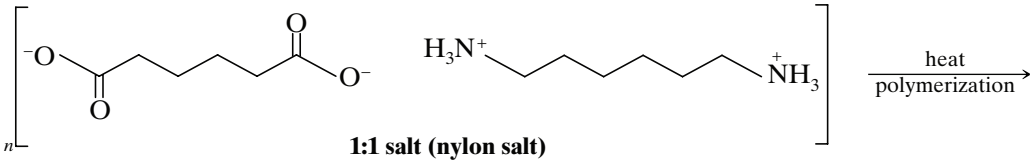
Depending on their linkage units, some important polymers formed by condensation polymerization are as follows:

1. **Polyamides:** Silk and wool are two naturally occurring polymers that humans have used for centuries to fabricate articles of clothing. The search for a synthetic material with properties similar to those of silk led to the discovery of a family of synthetic polyamides called nylons. Polyamides are polymers possessing an amide linkage and are prepared by condensation polymerization of dicarboxylic acids with diamines or amino acids with their lactams as in nylon-6,6 and nylon-6, respectively.

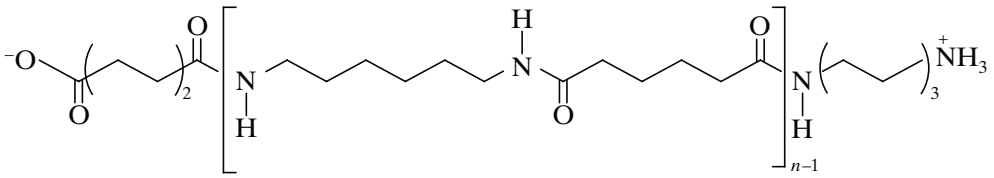
   (a) Nylon-6,6: One of the most important nylons, called nylon-6,6, can be prepared from the six-carbon dicarboxylic acid, adipic acid and the six-carbon diamine, hexamethylenediamine (hexane-1,6-diamine) by heating them at 553 K under high pressure. In the commercial process these two compounds are allowed to react in equimolar proportions in order to produce a 1:1 salt, which on heating to a temperature of 270°C at a pressure of 17 atm causes a polymerization to take place. Water molecules are lost as condensation reactions occur between $-\overset{\overset{O}{\|}}{C}-O^-$ and $-NH_3^+$ groups of the salt to give the polyamide.



Adipic acid + **Hexamethylenediamine** →



1:1 salt (nylon salt)



Nylon-6,6
(a polyamide)

The nylon-6,6 produced in this way has a molecular weight of about 10,000, has a melting point of about 250°C, and when molten can be spun into fibers from a melt. The fibers are then stretched to about four times their original length. This orients the linear polyamide molecules so that they are parallel to the fiber axis and allows hydrogen bonds to form between — NH — and — C═O groups on adjacent chains. Called cold drawing, this stretching greatly increases the fibers' strength.

Nylon-6,6 fibers are used for making fabric for clothing, socks, sportswear, carpets, etc. They are also used for making combs and bristles of the brushes; as also used for making sports gear, fishing lines and other recreational equipment.

(b) Nylon-6: It can be prepared by a ring-opening polymerization of ε-caprolactam in the presence of water at 533–543 K:

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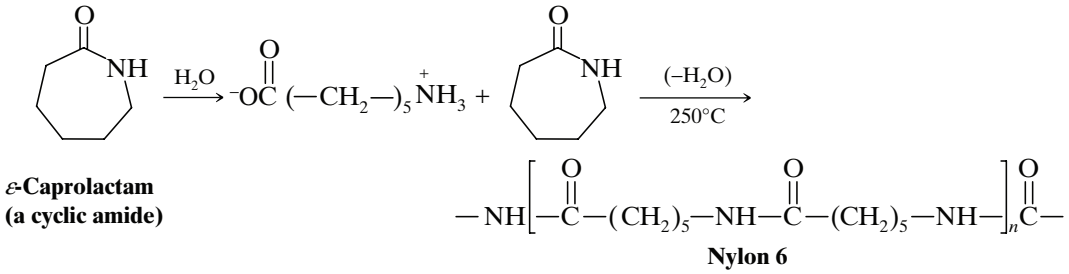


ε-Caprolactam (a cyclic amide)

Nylon 6

In this process, ε-caprolactam is allowed to react with water, converting some of it into ε-aminocaproic acid. Then, heating this mixture at 250°C drives off water as ε-caprolactam and ε-aminocaproic acid (6-aminohexanoic acid) react to produce the polyamide. Nylon-6 can also be converted into fibers by melt spinning. Nylon-6 is mainly used for making cords for tyres. It is also used for making ropes and fabrics.

Nylons find extensive use because of their unique thermo-mechanical properties as described below:

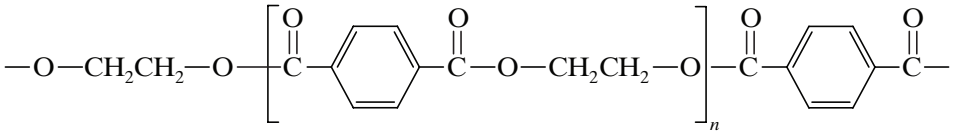
(i) Nylon fibers are linear structures in which the molecular chains are arranged parallel to each other and held together by hydrogen bonding. The strong intermolecular hydrogen bonding makes the structure of these fibers crystalline and imparts them high strength, elasticity and melting point.

(ii) They are chemically stable and resistant to abrasion.

(iii) The yarn is smooth, long-lasting and can be spun into fabric.

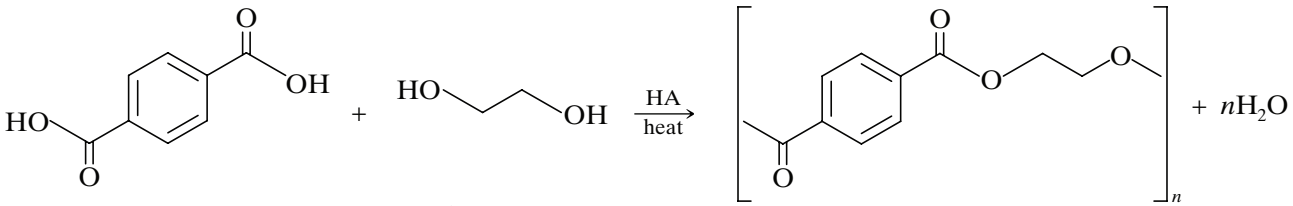
(iv) The fabric is tough, lustrous, moisture resistant, easy to dye, retains color and can be set by heat or steam.

2. **Polyesters:** These are formed from condensation of dicarboxylic acids and diols. One of the most important polyesters is poly (ethene terephthalate), a polymer that is marketed under the names Dacron, Terylene and Mylar.



Poly(ethene terephthalate) or PET (Dacron, Terylene, or Mylar)

Poly(ethene terephthalate) can be obtained by a direct acid-catalyzed esterification of ethylene glycol and terephthalic acid at 420–460 K. The catalyst used in the reaction is zinc acetate and antimony trioxide.



Terephthalic acid **1,2-Ethanediol** **Poly(ethylene terephthalate) (a polyester)**

The poly(ethene terephthalate) thus produced melts at about 270°C. It can be melt-spun into fibers to produce crease-resistant Dacron or Terylene; it can also be made into a film, in which form it is marketed as Mylar. It is also used in making safety helmets.

3. **Phenol–formaldehyde polymer (Bakelite and related polymers):** One of the first synthetic polymers to be produced was a polymer (or resin) known as Bakelite. It is made by a condensation reaction between phenol and formaldehyde; the reaction can be catalyzed by either acids or bases. A large excess of phenol on heating with an aqueous solution of formaldehyde in the presence of acid catalyst first gives a linear polymer of low molecular weight called novalac resin. Novolacs (used in paints) are phenol–formaldehyde polymers made when the molar ratio of formaldehyde to phenol is less than 1.

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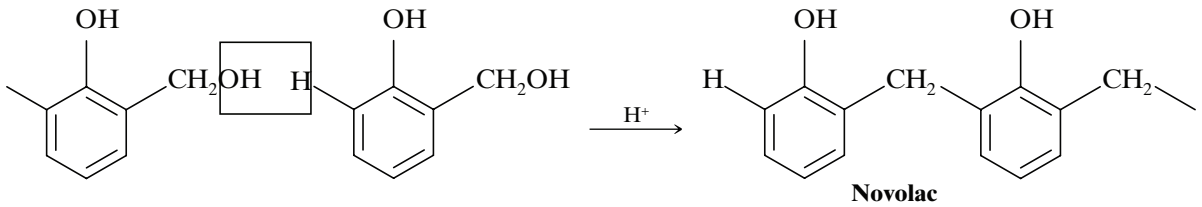
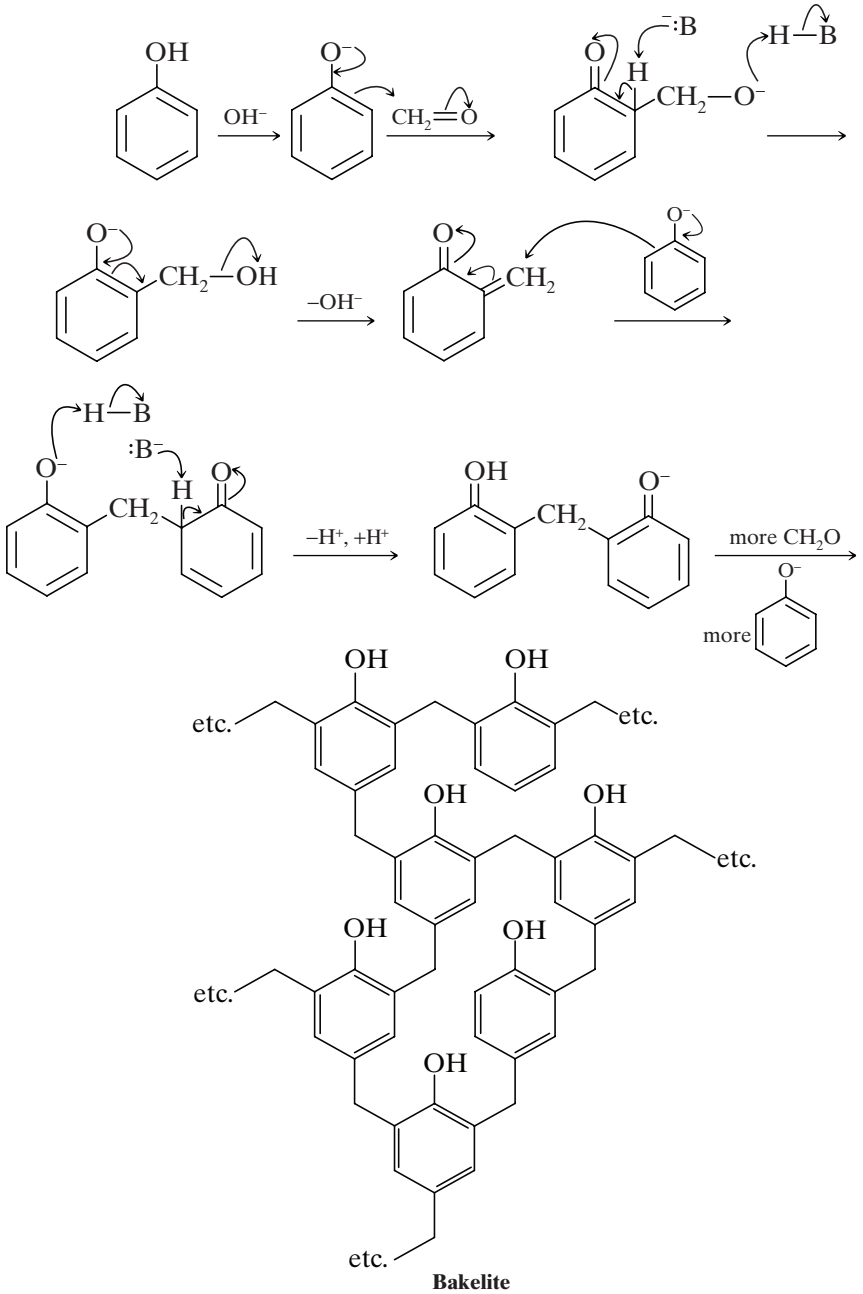


Novolac

Further cross-linking of novolac polymer can be done by adding excess of formaldehyde and heating to give highly cross-linked product called Bakelite. The mechanism for base-catalyzed reaction is shown in Fig. 24.3. Reaction can take place at the *ortho* and *para* positions of phenol and *o*- and/or *p*-hydroxymethyl phenol derivatives are formed first. These react further with phenol to form compounds with rings joined through the $-CH_2$ group.

Bakelite is used for making electrical equipment parts such as switches, plugs, switchboards, cooker handles, welding tongs, electric iron parts and telephone parts. Due to its hardness, it is used for making golf ball and heads



Bakelite

Figure 24.3 Mechanism for base-catalyzed reaction.

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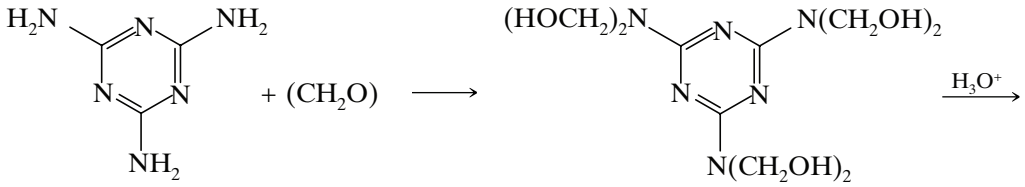
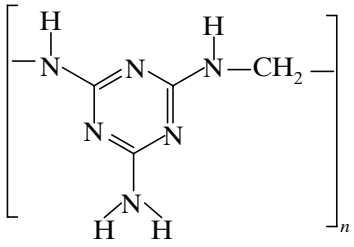
for typewriters. It is used as hot-setting adhesives for plywood, cement and for lamination of paper, cardboards and wood.

4. **Melamine-formaldehyde (MF) polymer:** Reaction of melamine with neutralized formaldehyde at about 80–100°C leads to the production of a mixture of water-soluble methylol melamines. On further heating, the methylol melamines condense and a point is reached where hydrophilic resin separates out on cooling. This resin on polymerization yields melamine–formaldehyde polymer commonly known as melamine. MF is hard, scratch resistant, fairly heat resistant and free from color with wide colorability.



Melamine **Formaldehyde** **Hexamethylolmelamine (Resin)**



Cross-linked MF

Some important thermo-mechanical properties that are responsible for its use are as follows:

(i) Bakelite is a rigid, hard, scratch resistance material.

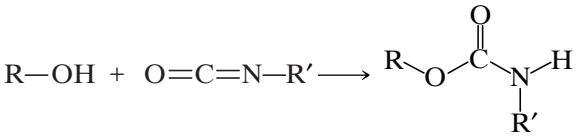
(ii) It shows good electrical insulation property.

(iii) It has thermal stability of up to 200°C and good dimensional stability.

(iv) It is resistant to water and shows low flammability.

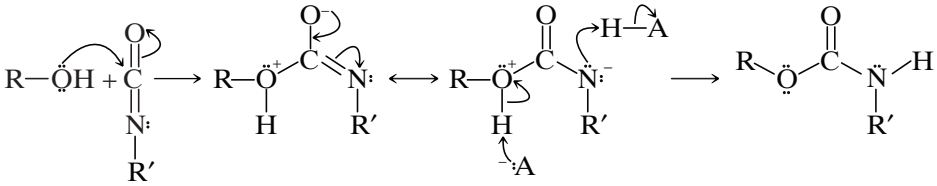
The principal application of melamine polymer is in the manufacture of unbreakable tableware. Cellulose-filled compounds find usage in outlet for trays, clock cases and radio cabinets. Mineral-filled powders are used in electrical applications and knobs and handles for kitchen utensils.

5. **Polyurethanes:** A *urethane* is the product formed when an alcohol reacts with an isocyanate:



Alcohol **An isocyanate** **A urethane (a carbamate)**

The reaction takes place in the following way:



A urethane is also called a carbamate because formally it is an ester of an alcohol (ROH) and a carbamic acid ($R'NHCO_2H$).

Polyurethanes are usually made by allowing a diol to react with a diisocyanate. The diol is typically polyester with $—CH_2OH$ end groups. The diisocyanate is usually toluene 2,4-diisocyanate:

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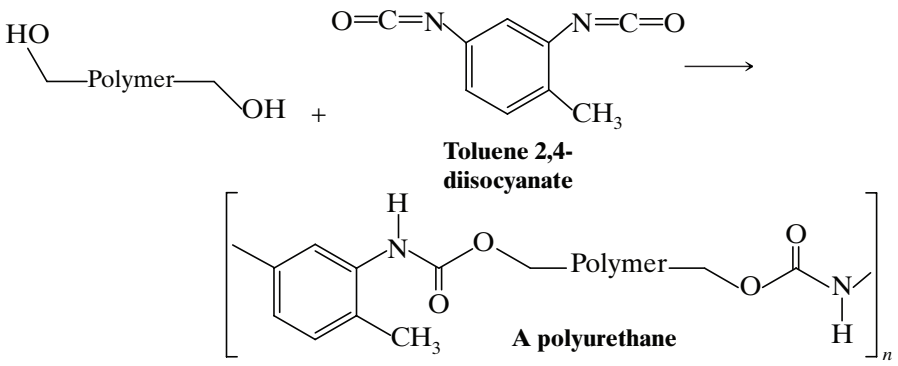
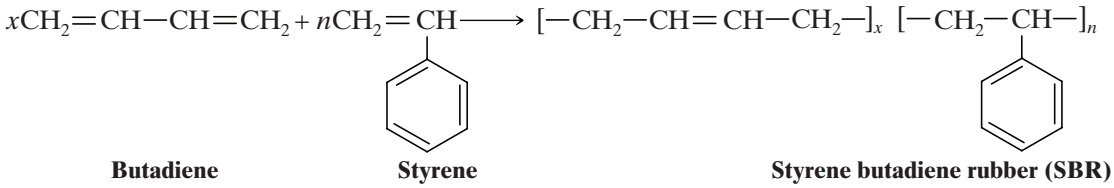


Polyurethane foams, as used in pillows and paddings, are made by adding small amounts of water to the reaction mixture during the polymerization with the diisocyanate. Some of the isocyanate groups react with water to produce carbon dioxide, and this gas acts as the foaming agent:

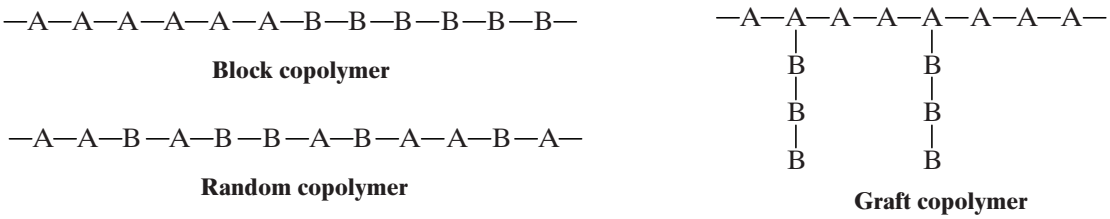
$$R{-}N{=}C{=}O + H_2O \longrightarrow R{-}NH_2 + CO_2\uparrow$$

24.3C Copolymerization

The polymerization of two or more different monomers resulting in the formation of a polymer containing both monomers linked in one chain is called **copolymerization**. It can be considered as a type of addition polymerization. The polymers so formed are called *copolymers*. They are formed both by chain growth and step growth polymerization reactions.



Copolymers can have any of the following three structures. If the various repeating units occur randomly along the chain structure, the polymer is called a random copolymer. When repeating units of each kind appear in blocks, it is called a *block copolymer*. *Graft copolymers* are formed when chains of one kind are attached to the backbone of a different polymer. For example, in case of linear chains synthesized from repeat units A and B, the block, random and graft copolymers can be represented as



Copolymers have properties different from homopolymers of the constituting monomers. For example, butadiene–styrene copolymer has high abrasion resistance and load-bearing capacity. It has low oxidation resistance and swells in oil and solvents, like natural rubber. It also vulcanizes to produce cold rubber, which has greater tensile strength and abrasion resistance. It is used in motor tyres, shoes soles, footwear components, insulation of wires and cables, carpet backing, gaskets and adhesives.

24.4 | NATURAL RUBBER

Natural rubber, the original elastomer, still plays an important role among elastomers. It is prepared from the milky juice (latex) which forms a colloidal dispersion of rubber in water, obtained from *Hevea* rubber trees or other sources like gutta-percha and balata. The rubber trees are found in India, Sri Lanka, Indonesia, Malaysia and South America. Natural rubber is a linear polymer of isoprene hence it is also called as polyisoprene.

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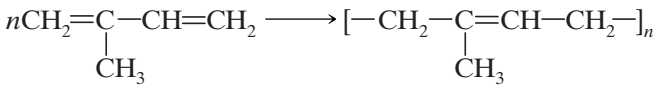
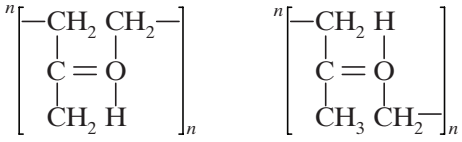


Chemically, natural rubber from *Hevea* trees is a linear polymer of isoprene (2-methyl-1,3-butadiene) also known as *cis*-1,4-polyisoprene and that tapped from other sources (gutta-percha and balata) is the *trans* isomer of polyisoprene.

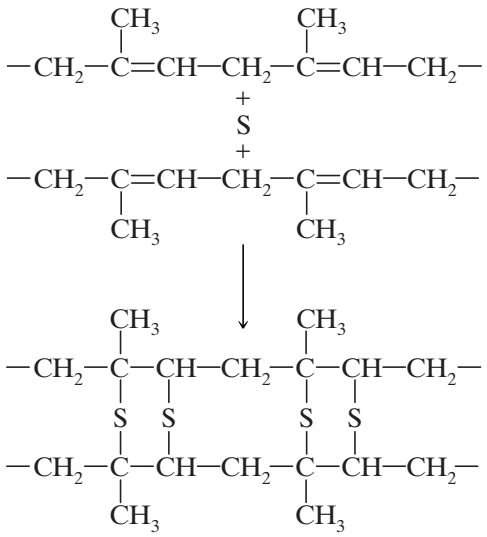


Natural rubber **Gutta-percha**

Rubber (mainly *cis*-1,4 polyisoprene) consists of long, coiled-up polymer chains that are interlinked at a few points and held together by van der Waals forces. This imparts properties of flexibility and extensibility to rubber. On application of force, the molecules straighten out in the direction in which they are being pulled and stretch like a spring. They are restored to their normal random arrangement on release.

24.4A Vulcanization of Rubber

The process of heating and mixing crude rubber with sulphur to a definite temperature for a specific time is known as **vulcanization**. At high temperature (>335 K), the natural rubber is soft and at low temperatures (< 283 K), it becomes brittle. It has high water absorption capacity, is soluble in non-polar solvents and is non-resistant to attack by oxidizing agents. The natural rubber is cured by vulcanization which modifies it to become more durable with better mechanical properties. The sulphur combines chemically at the double bonds forming cross-links between different polymer chains. This cross-linking brings about stiffness in the rubber, and subsequently prevents intermolecular sliding of rubber polymer chains.



The extent of stiffness of vulcanized rubber depends upon the amount of the sulphur added. For example, a rubber tyre contains 5% sulphur, whereas a battery case made from rubber may contain as much as 30% of sulphur. This highly vulcanized rubber is called ebonite.

Important properties of vulcanized rubber responsible for its use are as follows:

(i) It has good tensile strength and extensibility.

(ii) It has excellent resilience.

(iii) It possesses low water absorption capacity.

(iv) It has higher resistance to oxidation and to abrasion, wear and tear resistance.

(v) It is resistant to organic solvents such as petrol, benzene, CCl_4 and fats and oils. However, it swells in these liquids.

(vi) It exhibits good electrical insulation property.

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(vii) It has a wide useful temperature range from –40°C to 100°C.

(viii) It is very easy to tailor-make the properties of vulcanized rubber for the specific needs.

24.5 | SYNTHETIC RUBBERS

Synthetic rubbers are a substitute for natural rubber and have improved material properties to overcome the drawbacks associated with natural rubber. Synthetic rubber can get stretched to double its length, but can return back to normal once the stretching force is released. Synthetic rubbers are made from homopolymers of 1,3-butadiene derivatives or copolymers of 1,3-butadiene or its derivatives with another unsaturated monomer.

24.5A Preparation of Synthetic Rubbers

Neoprene (Polychloroprene)

Neoprene is prepared by polymerization of chloroprene in the presence of persulphate as initiator (free radical polymerization).

$$n\mathrm{CH_2{=}\underset{\displaystyle \mathrm{Cl}}{\underset{|}{C}}{-}CH{=}CH_2} \longrightarrow \left[-\mathrm{CH_2}-\underset{\displaystyle \mathrm{Cl}}{\underset{|}{C}}{=}\mathrm{CH}-\mathrm{CH_2}-\right]_n$$

2-Chloro-1,3-butadiene **Neoprene**

Neoprene rubber has greater resistance to vegetable and mineral oils as compared to natural rubber. It is used for manufacture of conveyor belts, car fan belts, gaskets, hoses, mouse pads, shoe heels, etc. It is also used for corrosion resistance coatings, lining material in reaction vessels and tubes for carrying oils and chemicals. It also finds use as adhesive in tapes and highway joints, and in gloves.

Buna-N

Buna-N rubber is a copolymer of acrylonitrile and 1,3-butadiene prepared in the presence of a peroxide catalyst.

$$x\mathrm{CH_2{=}CH{-}CH{=}CH_2} + n\mathrm{CH_2{=}\underset{\displaystyle \mathrm{CN}}{\underset{|}{CH}}} \longrightarrow \left[-\mathrm{CH_2}-\mathrm{CH}{=}\mathrm{CH}-\mathrm{CH_2}-\right]_x \left[-\mathrm{CH_2}-\underset{\displaystyle \mathrm{CN}}{\underset{|}{CH}}-\right]_n$$

Butadiene **Acrylonitrile** **Nitrile rubber (Buna-N)**

Nitrile rubber has low swelling and low solubility. It has good tensile strength and is resistant to action of petrol, lubricating oils and organic solvents. It also possesses good heat resistance. It is used in fuel tanks, gasoline hoses, as an adhesive and in the form of latex for impregnating paper, leather and textiles.

Synthetic rubbers have several advantages over natural rubber:

1. It is produced using monomers derived from petrochemical raw materials.
2. It is more economical than natural rubber.
3. It is superior to natural rubber in certain properties, such as tensile strength and abrasion resistance.
4. It can be tailor-made to the end properties and use.
5. It has low temperature flexibility and high temperature stability.

24.6 | MOLECULAR MASS OF POLYMERS

Molecular weight is an extremely important variable in polymers because it relates directly to the physical properties of macromolecules. In general, higher the molecular weight, tougher the polymer; however, too high molecular weight will lead to processing difficulties. The molecular weight and its distribution determine the viscous and elastic properties of the molten polymer. A variety of methods are available for molecular weight determination, and they are applicable in different ranges of molecular weight. Since any polymer sample contains a mixture of chain lengths of different sizes, the molecular weight is always expressed as average.

The number average molecular weight of a polymer is given by

$$\bar{M}_n = \frac{\sum M_i N_i}{N_i}$$

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where N_i is the number of molecules or the number of moles of those molecules having molecular weight M_i.

$$\bar{M}_w = \frac{\sum w_i M_i}{\sum w_i} = \frac{\sum N_i M_i^2}{\sum N_i M_i}$$

The weight average molecular weight is given by

$$\bar{M}_w = \frac{\sum w_i M_i}{\sum w_i} = \frac{\sum N_i M_i^2}{\sum N_i M_i}$$

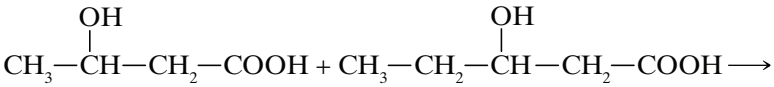
24.7 | BIODEGRADABLE POLYMERS

Biopolymers such as polysaccharides (starch and cellulose), proteins, nucleic acids, etc., undergo natural degradation by the action of naturally occurring microorganisms, such as bacteria, fungi and algae. Most of the synthetic polymers do not get degraded in this manner and thus pose many environmental problems. Therefore, some synthetic biodegradable polymers have now been designed and developed whose functional groups are similar to those of biopolymers and hence they undergo biodegradation. The biodegradation reactions of synthetic biodegradable polymers is same as that of natural polymers. These are enzyme-catalyzed and proceed in aqueous media. Biodegradable polymers can be broadly classified as

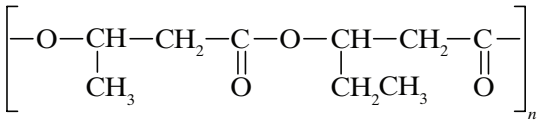
1. Natural biodegradable polymers that have been modified with additives and fillers.
2. Synthetic biodegradable polymers, primarily polyesters.

The major category of synthetic biodegradable polymers consists of aliphatic polyesters with a hydrolysable linkage along the polymer chain such as polylactic acid (PLA). Other widely available synthetic types include aliphatic/aromatic copolyesters. The following are some important examples:

1. **Poly β-hydroxybutyrate – co-β-hydroxy valerate (PHBV):** It is obtained by copolymerization of 3-hydroxybutanoic acid and 3-hydroxypentanoic acid. It can be degraded by the bacteria. It finds use in packaging orthopaedic devices and in controlled release of drugs.

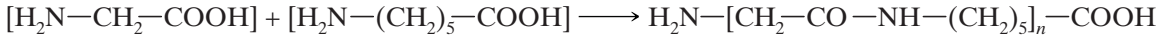


3-Hydroxybutanoic acid **3-Hydroxypentanoic acid**



PHBV

2. **Nylon-2-nylon-6:** It is a polyamide formed by copolymerization of glycine and amino caproic acid, and is biodegradable.



Some other biodegradable polymers are polyglycollic acid (used for stitching wounds), polylactic acid, poly(*e*-caprolactone; PCL).

24.8 | POLYMERS OF COMMERCIAL IMPORTANCE

The polymers of commercial importance are as given in Table 24.2.

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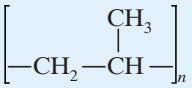
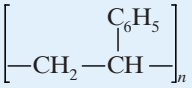
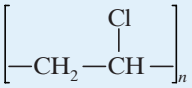
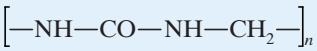
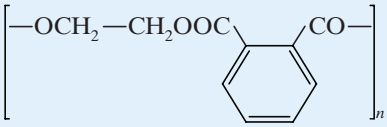
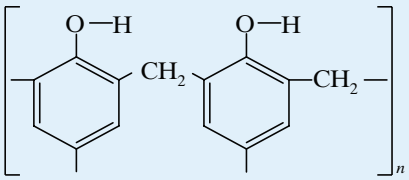
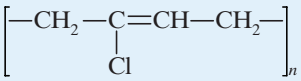
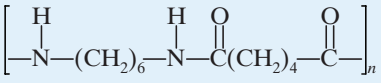
Table 24.2 Some Commercially Important Polymers

Polymer	Monomer	Structure	Uses
Polypropene	Propene		Manufacture of pipes, toys, etc.
Polystyrene	Styrene		Manufacturing of household wares, such as combs, toys, buttons, radio and television parts, video cassettes, refrigerator parts, machine housings, blister packs and high frequency electrical insulation material.
Polyvinyl chloride (PVC)	Vinyl chloride		in rigid pipes, flooring and vinyl siding, wire and cable insulations and in packaging, flooring, artificial leather, wall coverings and carpet backing, pipe fittings, electrical outlet boxes and parts for automotive bumpers.
Urea-formaldehyde Resin	(a) Urea (b) Formaldehyde		Used as adhesives for the particle board, plywood and furniture industries and as casting material in textile finishing, as foams to aid floral decoration and as artificial snow in cinema and television productions.
Glyptal	(a) Ethylene glycol (b) Phthalic acid		Used in paint and lacquer manufacturing.
Bakelite	(a) Phenol (b) Formaldehyde		Manufacture of switches, plugs, switchboards, cooker handles, welding tongs, electric iron parts and telephone parts.
Neoprene	(a) Chloroprene (b) Persulphate		Manufacture of conveyor belts, car fan belts, gaskets, hoses, mouse pads, shoe heels. Also used for corrosion resistance coatings, lining material in reaction vessels and tubes for carrying oils and chemicals. It also finds use as adhesive in tapes and highway joints, and in gloves.
Nylon-6,6	(a) Adipic acid (b) Hexamethylenediamine		Used for making fabric for clothing, socks, sportswear, carpets, etc. It is used for making combs and bristles of the brushes. It is also is used for making sports gear, fishing lines and other recreational equipment.

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ADDITIONAL OBJECTIVE QUESTIONS

Single Correct Choice Type

1. Monomers are converted to polymers by
   (a) hydrolysis of monomer.
   (b) condensation of monomers.
   (c) protonation of monomers.
   (d) none.
2. Nylon threads are made up of
   (a) polyvinyl polymer.
   (b) polyester polymer.
   (c) polyamide polymer.
   (d) polyethylene polymer.
3. The polymer containing strong intermolecular forces, that is, hydrogen bonding is
   (a) teflon.
   (b) nylon-6,6.
   (c) polystyrene.
   (d) natural rubber.
4. Which of the following is not a copolymer?
   (a) Plexiglass
   (b) Buna-S
   (c) Nylon-6,6
   (d) Dacron
5. Chemical name of melamine is
   (a) 2,4-diamino-1,3,5-triazine.
   (b) 2-amino-1,3,5-triazine.
   (c) 1,3,5-triazine-2,4,6-triamino.
   (d) 1,3,5-triamino-2,4,6-triazine.
6. Of the following which is a step growth polymer?
   (a) Bakelite
   (b) Polyethylene
   (c) Teflon
   (d) PVC
7. Which of the following monomers gives synthetic rubber on polymerization?
   (a) $CH_2 = CHCl$
   (b) $CCl_2 = CCl_2$
   (c) $CH_2 = C(CH_3) - CH = CH_2$
   (d) $CH_2 = CCl - CH = CH_2$
8. From the given statements, which one is not true?
   (a) Teflon is a macromolecule.
   (b) Teflon is a polymer.
   (c) Polyethene is a polymer.
   (d) Chlorophyll is a polymer.
9. In bakelite, the rings are joined to each other through
   (a) $-CH_2-$
   (b) $-\underset{\displaystyle H}{\overset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}-H$
   (c) $-O-O$
   (d) $-\overset{\displaystyle O}{\overset{\|}{C}}-O$
10. Beckmann rearrangement is involved in the synthesis of which of the following polymers?
    (a) PAN (b) Nylon-6,10
    (c) Nylon-6 (d) Melamine–formaldehyde
11. Benzoyl peroxide has a role in which of the following type of addition polymerization?
    (a) Cationic (b) Anionic
    (c) Free-radical (d) None of these.
12. Wool is a
    (a) polysaccharide. (b) polyester.
    (c) polyamide. (d) All of these.
13. Melamine polymer is copolymer of
    (a) melamine and acetaldehyde.
    (b) melamine and formaldehyde.
    (c) phenol and formaldehyde.
    (d) None of the above.
14. Bakelite is obtained from phenol and formaldehyde. The initial reaction between the two compounds is an example of
    (a) aromatic electrophilic substitution.
    (b) aromatic nucleophilic substitution.
    (c) free radical reaction.
    (d) aldol reaction.
15. Formaldehyde is not used in the manufacture of which of the following polymer?
    (a) Bakelite (b) Nylon-6
    (c) Urea resin (d) Melamine resin
16. The process of formation of macromolecules by combination of few monomers with the elimination of small molecules is called
    (a) condensation polymerization.
    (b) homo polymerization.
    (c) addition polymerization.
    (d) free radical polymerization.
17. Orlon is
    (a) Nylon-6,6 (b) Terylene
    (c) Poly(ethyl acrylate) (d) Polyacrelonilrile
18. Example of addition co-polymer is
    (a) Buna-S. (b) neoprene.
    (c) nylon-6,6. (d) dacron.
19. Which of the following is not an addition polymer?
    (a) Bakelite (b) PAB
    (c) PVC (d) Teflon
20. Caprolactam is obtained by the Beckmann rearrangement of the compound
    (a) cyclohexanone-oxime (b) benzophenone-oxime
    (c) acetone-oxime (d) propionaldehyde-oxime
21. The monomer of neoprene is the product of the following reaction
    (a) Acetylene + HCl (b) Vinyl acetylene + HCl
    (c) Divinyl acetylene + HCl (d) Ethylene + HCl
22. Which of the following is not the addition homopolymer?
    (a) Teflon (b) Buna-S
    (c) PVC (d) PAN

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23. Polymer used in lacquer and paints is
(a) glyptal. **(b)** Thiokol.
(c) PVC. **(d)** Koyalene

24. Amide containing polymer is
(a) polyethene. **(b)** polystyrene.
(c) terylene. **(d)** nylon.

25. Synthetic rubber is
(a) polyester. **(b)** polyamide.
(c) polysaccharide. **(d)** poly(halodiene).

26. Chief structural bond in protein is
(a) ether bond. **(b)** ester bond.
(c) peptide bond. **(d)** all of these.

27. Isoprene is used to make
(a) rubber. **(b)** nylon.
(c) teflon. **(d)** none.

28. Natural biopolymer is
(a) teflon. **(b)** rubber.
(c) nylon-6,6. **(d)** RNA.

29. In which of the following polymers strong intermolecular forces are present?
(a) Elastomer **(b)** Fibre
(c) Thermoplastic **(d)** Thermosetting polymer

30. Non-sticking cookwares are made from
(a) PVC.
(b) polystyrene.
(c) poly(ethylene terephthalate).
(d) poly(tetrafluoro ethylene).

31. In which of the following polymer only C, H and N are present?
(a) Nylon-6 **(b)** Melamine polymer
(c) Buna-S **(d)** Terylene

32. Cross-network polymer is
(a) Bakelite **(b)** PVC
(c) PVA **(d)** PAN

33. Buna-S is a copolymer of
(a) 75% butadiene + 14% styrene.
(b) 25% butadiene + 75% styrene.
(c) 50% butadiene + 50% styrene.
(d) none.

34. Polymer containing more than one monomer is called
(a) copolymer. **(b)** heteropolymer.
(c) both the above. **(d)** none of these.

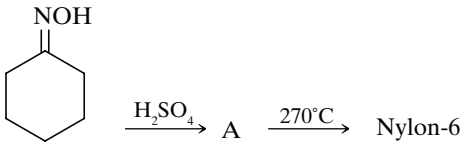
35. Match List-I (Monomers) with List-II (Polymers) and select the correct answer using the codes given below the lists:

List-I	List-II
A. Caprolactam	**a.** Polyester
B. Chloroprene	**b.** Nylon
C. Dimethyl terephthalate	**c.** Perspex
D. Methyl methacrylate	**d.** Synthetic rubber

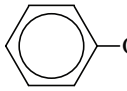
Codes:

	A	B	C	D
(a)	c	b	d	a
(b)	b	d	a	c
(c)	b	d	c	a
(d)	c	b	a	d

36.



Here A is:

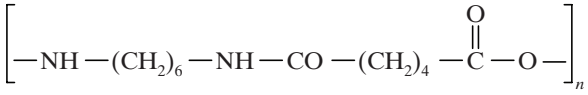
(a)  **(b)** Caprolactam

(c) Cyclohexanone **(d)** None

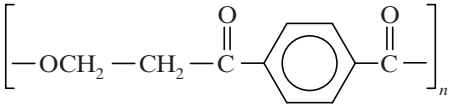
37. Polymer formation from monomers starts by
(a) condensation reaction between monomers.
(b) coordination reaction between monomers.
(c) conversion of monomer to monomer ions by protons.
(d) hydrolysis of monomers.

38. Which of the following is not correctly matched?

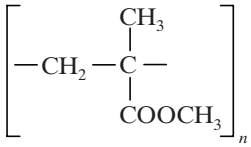
(a) Neoprene



(b) Nylon-6,6

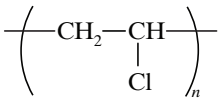
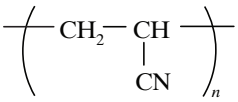


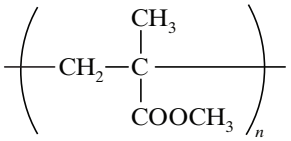
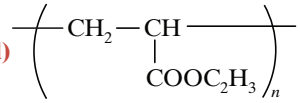
(c) Terylene



(d) PMMA

39. Acrilan is a hard, horny and a high melting material. Which of the following represents its structure?

(a)  **(b)** 

(c)  **(d)** 

40. Treatment of rubber with sulphur is called
(a) vulcanization. **(b)** sulphonation.
(c) both the above. **(d)** none of the above.

41. Match List I with List II and select the correct answer using the code given below the lists:

List-I	List-II
A. Coordination polymerization	**a.** Polypeptide
B. Free radical polymerization	**b.** Nylon-6,6
C. Addition polymerization	**c.** Ziegler-Natta catalyst
D. Natural rubber	**d.** Azo *bis*-isobutyronitrile
	e. *cis*-1,4-polyisoprene

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Code:

	A	B	C	D
(a)	c	e	b	d
(b)	b	b	a	e
(c)	c	d	b	e
(d)	b	e	a	d

42. The number average molecular mass and mass average molecular mass of polymer is respectively 30,000 and 40,000. The poly dispersity index of the polymer is
(a) < 1
(b) > 1
(c) 1
(d) 0

43. The vulcanized rubber has
(a) high water absorption, resistant to oxidation and good elasticity.
(b) high water absorption, susceptible to oxidation and no elasticity.
(c) low water absorption, resistance to oxidation and good elasticity.
(d) low water absorption, susceptible to oxidation and no elasticity.

44. Which of the following polymer has ester linkages?
(a) Nylon **(b)** Bakelite
(c) Terylene **(d)** PVC

45. Soft drinks and baby feeding bottles are generally made up of
(a) polyester. **(b)** polyurethane.
(c) polystyrene. **(d)** polyamide.

Multiple Correct Choice Type

1. Which of the following contain ethylene glycol as one of the monomers?
(a) Melamine **(b)** Polystyrene
(c) Glyptal **(d)** Terylene

2. Which of the following fibers are made of polyamides?
(a) Wool **(b)** Natural silk
(c) Rayon **(d)** Nylon

3. Which of the following statements are not correct?
(a) Polyester is not a copolymer.
(b) Polystyrene is a thermoplastic.
(c) Dacron is a fiber.
(d) Natural rubber behaves as thermosetting polymer.

4. Vinyl polymerization may occur through intermediate formation of
(a) carbocations. **(b)** carbanions.
(c) free radicals. **(d)** carbenes.

Linked Comprehension Type

The utility of the polymers in various fields is due to their mechanical properties like tensile strength, elasticity, toughness etc. These properties mainly depend upon intermolecular forces like van der Waals forces and hydrogen bonding operating in polymer molecules. Polymers have been classified on this basis, for example, (1) elastomers (2) fibres (3) thermoplastics (4) thermosetting. Hence,

1. The molecular forces of attraction are weakest in
(a) elastomers.
(b) fibres.
(c) thermoplastics.
(d) thermosetting polymers.

2. Which of the following have usually a linear structure?
(a) Thermoplastics
(b) Thermosetting polymers
(c) Polyethylene
(d) Nylon-6,6

3. Which of the following is hard?
(a) Elastomer
(b) Fibre
(c) Thermoplastic
(d) Thermosetting polymers

Integer Type

1. The number of nitrogen atoms present in the monomer of urea-formaldehyde resin is ____.

2. The number of double bonds present in the repeating structural units of natural rubber is ____.

3. Amongst the following, the total number of elastomers is ____.

Natural rubber, polypropylene, polyethene, vulcanized rubber, nylon-6, polyvinyl chloride, Buna-N, chloroprene, Buna-S, polystyrene.

4. Amongst the following, the total number of thermoplastics is ____.

Polyester, bakelite, polyethene, PVC, teflon, PAN, PMMA, nylon-6, melamine-formaldehyde.

Matrix Match Type

1. Match the polymer with its property.

Column I	Column II
(a) Nylon-2-nylon-6	**(p)** Elastomer
(b) Nylon-6,6	**(q)** Prepared by condensation polymerization
(c) Natural rubber	**(r)** Synthetic fiber
(d) Melamine-formaldehyde	**(s)** Biodegradable

2. Match the polymer with its monomers.

Column I	Column II
(a) Bakelite	**(p)** Chloroprene and persulphate
(b) Nylon-6,6	**(q)** Terephthalic acid and ethylene glycol
(c) Dacron	**(r)** Hexamethylenediamine and adipic acid
(d) Neoprene	**(s)** Phenol and formaldehyde

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ANSWER KEY

Single Correct Choice Type

1. (b)	**2.** (c)	**3.** (b)	**4.** (a)	**5.** (c)
6. (a)	**7.** (d)	**8.** (d)	**9.** (a)	**10.** (c)
11. (c)	**12.** (c)	**13.** (b)	**14.** (a)	**15.** (b)
16. (a)	**17.** (d)	**18.** (a)	**19.** (a)	**20.** (a)
21. (b)	**22.** (b)	**23.** (a)	**24.** (d)	**25.** (d)
26. (c)	**27.** (a)	**28.** (d)	**29.** (b)	**30.** (d)
31. (b)	**32.** (a)	**33.** (a)	**34.** (c)	**35.** (b)
36. (b)	**37.** (a)	**38.** (b)	**39.** (b)	**40.** (a)
41. (c)	**42.** (b)	**43.** (d)	**44.** (c)	**45.** (c)

Multiple Correct Choice Type

1. (c), (d)	**2.** (a), (b), (d)	**3.** (a), (d)	**4.** (a), (b), (c)

Linked Comprehension Type

1. (a)	**2.** (a)	**3.** (d)

Integer Type

1. (2)	**2.** (1)	**3.** (5)	**4.** (7)

Matrix Match Type

1. $a \rightarrow (q, r, s); b \rightarrow (q, r); c \rightarrow (p); d \rightarrow (q)$

2. $a \rightarrow (s); b \rightarrow (r); c \rightarrow (q); d \rightarrow (p)$

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APPENDIX

A

Answers to Selected Problems

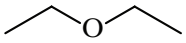
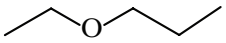
Chapter 1

1.11 **(a)** and **(d)**; **(b)** and **(e)**; and **(c)** and **(f)**.

1.17 **(a)**, **(g)**, **(i)**, **(l)**, represent different compounds that are not isomeric; (**b–e**), **(h)**, **(j)**, **(m)**, **(n)**, **(o)** represent the same compound; **(f)**, **(k)**, **(p)** represent constitutional isomers.

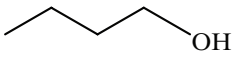
1.23 **(a)** The structures differ in the positions of the nuclei. **(b)** The anions are resonance structures.

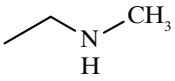
Chapter 2

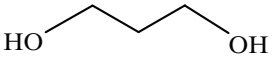
2.8 **(a)**  **(b)** 

(e) diisopropyl ether.

2.13

(a) 

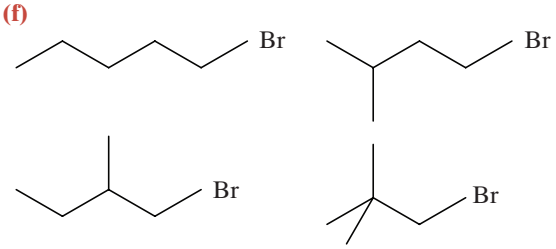
(b) 

(c) 

2.16 **(a)** ketone; **(c)** 2° alcohol; **(e)** 2° alcohol.

2.17 **(a)** 3 alkene groups, and a 2° alcohol; **(c)** phenyl and 1° amine; **(e)** phenyl, ester and 3° amine; **(g)** alkene and 2 ester groups.

2.23 **(f)**



2.35 Ester

Chapter 3

3.2 **(a)**, **(c)**, **(d)**, and **(f)** are Lewis bases; **(b)** and **(e)** are Lewis acids.

3.7 **(a)** $[H_3O^+] = [HCO_2^-] = .0042$ M; **(b)** Ionization = 4.2%.

3.8 **(a)** $pK_a = 7$; **(b)** $pK_a = -0.7$; **(c)** Because the acid with a $pK_a = 5$ has a larger K_a, it is the stronger acid.

3.11 The pK_a of the methylaminium ion is equal to 10.6 (Section 3.6B). Because the pK_a of the anilinium ion is equal to 4.6, the anilinium ion is a stronger acid than the methylaminium ion, and aniline ($C_6H_5NH_2$) is a weaker base than methylamine (CH_3NH_2).

3.16 **(a)** $CHCl_2CO_2H$ would be the stronger acid because the electron-withdrawing inductive effect of two chlorine atoms would make its hydroxyl proton more positive. **(c)** CH_2FCO_2H would be the stronger acid because a fluorine atom is more electronegative than a bromine atom and would be more electron withdrawing.

3.28 **(a)** $pK_a = 3.752$; **(b)** $K_a = 10^{-13}$.

Chapter 4

4.1 **(a)** achiral; **(c)** chiral; **(e)** chiral.

4.2 **(a)** Yes; **(c)** no.

4.3 **(a)** They are the same. **(b)** They are enantiomers.

4.6 The following possess a plane of symmetry and are, therefore, achiral: screwdriver, baseball bat, hammer.

4.10 **(a)** —Cl > —SH > —OH > —H

(c) —OH > CHO > $—CH_3$ > —H

(e) $—OCH_3$ > $—N(CH_3)_2$ > $—CH_3$ > —H

4.12 **(a)** enantiomers; **(c)** enantiomers.

4.16 **(a)** diastereomers; **(c)** no; **(e)** no.

4.18 **(a)** represents **A**; **(b)** represents **C**; **(c)** represents **B**.

Chapter 5

5.8 **(a)** (1,1-dimethylethyl)cyclopentane or *tert*-butyl-cyclopentane; **(c)** butylcyclohexane; **(e)** 2-chlorocyclopentanol.

5.9 **(a)** 2-Chlorobicyclo[1.1.0]butane; **(c)** bicyclo[2.1.1]hexane; **(e)** 2-methylbicyclo[2.2.2]octane.

5.10 **(a)** *trans*-3-Heptene; **(c)** 4-ethyl-2-methyl-1-hexene

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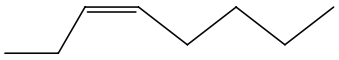
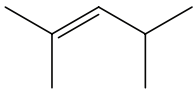
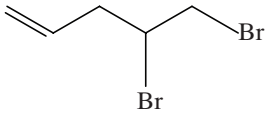
5.11 **(a)**



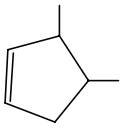
(c)



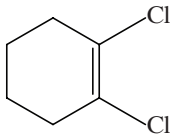
(e)



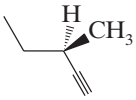
(g)



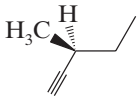
(i)



5.12



(*R*)-3-Methyl-1-pentyne



(*S*)-3-Methyl-1-pentyne

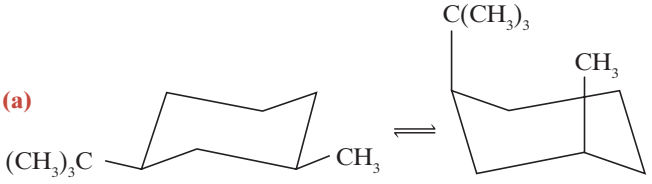
1-Hexyne,
2-Hexyne,
3-Hexyne,
4-Methyl-1-pentyne,
4-Methyl-2-pentyne
3,3-Dimethyl-1-butyne

5.21 **(a)** 5-ethyl-7-isopropyl-2,3-dimethyldecane; **(c)** 4-bromo-6-chloro-3-methyloctane; **(e)** 2-Bromobicyclo[3.3.1]nonane; **(g)** 5,6-dimethyl-2-heptene

5.33 **(a)** Pentane would boil higher because its chain is unbranched. **(c)** 2-Chloropropane because it is more polar and has a higher molecular weight. **(e)** CH_3COCH_3 because it is more polar.

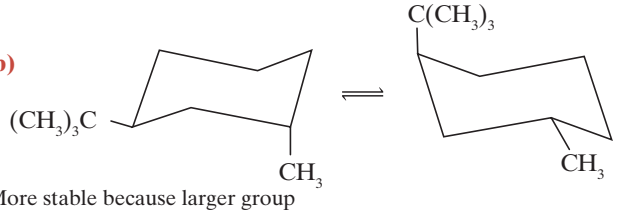
5.36

(a)



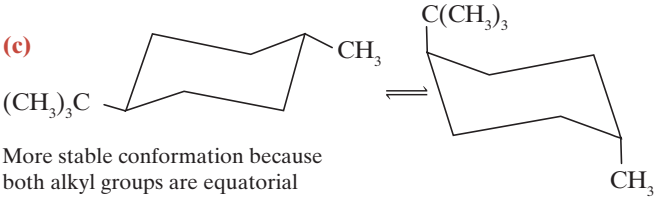
More stable conformation because both alkyl groups are equatorial

(b)



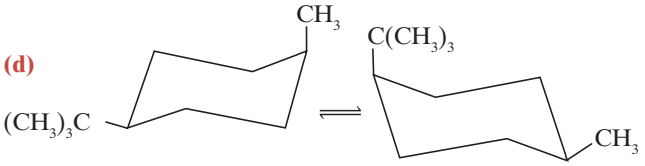
More stable because larger group is equatorial

(c)



More stable conformation because both alkyl groups are equatorial

(d)



More stable because larger group is equatorial

Chapter 6

6.5 **(a)** The reaction is S_N2 and, therefore, occurs with inversion of configuration. Consequently, the configuration of (+)-2-chlorobutane is opposite [i.e., (*S*)] to that of (−)-2-butanol [i.e., (*R*)]. **(b)** The configuration of (−)-2-iodobutane is (*R*).

6.13 Protic solvents are formic acid, formamide, ammonia, and ethylene glycol. The others are aprotic.

6.15 **(a)** CH_3O^-; **(c)** $(CH_3)_3P$.

6.19 **(a)** 1-Bromopropane would react more rapidly, because, being a primary halide, it is less hindered. **(c)** 1-Chlorobutane, because the carbon bearing the leaving group is less hindered than in 1-chloro-2-methylpropane. **(e)** 1-Chlorohexane because it is a primary halide. Phenyl halides are unreactive in S_N2 reactions.

6.20 **(a)** Reaction (1) because ethoxide ion is a stronger nucleophile than ethanol; **(c)** reaction (2) because triphenylphosphine, $(C_6H_5)_3P$, is a stronger nucleophile than triphenylamine. (Phosphorus atoms are larger than nitrogen atoms.)

6.21 **(a)** Reaction (2) because bromide ion is a better leaving group than chloride ion; **(c)** reaction (2) because the concentration of the substrate is twice that of reaction (1).

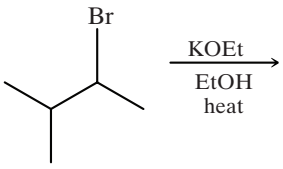
6.25 The better yield is obtained by using the secondary halide, 1-bromo-1-phenylethane, because the desired reaction is E2. Using the primary halide will result in substantial S_N2 reaction as well, producing the alcohol instead of the desired alkene.

6.33 **(a)** You should use a strong base, such as RO^-, at a higher temperature to bring about an E2 reaction. **(b)** Here we want an S_N1 reaction. We use ethanol as the solvent *and as the nucleophile*, and we carry out the reaction at a low temperature so that elimination is minimized.

Chapter 7

7.4 **(a)** 2,3-Dimethyl-2-butene would be the more stable because the double bond is tetrasubstituted. **(c)** *cis*-3-Hexene would be more stable because its double bond is disubstituted.

7.7 **(a)**



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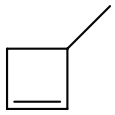
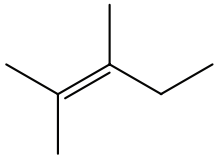
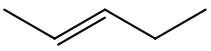
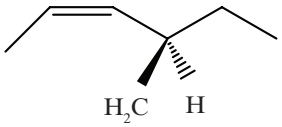
(trisubstituted, more stable) **(monosubstituted, less stable)**

Major product **Minor product**

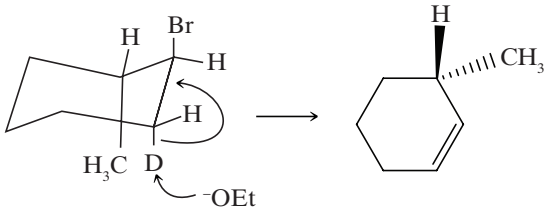
7.25 **(a)** We designate the position of the double bond by using the *lower* of the two numbers of the doubly bonded carbon atoms, and the chain is numbered from the end nearer the double bond. The correct name is *trans*-2-pentene. **(c)** We use the lower number of the two doubly bonded carbon atoms to designate the position of the double bond. The correct name is 1-methylcyclohexene.

7.26 **(a)**  **(c)** 

(e)  **(g)** 

7.28 **(a)** (*E*)-3,5-Dimethyl-2-hexene; **(c)** 6-methyl-3-heptyne; **(e)** (3*Z*, 5*R*)-5-chloro-3-hepten-6-yne.

7.43 Only the deuterium atom can assume the anti coplanar orientation necessary for an E2 reaction to occur.

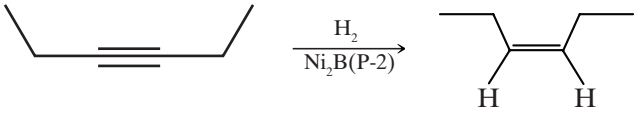


Chapter 8

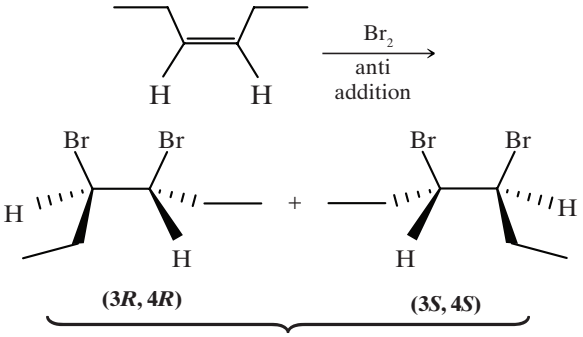
8.1 2-Bromo-1-iodopropane.

8.6 The order reflects the relative ease with which these alkenes accept a proton and form a carbocation. 2-Methylpropene reacts fastest because it leads to a 3° cation; ethene reacts slowest because it leads to a 1° cation.

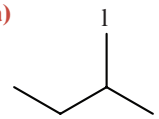
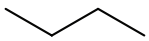
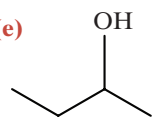
8.20 By converting the 3-hexyne to *cis*-3-hexene using H_2/Ni_2B (P-2).

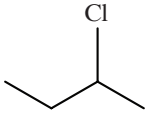
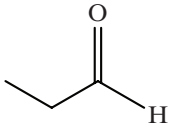


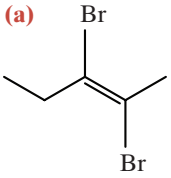
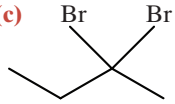
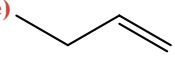
Then, addition of bromine to *cis*-3-hexene will yield (3*R*, 4*R*), and (3*S*, 4*S*)-3,4-dibromohexane as a racemic form.

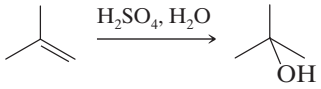


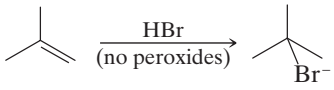
Racemic 3,4-dibromohexane

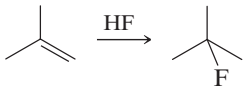
8.21 **(a)**  **(b)**  **(e)** 

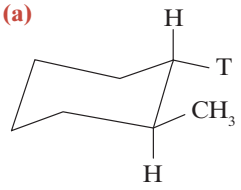
(i)  **(j)** 

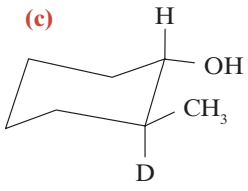
8.24 **(a)**  **(c)**  **(e)** 

8.28 **(a)** 

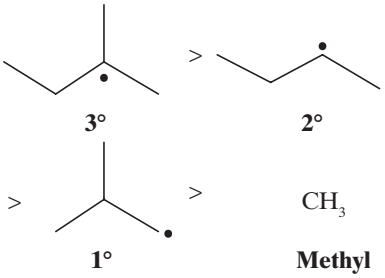
(c) 

(d) 

8.29 **(a)** 

(c) 

Chapter 9

9.1 

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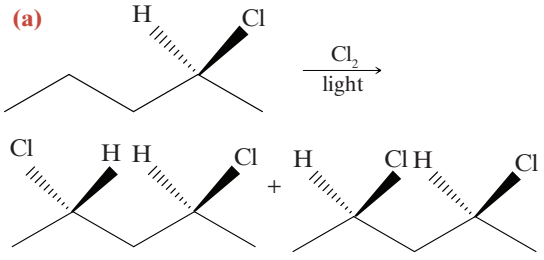
9.4 **(a)**



(2*S*, 4*S*)-2,4-Dichloropentane **(2*R*, 4*S*)-2,4-Dichloropentane**

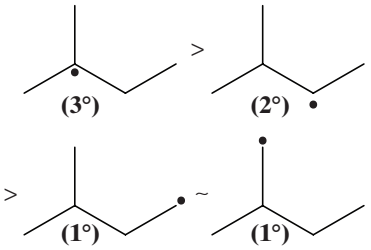
(c) No, (2*R*, 4*S*)-2,4-dichloropentane is achiral because it is a meso compound. (It has a plane of symmetry passing through C3.)

(e) Yes, by fractional distillation or by gas–liquid chromatography. (Diastereomers have different physical properties. Therefore, the two isomers would have different vapor pressures.)

9.5 **(a)** The only fractions that would contain chiral molecules (as enantiomers) would be those containing 1-chloro 2-methylbutane and the two diastereomers of 2-chloro-3-methylbutane. These fractions would not show optical activity, however, because they would contain racemic forms of the enantiomers.

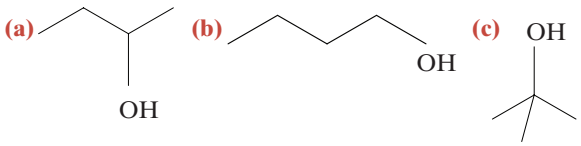
(b) Yes, the fractions containing 1-chloro-2-methylbutane and the two containing the 2-chloro-3-methylbutane diastereomers.

9.16



Chapter 10

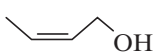
10.3 **(a)** **(b)** **(c)**



10.20 **(a)** 3,3-Dimethyl-1-butanol; **(c)** 2-methyl-1,4-butanediol; **(e)** 1-methyl-2-cyclopenten-1-ol.

10.21

(a)



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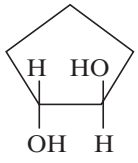

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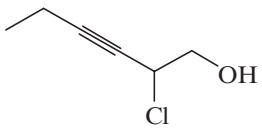

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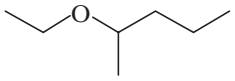

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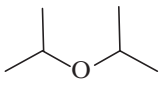
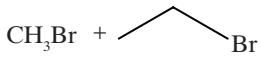


10.28 **(a)**



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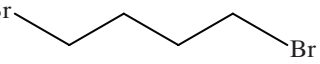
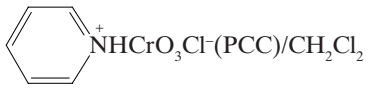


Chapter 11

11.1 **(a)** $LiAlH_4$; **(c)** $NaBH_4$

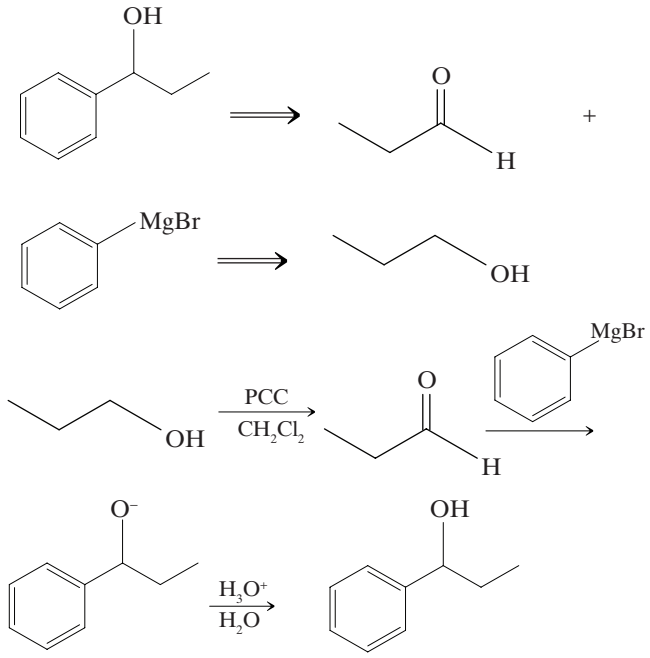
11.2 **(a)**



(c) H_2CrO_4/acetone

11.8

(a)



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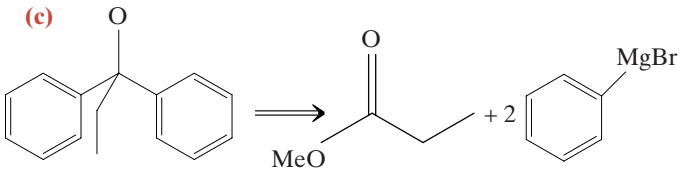

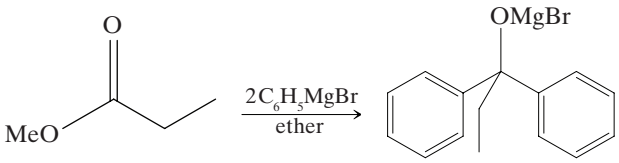

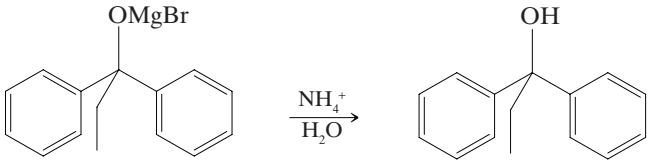

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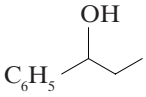
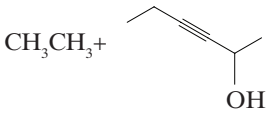
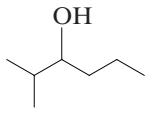
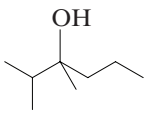
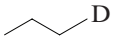
11.9 **(a)** CH_3CH_3; **(b)** CH_3CH_2D;

(c) 

(g) 

11.10 **(a)** 

(b) 

(e) 

Chapter 12

12.1 **(b)** 1,4-Cyclohexadizene and 1,4-pentadiene are isolated dienes.

12.4 **(a)** 1,4-Dibromobutane + *t*-BuOK, and heat;
(g) $HC{\equiv}CCH{=}CH_2 + H_2, Ni_2B$ (P-2).

12.8 **(a)** 1-Butene + *N*-bromosuccinimide, then *t*-BuOK and heat; **(e)** cyclopentane + Br_2, *hv*, then *t*-BuOK and heat, then *N*-bromosuccinimide.

Chapter 13

13.1 **(a)** 4-Bromobenzoic acid (or *p*-bromobenzoic acid)
(b) 2-Benzyl-1.3-cyclohexadiene
(c) (2-chloro-2-pentyl) benzene
(d) Phenyl propyl ether

13.12 Hückel's rule should apply to both pentalene and heptalene. Pentalene's antiaromaticity can be attributed to its having 8 π electrons. Heptalene's lack of aromaticity can be attributed to its having 12 π electrons. Neither 8 nor 12 is a Hückel number.

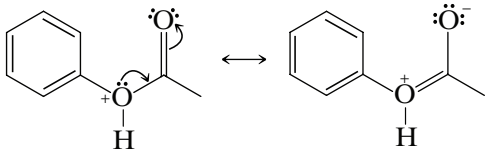
13.14 The bridging $—CH_2—$ group causes the 10 π electron ring system to become planar. This allows the ring to become aromatic.

13.16 **(a)** The cyclononatetraenyl anion, with 10 π electrons, obeys Hückel's rule.

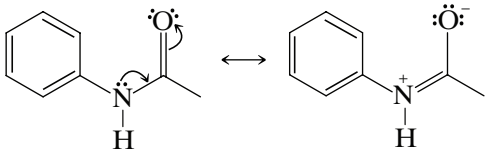
Chapter 14

14.6 If the methyl group had no directive effect on the incoming electrophile, we would expect to obtain the products in purely statistical amounts. Since there are two ortho hydrogen atoms, two meta hydrogen atoms, and one para hydrogen, we would expect to get 40% ortho (2/5), 40% meta (2/5), and 20% para (1/5). Thus, we would expect that only 60% of the mixture of mononitrotoluenes would have the nitro group in the ortho or para position. And, we would expect to obtain 40% of *m*-nitrotoluene. In actuality, we get 96% of combined *o*- and *p*-nitrotoluene and only 4% *m*-nitrotoluene. This result shows the ortho–para directive effect of the methyl group.

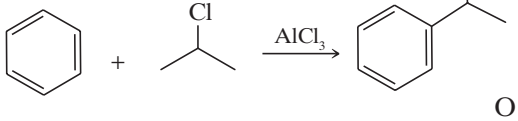
14.9 **(b)** Structures such as the following compete with the benzene ring for the oxygen electrons, making them less available to the benzene ring.

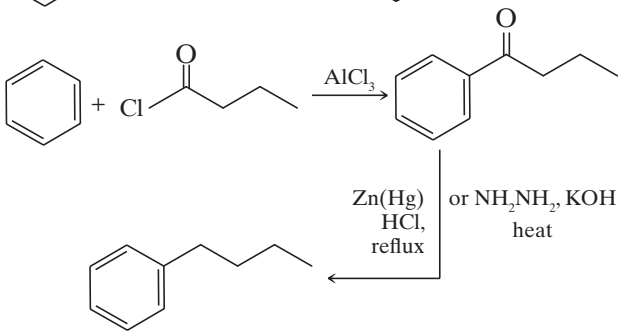


(d) Structures such as the following compete with the benzene ring for the nitrogen electrons, making them less available to the benzene ring.

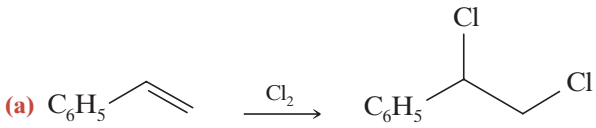


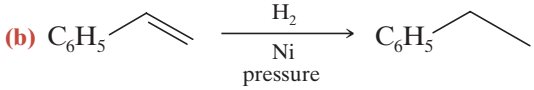
14.28

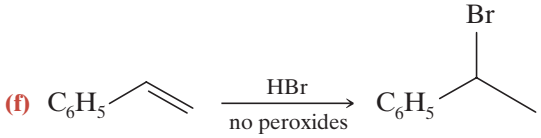
(a) 

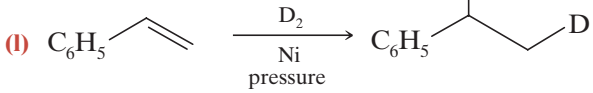
(d) 

14.29

(a) 

(b) 

(f) 

(l) 

Chapter 15

15.2 **(a)** 1-Pentanol; **(c)** pentanal; **(e)** benzyl alcohol.

15.6 A hydride ion.

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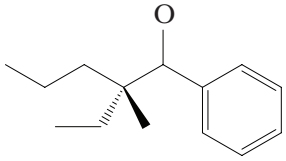
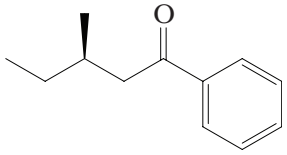
15.17 **(b)** CH_3CH_2Br + $(C_6H_5)_3P$, then strong base, then $C_6H_5COCH_3$; **(d)** CH_3I + $(C_6H_5)_3P$, then strong base, then cyclopentanone; **(f)** $CH_2{=}CHCH_2Br$ + $(C_6H_5)_3P$, then strong base, then C_6H_5CHO.

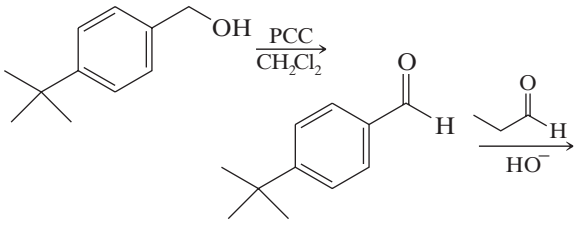
15.20 **(a)** $CH_3CH_2CH_2OH$;
(c) $CH_3CH_2CH_2OH$
(h) $CH_3CH_2CH{=}CHCH_3$;
(j) $CH_3CH_2CO_2^-NH_4^+ + Ag\downarrow$
(l) $CH_3CH_2CH{=}NNHCONH_2$;
(n) $CH_3CH_2CO_2^-$

Chapter 16

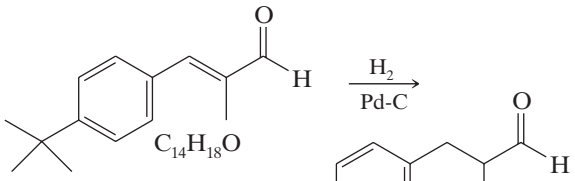
16.1 The enol form is phenol. It is especially stable because it is aromatic.

16.2 No.  does not have a hydrogen attached to its α-carbon atom (which is a chirality center) and thus enol formation involving the chirality center is not possible. With  the chirality center is a β carbon and thus enol formation does not affect it.

16.5 Base is consumed as the reaction takes place. A catalyst, by definition, is not consumed.

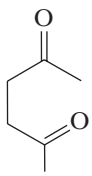
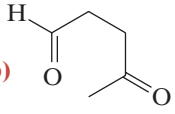
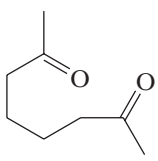
16.10 

$C_{11}H_{14}O$



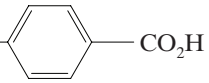
$C_{14}H_{18}O$

Lily aldehyde ($C_{14}H_{20}O$)

16.17 **(a)**  **(b)**  **(c)** 

16.20 In a polar solvent, such as water, the keto form is stabilized by solvation. When the interaction with the solvent becomes minimal, the enol form achieves stability by internal hydrogen bonding.

Chapter 17

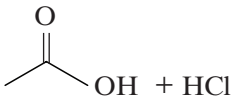
17.1 **(a)** CH_2FCO_2H; **(c)** $CH_3CH_2CHFCO_2H$;
(e) 

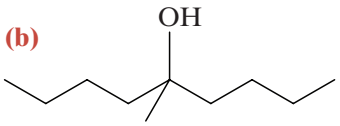
17.4 **(a)** $C_6H_5CH_2Br$ + Mg in diethyl ether, then CO_2, then H_3O^+; **(c)** $CH_2{=}CHCH_2Br$ + Mg in diethyl ether, then CO_2, then H_3O^+.

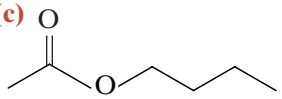
17.5 **(a)**, **(c)**, and **(e)**.

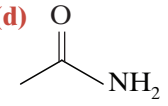
17.7 In the carboxyl group of benzoic acid.

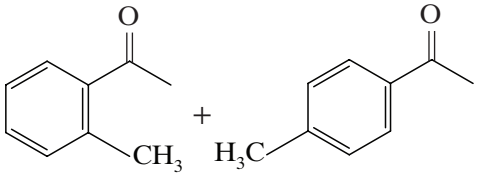
17.10 **(a)** $(CH_3)_3CCO_2H$ + $SOCl_2$, then NH_3, then P_4O_{10}, heat;
(b) 

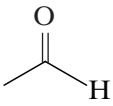
17.16
(a) 

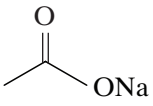
(b) 

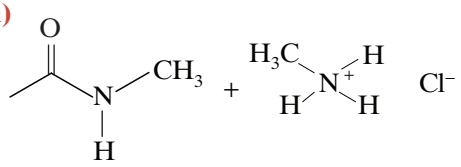
(c) 

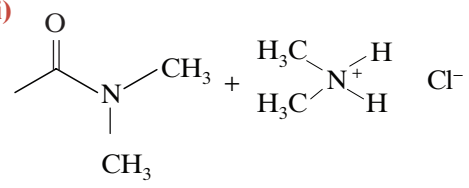
(d) 

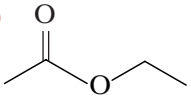
(e) 

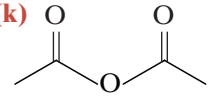
(f) 

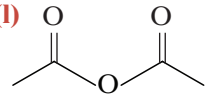
(g) 

(h) 

(i) 

(j) 

(k) 

(l) 

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Chapter 18

18.3 **(a)** $CH_3(CH_2)_3CHO + NH_3 \xrightarrow{H_2, Ni} CH_3(CH_2)_3CH_2NH_2$

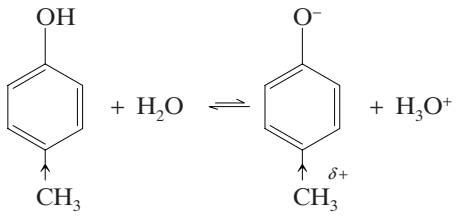
(c) $CH_3(CH_2)_4CHO + C_6H_5NH_2 \xrightarrow{LiBH_3CN} CH_3(CH_2)_4CH_2NHC_6H_5$

18.4 The reaction of a secondary halide with ammonia is almost always accompanied by some elimination.

18.5 **(a)** Methoxybenzene + HNO_3 + H_2SO_4, then Fe + HCl;
(b) Methoxybenzene + CH_3COCl + $AlCl_3$, then NH_3 + H_2 + Ni;
(c) toluene + Cl_2 and light, then $(CH_3)_3N$;
(d) *p*-nitrotoluene + $KMnO_4$ + HO^-, then H_3O^+, then $SOCl_2$ followed by NH_3, then NaOBr (Br_2 in NaOH);
(e) toluene + *N*-bromosuccinimide then KCN, then $LiAlH_4$.

Chapter 19

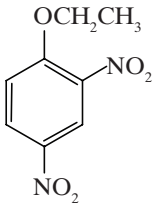
19.1 The electron-releasing group (i.e., —CH_3) changes the charge distribution in the molecule so as to make the hydroxyl oxygen less positive, causing the proton to be held more strongly; it also destabilizes the phenoxide anion by intensifying its negative charge. These effects make the substituted phenol less acidic than phenol itself.



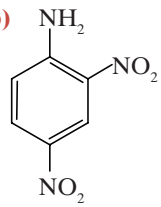
Electron-releasing—CH_3 destabilizes the anion more then the acid. pK_a is larger than for phenol.

19.4 **(a)** The para-sulfonated phenol.
(b) For ortho sulfonation.

19.7 **(a)**



(b)



19.9 **(a)** 4-Fluorophenol because a fluorine substituent is more electron withdrawing than a methyl group. **(e)** 4-Fluorophenol because fluorine is more electronegative than bromine.

19.11 **(a)** 4-Chlorophenol will dissolve in aqueous NaOH; 4-chloro-1-methylbenzene will not. **(c)** Phenyl vinyl ether will react with bromine by addition (thus decolorizing the solution); ethyl phenyl ether will not. **(e)** 4-Ethylphenol will dissolve in aqueous NaOH; ethyl phenyl ether will not.

Chapter 20

20.1 **(a)** Two; **(b)** two; **(c)** four.

20.4 Acid catalyzes hydrolysis of the glycosidic (acetal) group.

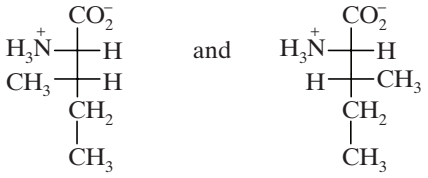
20.8 **(a)** 2 CH_3CHO, one molar equivalent HIO_4; **(b)** HCHO + HCO_2H + CH_3CHO, two molar equivalents HIO_4; **(c)** HCHO + $OHCCH(OCH_3)_2$, one molar equivalent HIO_4; **(d)** HCHO + HCO_2H + CH_3CO_2H, two molar equivalents HIO_4; **(e)** 2 CH_3CO_2H + HCO_2H, two molar equivalents HIO_4

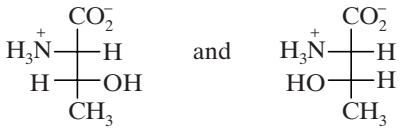
20.14 **A** is D-altrose; **B** is D-talose, **C** is D-galactose

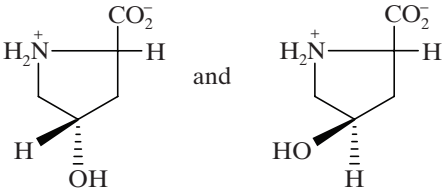
Chapter 21

21.5 **(a)** Isoleucine, threonine, hydroxyproline, and cystine.

(b)







(c) Diastereomers

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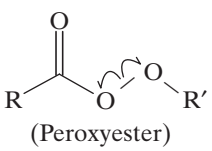
APPENDIX B

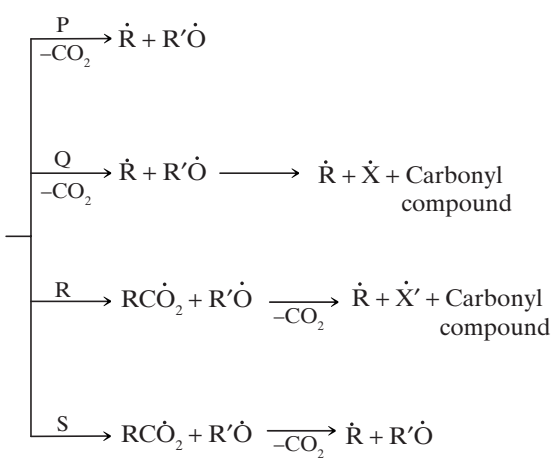
Chapterwise Solved JEE (Advanced) Questions (2011–2017)

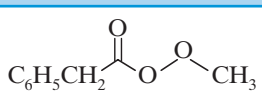
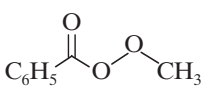
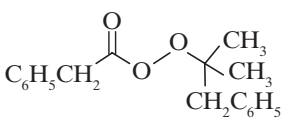
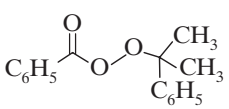
Chapter 1 The Basics: Bonding and Molecular Structure

1. Different possible thermal decomposition pathways for peroxyesters are shown below. Match each pathway from **List I** with an appropriate structure from **List II** and select the correct answer using the code given below the lists.



(Peroxyester)



List-I	List-II
(p) Pathway P	(1) 
(q) Pathway Q	(2) 
(r) Pathway R	(3) 
(s) Pathway S	(4) 

Code:

	P	Q	R	S
(a)	1	3	4	2
(b)	2	4	3	1
(c)	4	1	2	3
(d)	3	2	1	4

(JEE Advanced 2014)

Solution

(a) The reactions are as follows:

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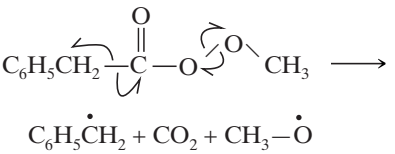
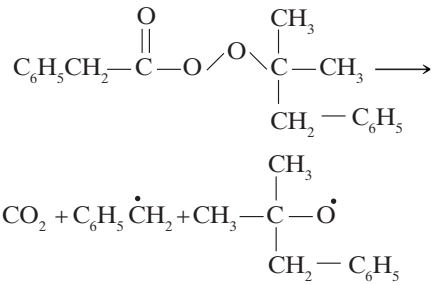
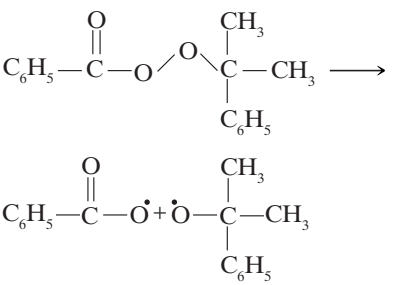
From pathway P→(1)



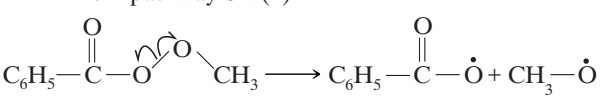
From pathway Q→(3)



From pathway R→(4)



From pathway S→(2)



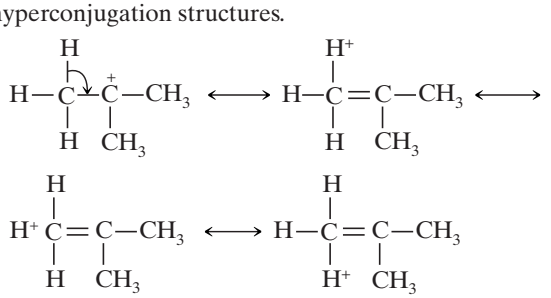
2. The hyperconjugative stabilities of *tert*-butyl cation and 2-butene, respectively, are due to

(a) $\sigma \rightarrow \pi$(empty) and $\sigma \rightarrow \pi^*$ electron delocalizations.
(b) $\sigma \rightarrow \sigma^*$ and $\sigma \rightarrow \pi$ electron delocalizations.
(c) $\sigma \rightarrow \pi$(filled) and $\sigma \rightarrow \pi$ electron delocalizations.
(d) π(filled) $\rightarrow \sigma^*$ and $\sigma \rightarrow \pi^*$ electron delocalizations.

(JEE Advanced 2013)

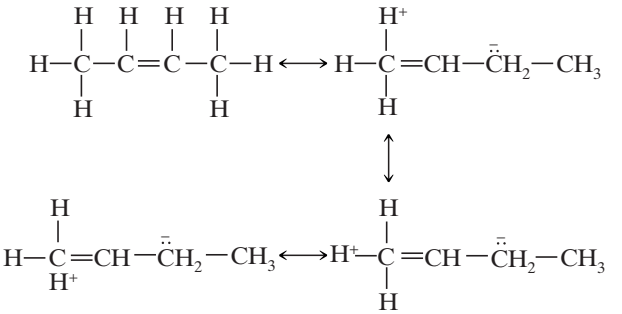
Solution

(a) The hyperconjugation for *tert*-butyl carbocation involves $\sigma \rightarrow p$ (empty) electron delocalization. This is because carbon having + charge has one vacant *p*-orbital. It has nine α-hydrogens and hence nine hyperconjugation structures.



(Plus six more such structures from the other two methyl groups)

The hyperconjugation for 2-butene involves $\sigma \rightarrow \pi^*$ electron delocalization. It has six α-hydrogens and hence six hyperconjugation structures.



(Similarly three more structures from the other methyl group)

3. In allene (C_3H_4), the type(s) of hybridization of the carbon atoms is (are)

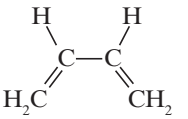
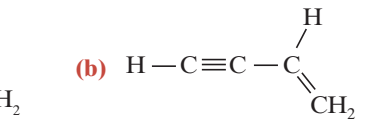
(a) *sp* and sp^3. **(b)** *sp* and sp^2.
(c) only sp^2. **(d)** sp^2 and sp^3.

(IIT-JEE 2012)

Solution

(b) The structure of allene is $CH_2=C=CH_2$. Here both the terminal carbons are sp^2 hybridized while the central carbon is *sp* hybridized.

4. Among the given options, the compound(s) in which all the atoms are in one plane in all the possible conformations (if any), is(are)

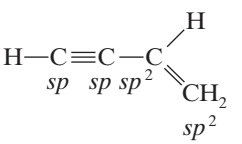
(a)  **(b)** 

(c) $H_2C=C=O$ **(d)** $H_2C=C=CH_2$

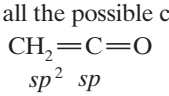
(IIT-JEE 2011)

Solution

(b), (c) For compound in option (a): Only two of the conformers (cisiod and transoid) have all the atom in the same plane.
For compound in option (b): The terminal hydrogen of allene will be perpendicular to each other plane.



For compound in option (c): All the atoms are in one plane in all the possible conformations. There is no atom on oxygen.



5. The total number of contributing structures showing hyper-conjugation (involving C — H bonds) for the following carbocation is_____.

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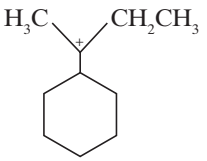
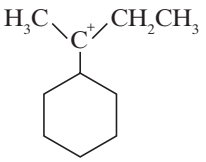


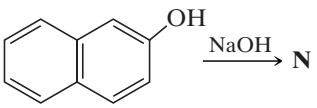
(IIT-JEE 2011)

Solution

(6) The given carbocation structure has six α-hydrogen atoms, so the possible number of contributing structures showing hyper-conjugation is 6.



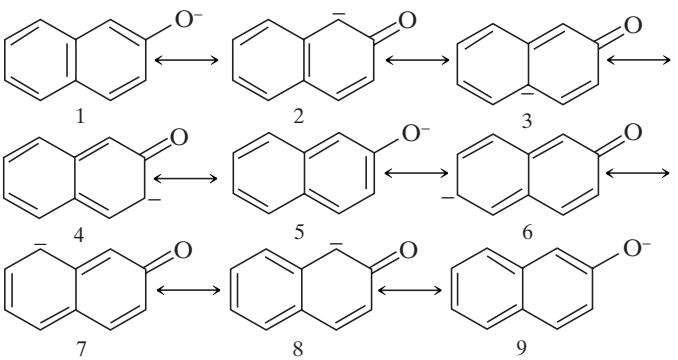
6. The number of resonance structure for **N** is _____.



(JEE Advanced 2015)

Solution

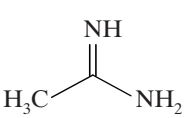
The possible resonance structures for the given compound on loss of proton are:



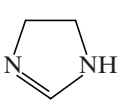
Hence the number of possible resonance structures is nine.

Chapter 3 An Introduction to Organic Reactions and Their Mechanisms: Acids and Bases

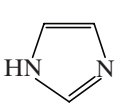
7. The order of basicity among the following compounds is



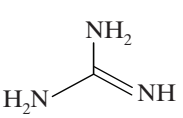
I



II



III



IV

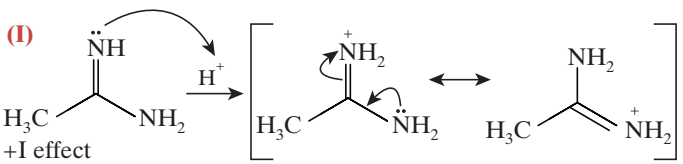
(a) II > I > IV > III **(b)** IV > II > III > I
(c) IV > I > II > III **(d)** I > IV > III > II

(JEE Advanced 2017)

Solution

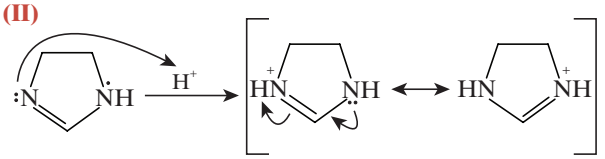
(c) The stronger the base, the weaker will be its conjugate acid.

(I)

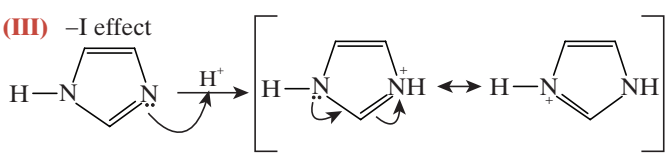


+I effect of alkyl group increases the basic strength.

(II)

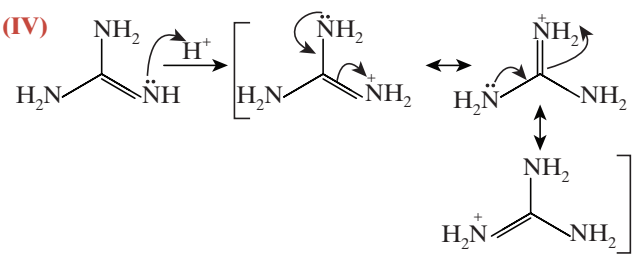


(III) –I effect



–I effect $\propto$ 1/basic strength. More the *s* character of an orbital, the more strongly it holds its electrons. This makes an sp^2 hybridized carbon more electron withdrawing.

(IV)

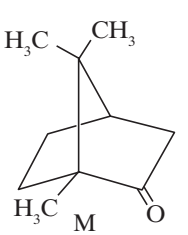


On protonation the positive charge can be delocalized over three nitrogen atoms to give a very stable cation. It has three equal contributions in resonance hybrid. This makes it strongest base.

Hence, the correct order of basicity is (IV) > (I) > (II) > (III).

Chapter 4 Stereochemistry: Chiral Molecules

8. The total number of stereoisomers that can exist for **M** is _____.



(JEE Advanced 2015)

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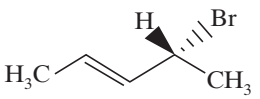
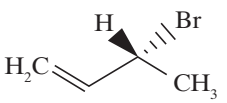
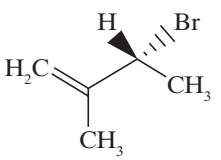
Solution

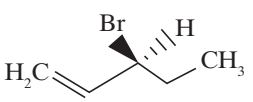
Total number of stereoisomers = $2^n = 2^2 = 4$, where n is the number of chiral centres.
But in bridge/bicycle compounds, the number of stereoisomers is equal to the number of chiral centres because no carbon centres rotation is possible. Therefore, two stereoisomers would be possible for the given compound.

9. Compound(s) that on hydrogenation produce(s) optically inactive compound(s) is (are)

(a) 

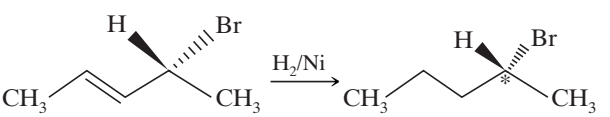
(b) 

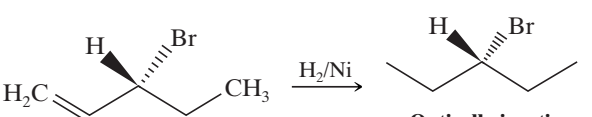
(c) 

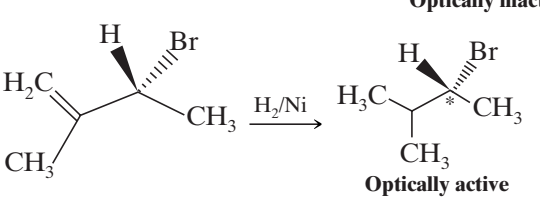
(d) 

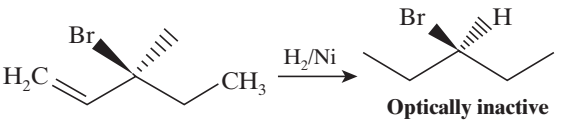
(JEE Advanced 2015)

Solution

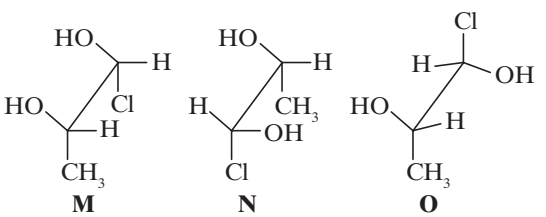
(a) 

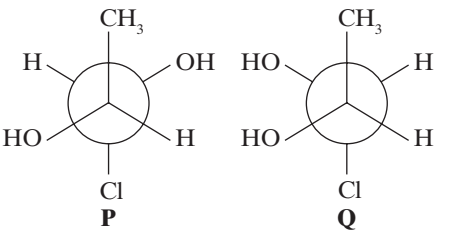
(b) 

(c) 

(d) 

10. Which of the given statement(s) about **N**, **O**, **P** and **Q** with respect to **M** is (are) correct?



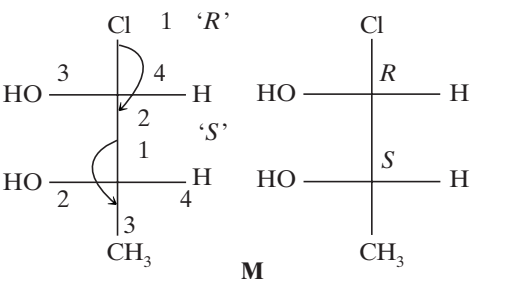


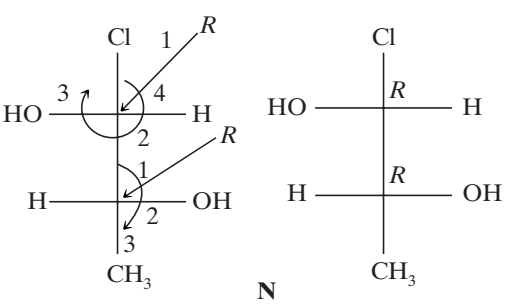
(a) **M** and **N** are non–mirror image stereoisomers.
(b) **M** and **O** are identical.
(c) **M** and **P** are enantiomers.
(d) None of these.

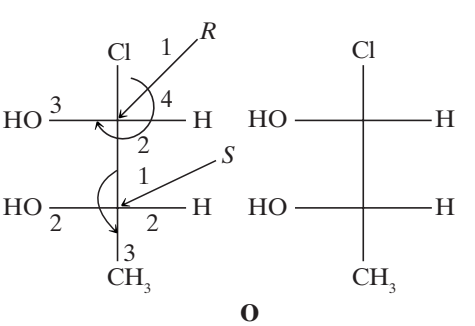
(IIT-JEE 2012)

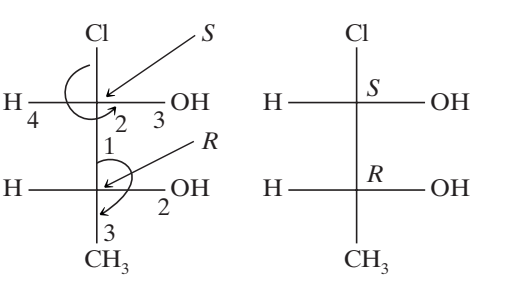
Solution

(b), (d) The given structures can be represented as









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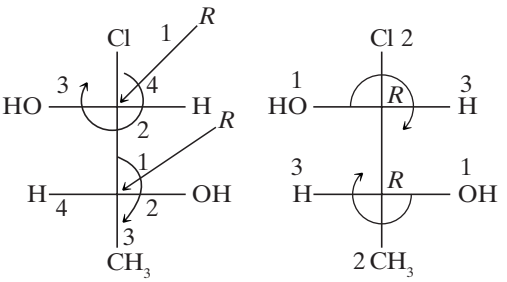
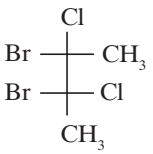


Q

M and **N** are diastereomers.
M and **O** are identical.
M and **P** are enantiomers (non-superimposable mirror images).
M and **Q** are diastereomers.

Chapter 5 Nomenclature and Conformations of Alkanes and Cycloalkanes

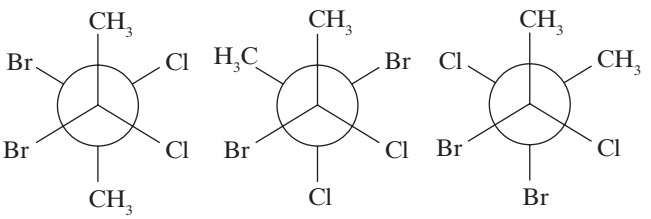
11. The total number(s) of **stable** conformers with **non-zero** dipole moment for the following compound is (are) _____.



(JEE Advanced 2014)

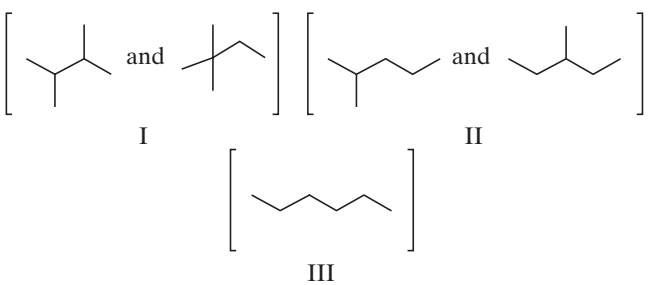
Solution

(3) The conformers in Newman projection are as shown:



So there are a total of three such stable conformers.

12. Isomers of hexane, based on their branching, can be divided into three distinct classes as shown in the figure.



The correct order of their boiling point is

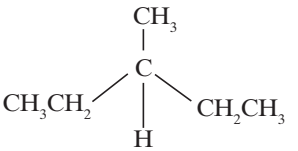
(a) I > II > III **(b)** III > II > I
(c) II > III > I **(d)** III > I > II

(JEE Advanced 2014)

Solution

(b) As the branching increases, the boiling point decreases. This is because the van der Waals forces of attraction decrease.

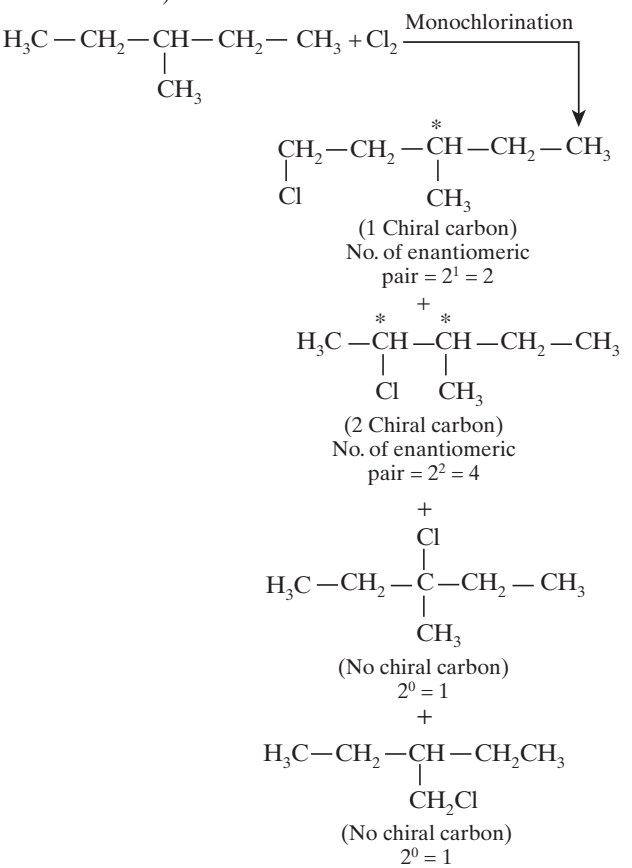
13. The maximum number of isomers (including stereoisomers) that are possible on monochlorination of the following compound, is _____.



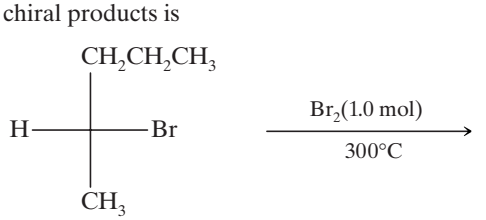
(IIT-JEE 2011)

Solution

(8) The maximum number of isomers (including stereoisomers) on monochlorination is 8.



14. In the following monobromination reaction, the number of possible chiral products is



(1.0 mol) (Enantiomerically pure)

(JEE Advanced 2016)

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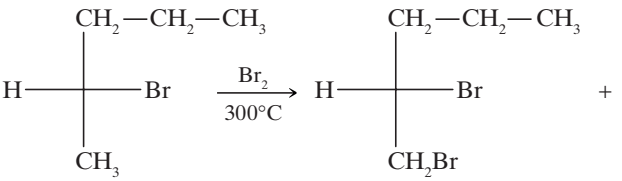
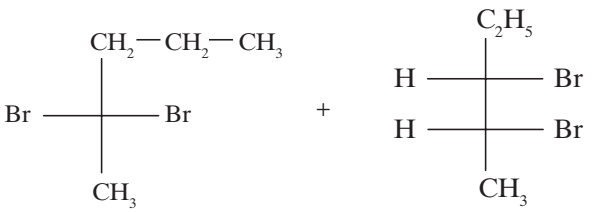
Solution

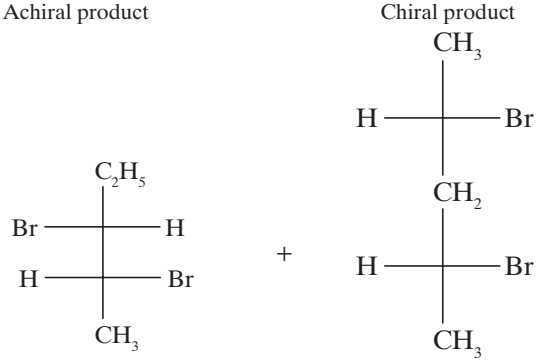
(5) A total of 5 chiral and 2 achiral products are possible on monobromination of the given compound.



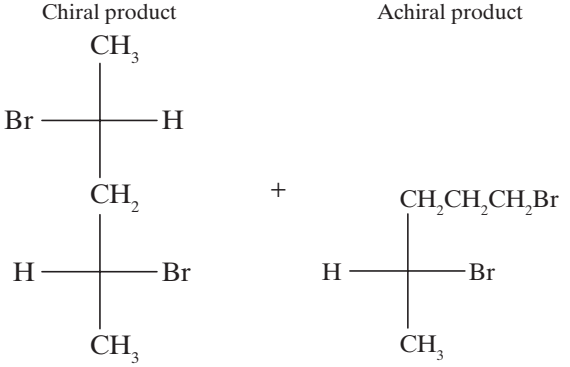
Chiral product



Achiral product Chiral product



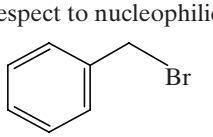
Chiral product Achiral product



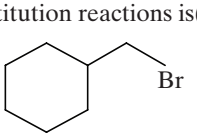
Chiral product Chiral product

Chapter: 6 Ionic Reactions: Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

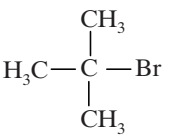
15. For the following compounds, the correct statement(s) with respect to nucleophilic substitution reactions is(are)



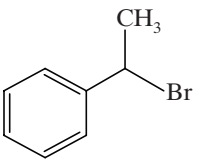
I



II



III



IV

(a) I and III follow S_N1 mechanism.
(b) I and II follow S_N2 mechanism.
(c) Compound IV undergoes inversion of configuration.
(d) The order of reactivity for I, III and IV is: IV > I > III.

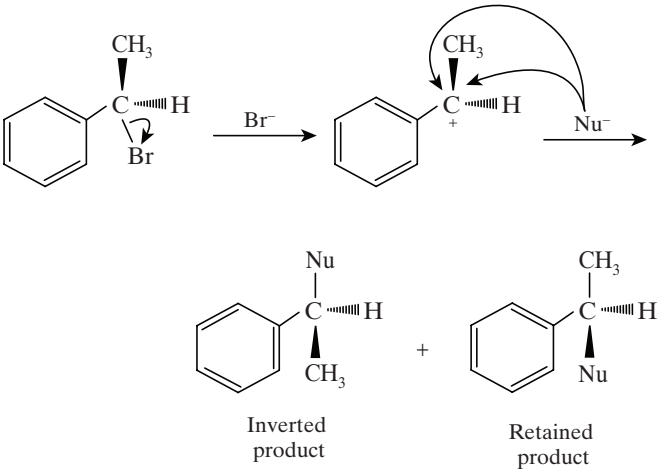
(JEE Advanced 2017)

Solution

(a), (b), (c), (d) Option (a): Correct. The primary factor that determines the reactivity of organic substrates in an S_N1 reaction is the relative stability of the carbocation that is formed. Both tertiary and benzyl carbocation are stable, therefore, both follow S_N1 mechanism.

Option (b): Correct. Primary alkyl halides react rapidly by S_N2 mechanism. S_N2 reaction involves the attack of nucleophile to the carbon atom bearing leaving group. Bulky groups or atoms of a molecule hinders with the approaching nucleophile, hence, retard the reaction.

Option (c): Correct. In S_N1 reaction, the nucleophile approaches the substrate carbon from the back side with respect to the leaving group. Nucleophilic displacement of the leaving group in an S_N2 reaction causes inversion of configuration at the substrate carbon.



Inverted product Retained product

Option (d): Correct. The order of reactivity depends on the stability of carbocation. Both compounds I and IV form resonance stabilized benzyl carbocation. Compound IV is most stable due to additional +I effect of alkyl group. Thus, the correct order is IV > I > III.

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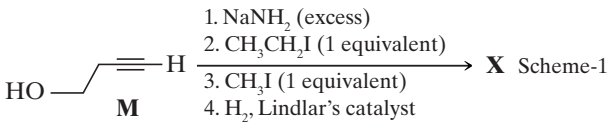
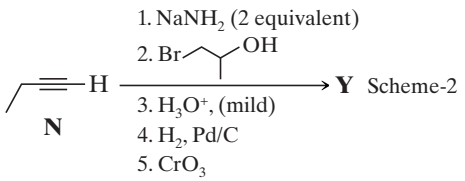
Chapter 7 Alkenes and Alkynes I: Properties and Synthesis, Elimination Reactions of Alkyl Halides

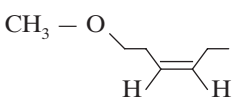
Paragraph for Questions 16 and 17: Schemes **1** and **2** describe sequential transformation of alkynes **M** and **N**. Consider only the major products formed in each step for both the schemes.

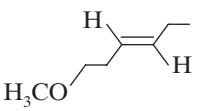


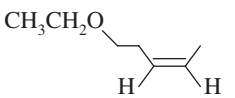


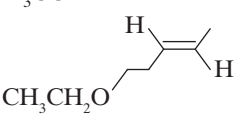
(JEE Advanced 2014)

16. The product X is

(a) 

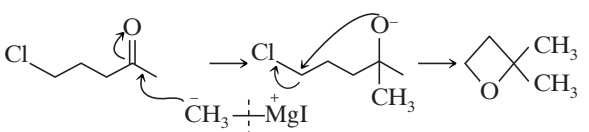
(b) 

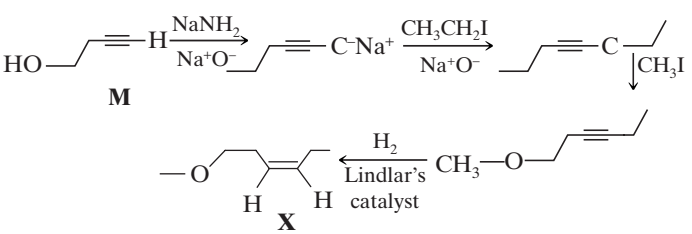
(c) 

(d) 

Solution

(a) The reactions involved are





17. The correct statement with respect to product **Y** is

(a) It gives a positive Tollens test and is a functional isomer of **X**.

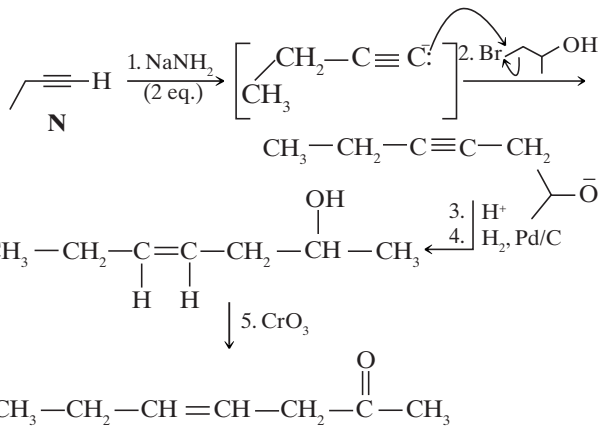
(b) It gives a positive Tollens test and is a geometrical isomer of **X**.

(c) It gives a positive iodoform test and is a functional isomer of **X**.

(d) It gives a positive iodoform test and is a geometrical isomer of **X**.

Solution

(c) The sequence of reactions for formation of Y are



As it has a CH_3CO- group so it gives positive iodoform test and it is a functional isomer of **X** as only the functional groups are different.

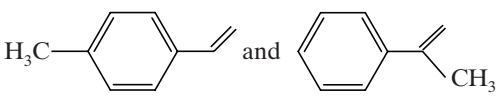
Chapter: 8 Alkenes and Alkynes II: Addition Reactions

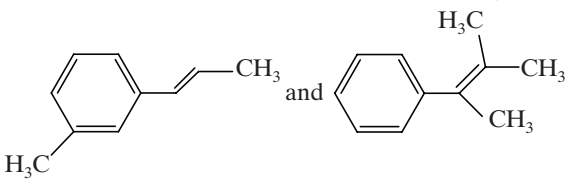
18. Compounds **P** and **R** upon ozonolysis produce **Q** and **S**, respectively. The molecular formula of **Q** and **S** is C_8H_8O. **Q** undergoes Cannizzaro reaction but not haloform reaction, whereas **S** undergoes haloform reaction but not Cannizzaro reaction.

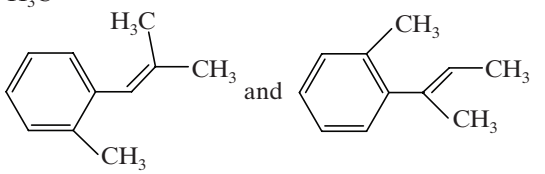
(i) $\mathbf{P} \xrightarrow[2.\ Zn/H_2O]{1.\ O_3/CH_2Cl_2} \underset{(C_8H_8O)}{\mathbf{Q}}$

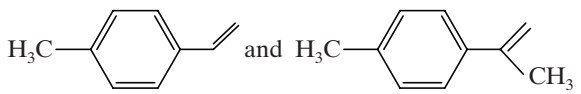
(ii) $\mathbf{R} \xrightarrow[2.\ Zn/H_2O]{1.\ O_3/CH_2Cl_2} \underset{(C_8H_8O)}{\mathbf{S}}$

The option(s) with suitable combination of **P** and **R**, respectively, is(are)

(a) 

(b) 

(c) 

(d) 

(JEE Advanced 2017)

Solution

(a), (b) Option (a): Correct

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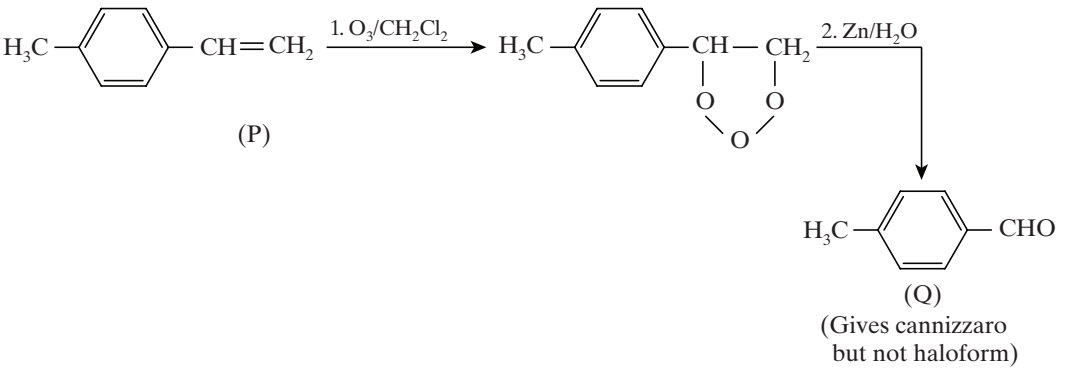
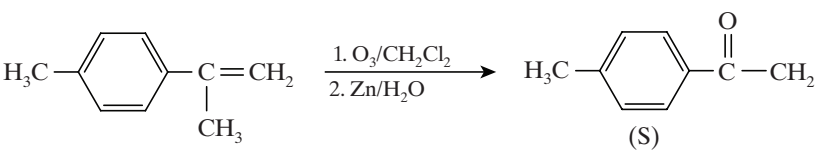


(P)

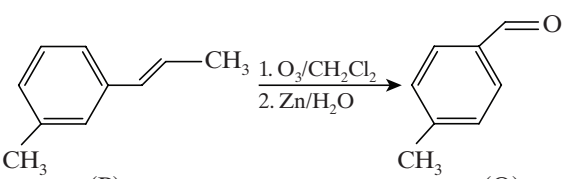
(Q)
(Gives cannizzaro but not haloform)



(R)

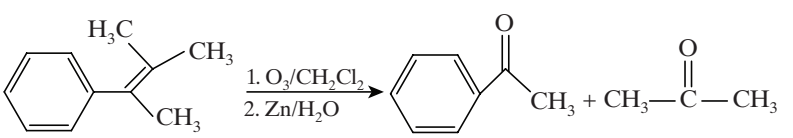
(S)
(Gives haloform but not cannizzaro)

Option (b): Correct



(P)

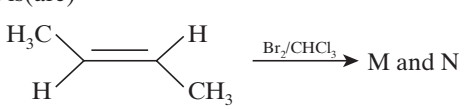
(Q)
(Gives cannizzaro but not haloform)



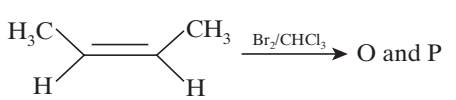
(R)

(S)
(Gives haloform but not cannizzaro)

19. The correct statement(s) for the following addition reactions is(are)

I 

M and N

II 

O and P

(a) **O** and **P** are identical molecules.
(b) (**M** and **O**) and (**N** and **P**) are two pairs of diastereomers.
(c) (**M** and **O**) and (**N** and **P**) are two pairs of enantiomers.
(d) Bromination proceeds through *trans*-addition in both the reactions.

(JEE Advanced 2017)

Solution

(b), (d) When *trans*-2-butene adds bromine, the product is the meso compound, (2*R*, 3*S*)-2,3-dibromobutane. When *cis*-2-butene adds bromine, the product is a racemic mixture of (2*R*, 3*R*)-2,3-dibromobutane and (2*S*, 3*S*)-2,3-dibromobutane.

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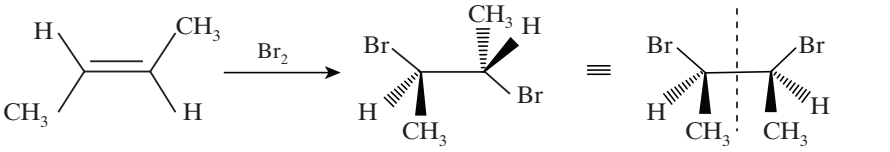
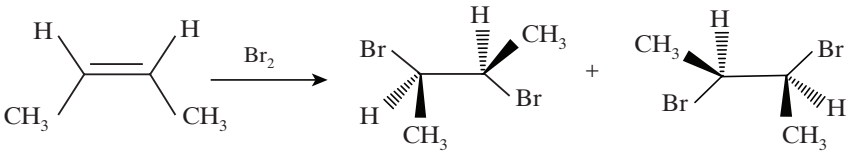


trans-2-Butene (2*R*, 3*S*)-2,3-Dibromobutane (a meso compound)

M = N



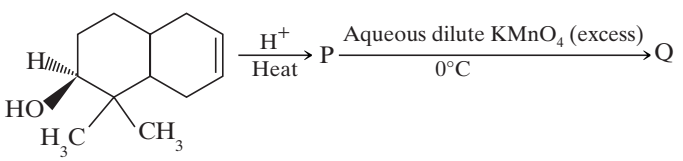
cis-2-Butene (2*R*, 3*R*) + (2*S*, 3*S*)

O P

(a pair of enantiomers)

(M and O) and (N and P) are two pairs of diaseteroisomers. The addition of bromine or chlorine to an alkene is an anti or *trans* addition.

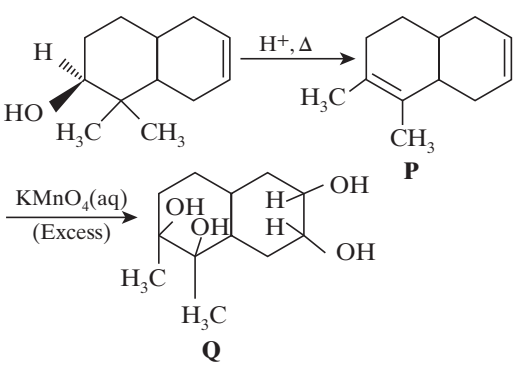
20. The number of hydroxyl group(s) in **Q** is _____.



(JEE Advanced 2015)

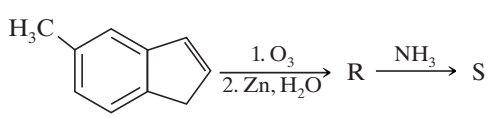
Solution

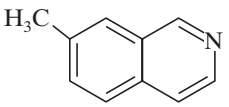
(4)

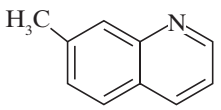


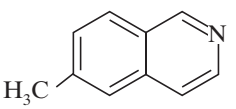
Therefore, the number of hydroxyl groups is 4.

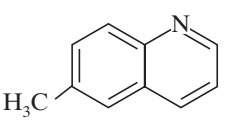
21. In the following reactions, the product **S** is



(a) 

(b) 

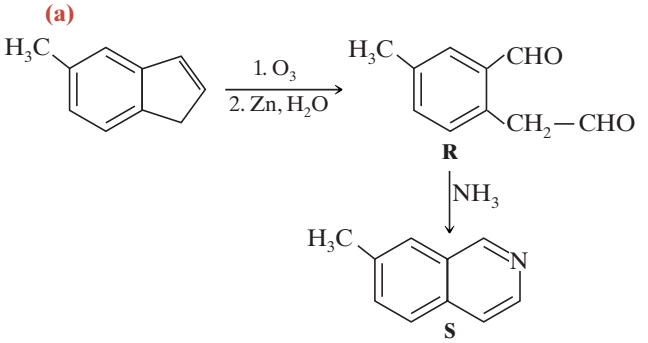
(c) 

(d) 

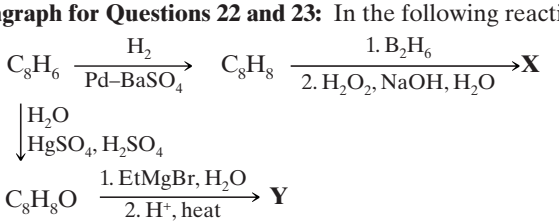
(JEE Advanced 2015)

Solution

(a)

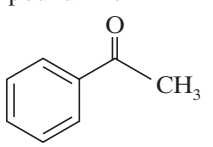


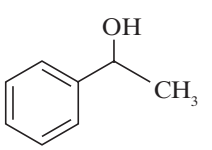
Paragraph for Questions 22 and 23: In the following reactions



(JEE Advanced 2015)

22. Compound **X** is

(a) 

(b) 

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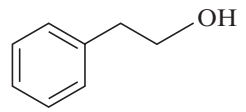
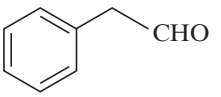
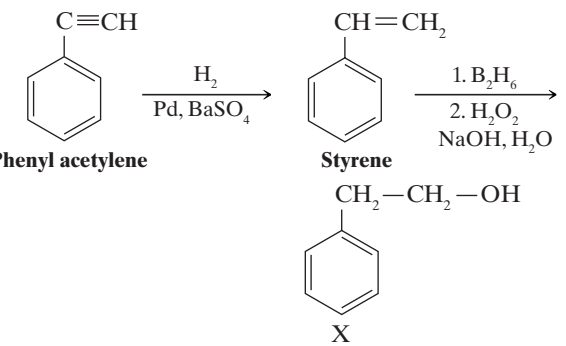
(c) 

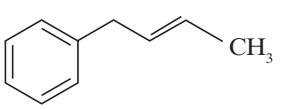
(d) 

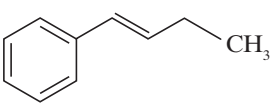
Solution

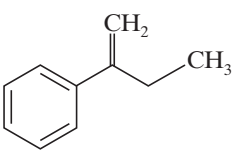
(c) 

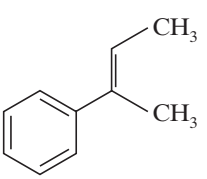
Phenyl acetylene | Styrene | X

23. The major compound **Y** is

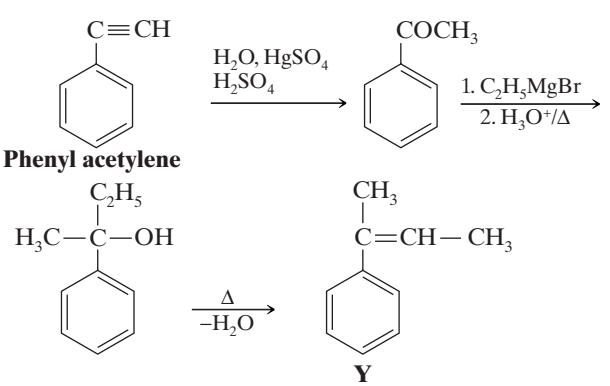
(a) 

(b) 

(c) 

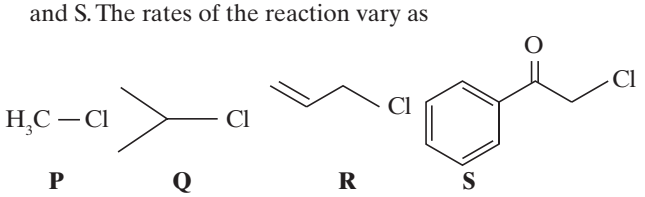
(d) 

Solution

(d) 

Phenyl acetylene | Y

24. KI in acetone, undergoes S_N2 reaction with each of P, Q, R and S. The rates of the reaction vary as



P **Q** **R** **S**

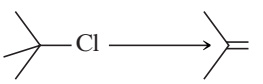
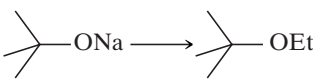
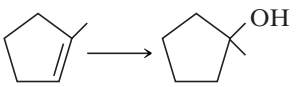
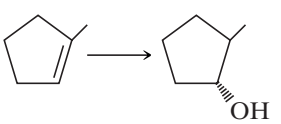
(a) P > Q > R > S (b) S > P > R > Q
(c) P > R > Q > S (d) R > P > S > Q

(JEE Advanced 2013)

Solution

(b) The relative reactivities towards S_N2 reaction S > P > R > Q.

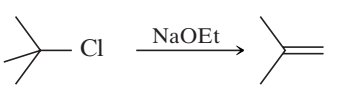
25. Match the chemical conversions in **List I** with the appropriate reagents in **List II** and select the correct answer using the code given below the lists:

List I	List II
(p) 	(1) (i) $Hg(OAc)_2$; (ii) $NaBH_4$
(q) 	(2) NaOEt
(r) 	(3) Et–Br
(s) 	(4) (i) BH_3; (ii) H_2O_2/NaOH

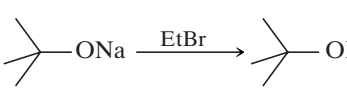
(JEE Advanced 2013)

Solution

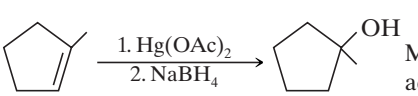
(a) The reactions involved are

(p) 

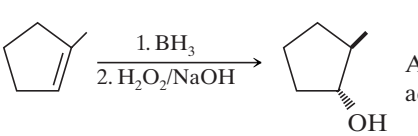
E_2 reaction

(q) 

S_N2 reaction

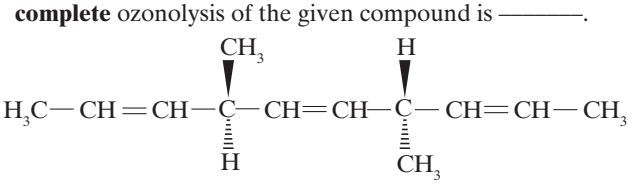
(r) 

Markovnikov addition

(s) 

Anti-Markovnikov addition

26. The number of optically active products obtained from the **complete** ozonolysis of the given compound is ———.



(a) 0 (b) 1 (c) 2 (d) 4

(IIT-JEE 2012)

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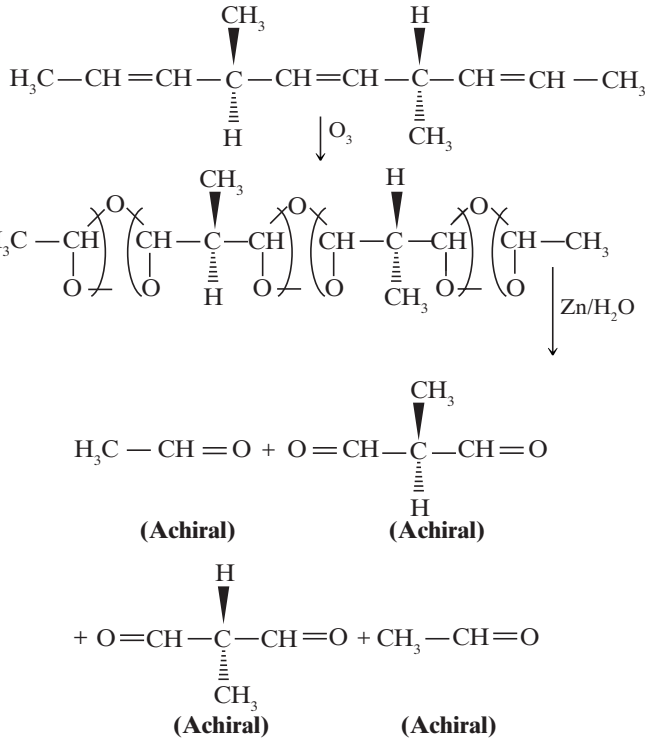
Solution

(a) The reaction is



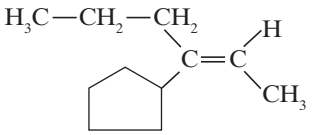
27. The total number of alkenes possible by dehydrobromination of 3-bromo-3-cyclopentylhexane using alcoholic KOH is

(IIT-JEE 2011)

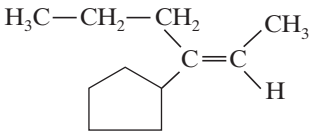
Solution

(5) The total number of alkenes is 5 as shown below.

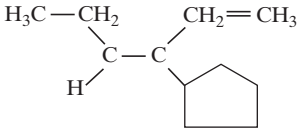
(1)



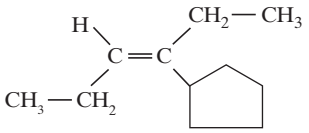
(2)



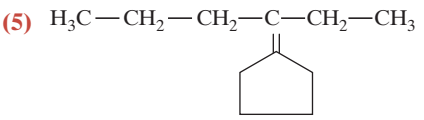
(3)



(4)

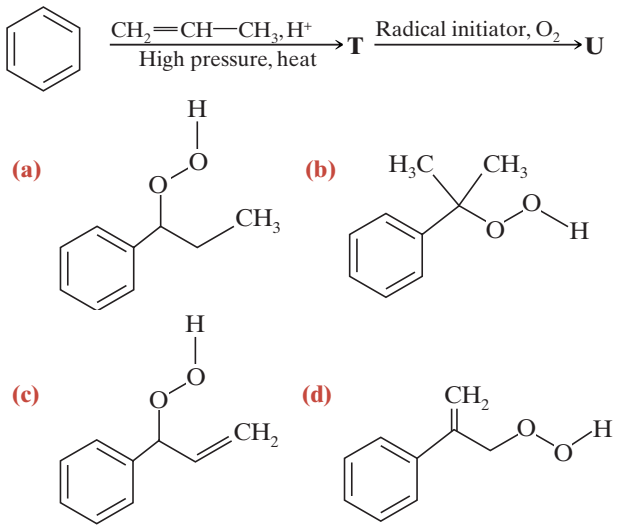


(5)



Chapter 9 Radical Reactions

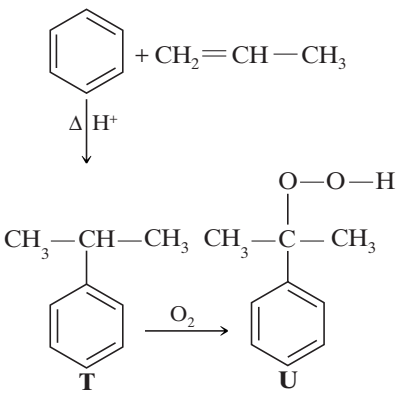
28. The major product **U** in the following reactions is



(JEE Advanced 2015)

Solution

(b) The reaction is



Chapter 10 Alcohols and Ethers

29. The correct combination of names for isomeric alcohols with molecular formula $C_4H_{10}O$ is/are

(a) *tert*-butanol and 2-methylpropan-2-ol.
(b) *tert*-butanol and 1,1-dimethylethan-1-ol.
(c) *n*-butanol and butan-1-ol.
(d) isobutyl alcohol and 2-methylpropan-1-ol.

(JEE Advanced 2014)

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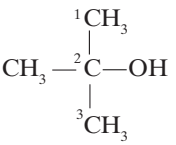
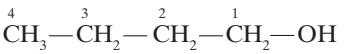
Solution

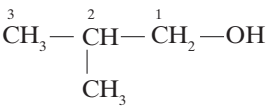
(a), (c), (d)



3-Butanol or
2-Methylpropan-2-ol

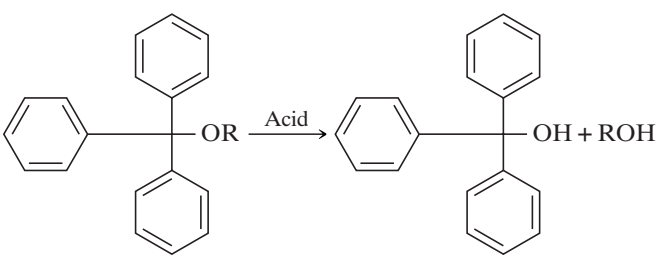


***n*-Butanol or**
Butan-1-ol



Isobutyl alcohol or
2-Methylpropan-2-ol

30. The acidic hydrolysis of ether **(X)** shown below is fastest when



(X)

(a) one phenyl group is replaced by a methyl group.
(b) one phenyl group is replaced by a *para*-methoxyphenyl group.
(c) two phenyl groups are replaced by two *para*-methoxyphenyl groups.
(d) no structural change is made to X.

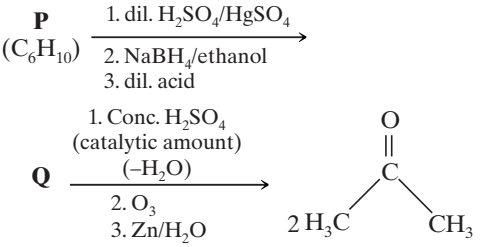
(JEE Advanced 2014)

Solution

(c) The acidic hydrolysis is fastest when two phenyl groups are replaced by two *para*-methoxyphenyl groups.

This is because $-OCH_3$ is an electron donating group which increases the stability of the carbocation.

Paragraph for Questions 31 and 32: An acyclic hydrocarbon **P,** having molecular formula C_6H_{10}, gave acetone as the only organic product through the following sequence of reactions, in which **Q** is an intermediate organic compound.



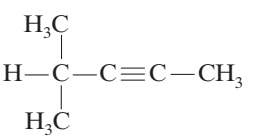
(IIT-JEE 2011)

31. The structure of compound **P** is

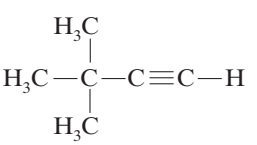
(a) $CH_3CH_2CH_2CH_2-C\equiv C-H$

(b) $H_3CH_2C-C\equiv C-CH_2CH_3$

(c)



(d)

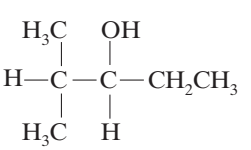


Solution

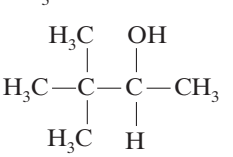
(d)

32. The structure of the compound **Q** is

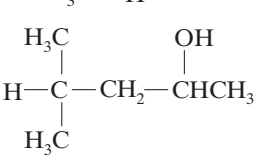
(a)



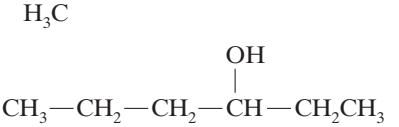
(b)



(c)



(d)



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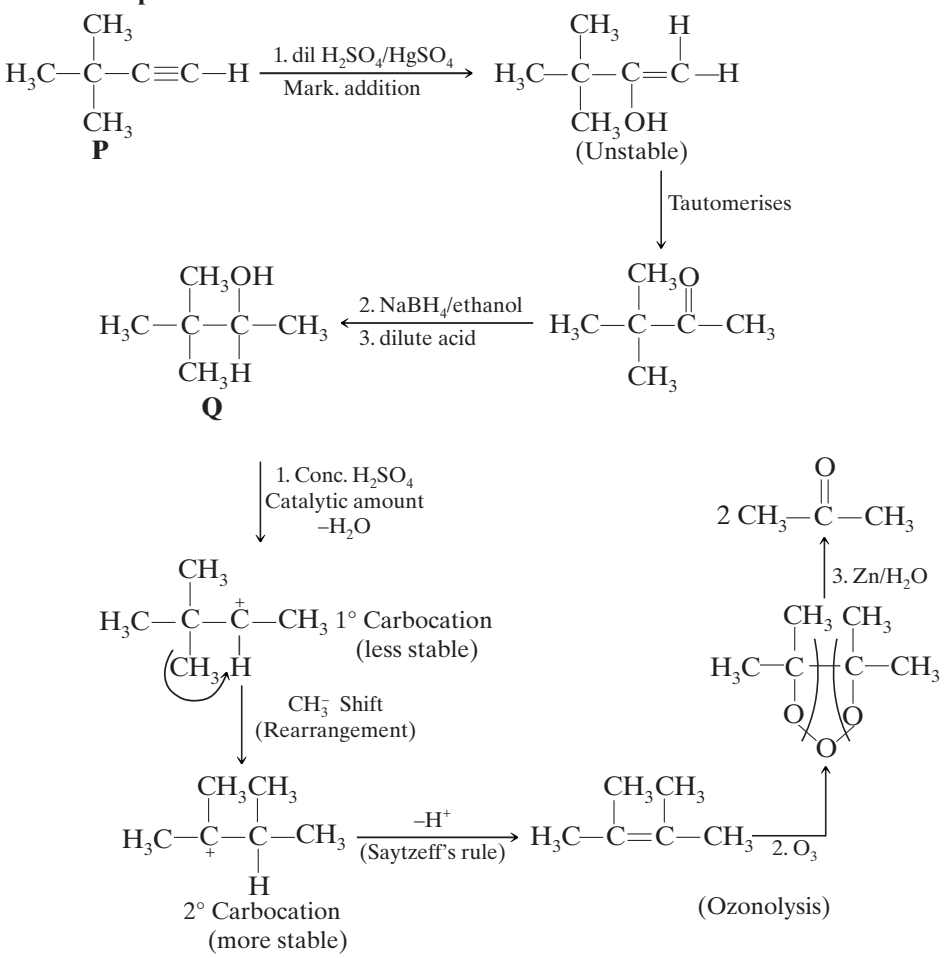
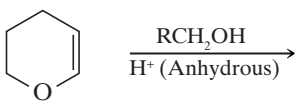
Solution

(b)

Common Explanation



33. The major product of the following reaction is

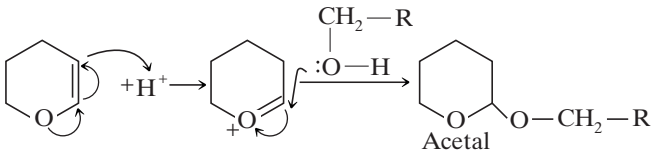


(a) a hemiacetal. **(b)** an acetal.
(c) an ether. **(d)** an ester.

(IIT-JEE 2011)

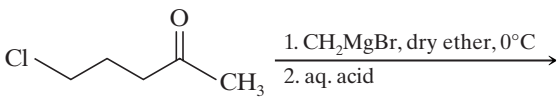
Solution

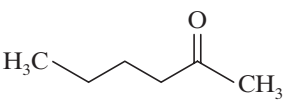
(b) The product obtained is an acetal.

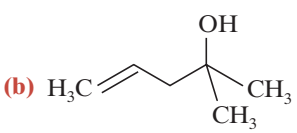


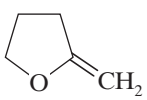
Chapter 11 Alcohols from Carbonyl Compounds

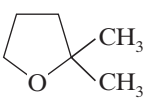
34. The major product in the following reaction is



(a) 

(b) 

(c) 

(d) 

(JEE Advanced 2014)

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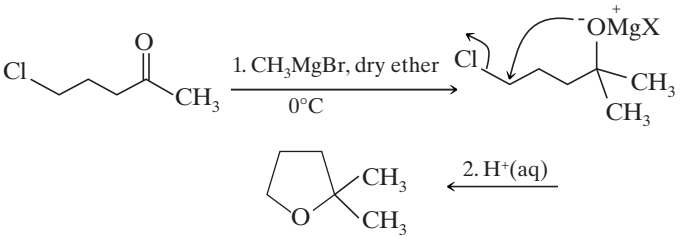
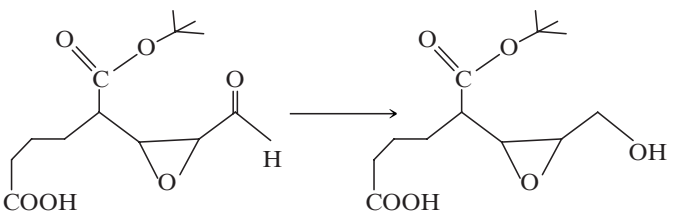
Solution

(d) The reaction is



35. Reagent(s) which can be used to bring about the following transformation is(are)



(a) $LiAlH_4$ in $(C_2H_5)_2O$
(b) BH_3 in THF
(c) $NaBH_4$ in C_2H_5OH
(d) Raney Ni/H_2 in THF

(JEE Advanced 2016)

Solution

(c), (d) Option (a): $LiAlH_4$ in $(C_2H_5)_2$ reduces ester (–COOR), carboxylic acid (–COOH) epoxide, aldehydes and ketones.

Option (b): BH_3 in THF reduces –COOH and aldehydes into alcohols. However, it does not reduce esters and epoxides.

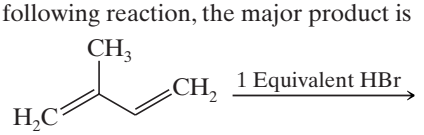
Option (c): $NABH_4$ in C_2H_5OH reduces only aldehydes and ketones into alcohols, but it does not reduce to others.

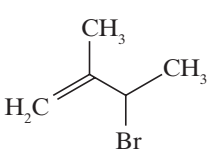
Option (d): Raney Ni/H_2 in THF does not reduce to –COOH, –COOR and epoxide but it can reduce aldehyde into alcohols.

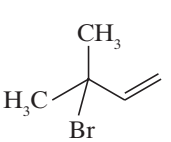
Hence, options (c) and (d) are correct.

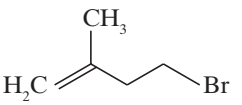
Chapter 12 Conjugated Unsaturated Systems

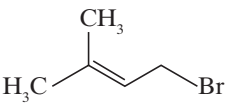
36. In the following reaction, the major product is



(a) 

(b) 

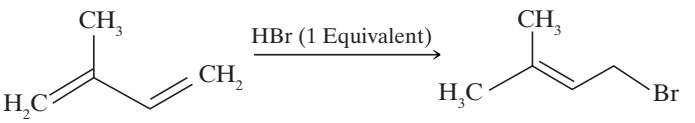
(c) 

(d) 

(JEE Advanced 2015)

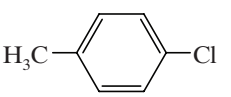
Solution

(d) 1,4-addition is the major product as it is the result of the formation of a stable allylic carbocation.



Chapter 13 Aromatic Compounds

37. The IUPAC name(s) of the following compound is(are)

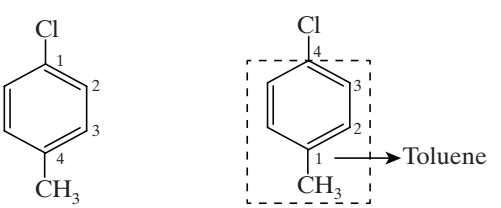


(a) 1-chloro-4-methylbenzene.
(b) 4-chlorotoluene.
(c) 4-methylchlorobenzene.
(d) 1-methyl-4-chlorobenzene.

(JEE Advanced 2017)

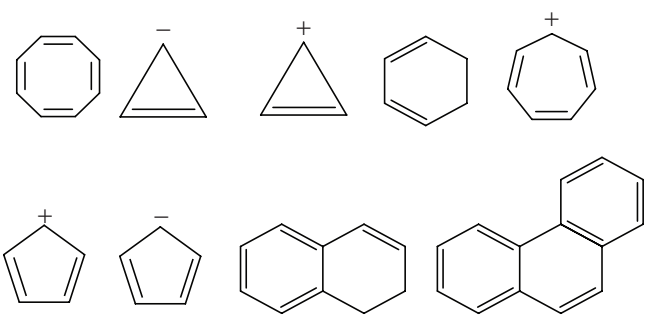
Solution

(b), (c) The IUPAC names of the given compound is



1-Chloro-4-methylbenzene 4-Chlorotoluene

38. Among the following, the number of aromatic compound(s) is



(JEE Advanced 2017)

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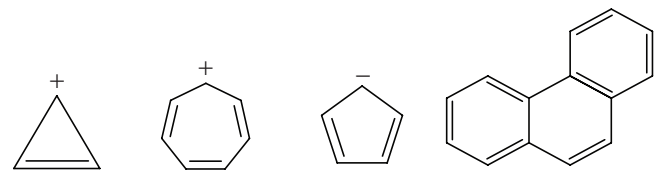
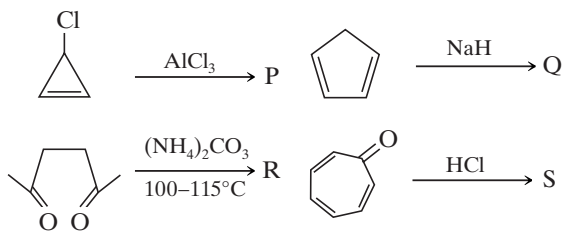
Solution

(d) Huckel's rule states that a conjugated, planar, cyclic system will be aromatic if it contains $(4n + 2)$ delocalized π electrons, where n is zero or integers like 1, 2, 3.... Aromatic compounds are as follows:



(2π electrons) (6π electrons) (6π electrons) (14π electrons)

39. Among P, Q, R and S, the aromatic compound(s) is/are



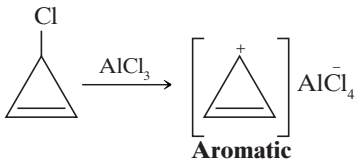
(a) P **(b)** Q
(c) R **(d)** S

(JEE Advanced 2013)

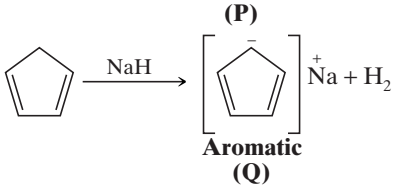
Solution

(a), (b), (c), (d) The reactions involved are

(a)

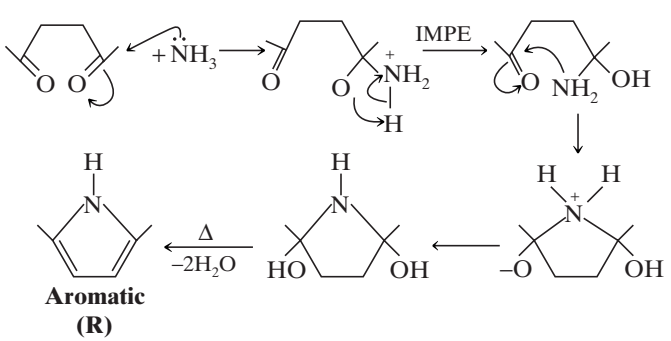


(b)

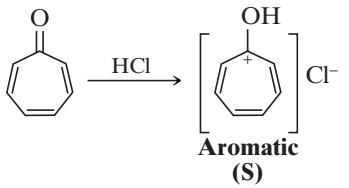


(c)

$$(NH_4)_2CO_3 \xrightarrow{\Delta} 2NH_3 + CO_2 + H_2O$$



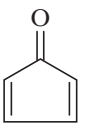
(d)

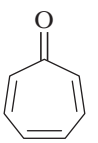


40. Which of the following molecules, in pure form, is (are) **unstable** at room temperature?

(a) 

(b) 

(c) 

(d) 

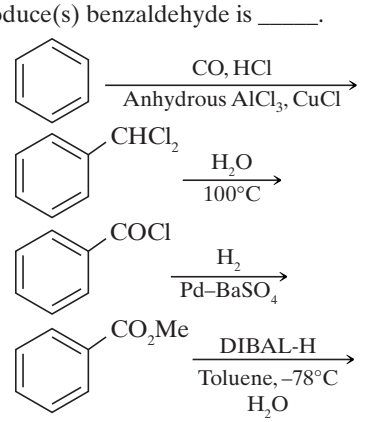
(IIT-JEE 2012)

Solution

(b), (c) The compounds in option (b) and (c) do not follow Huckel's rule, that is, they do not have $(4n + 2)\pi$ electrons, so they are anti aromatic and are unstable at room temperature.

Chapter 14 Reactions of Aromatic Compounds

41. Among the following the number of reaction(s) that produce(s) benzaldehyde is _____.

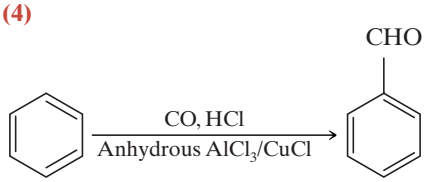


(JEE Advanced 2015)

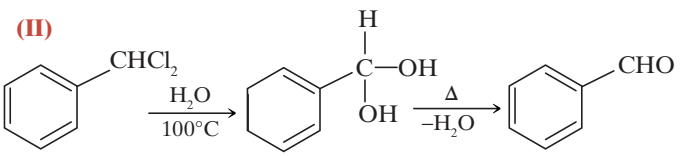
Solution

(4)

(I)



(II)



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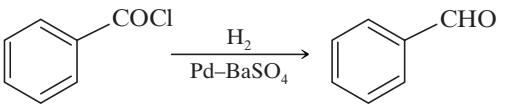
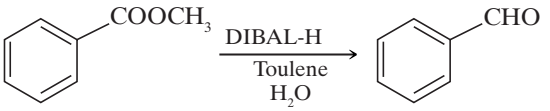
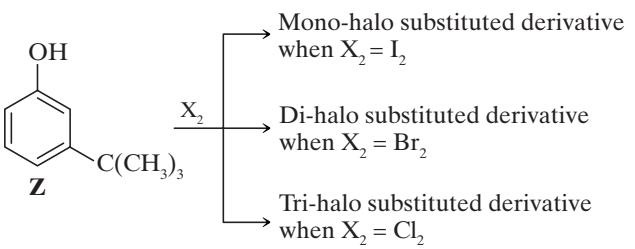
(III) 

(IV) 

Therefore, the number of reactions leading to the formation of benzaldehyde is 4.

42. The reactivity of compound **Z** with different halogens under appropriate conditions is given below:



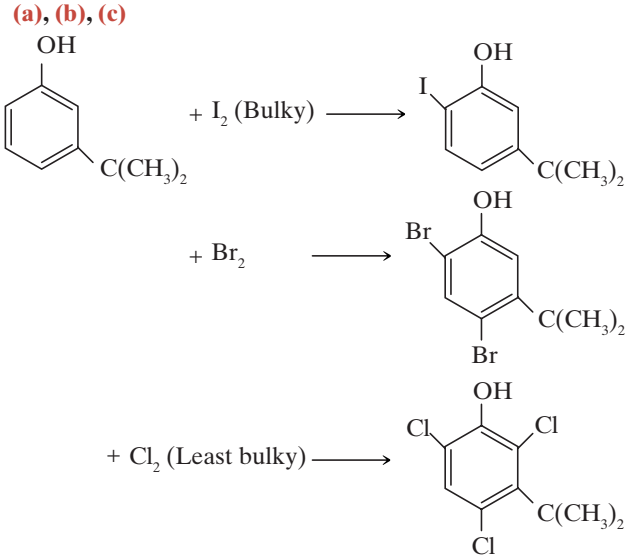
The observed pattern of electrophilic substitution can be explained by

(a) the steric effect of the halogen.
(b) the steric effect of the *tert*-butyl group.
(c) the electronic effect of the phenolic group.
(d) the electronic effect of the *tert*-butyl group.

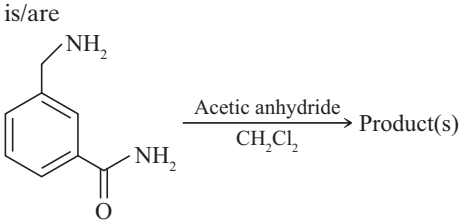
(JEE Advanced 2014)

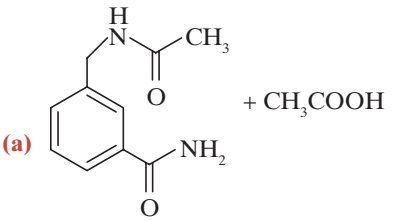
Solution

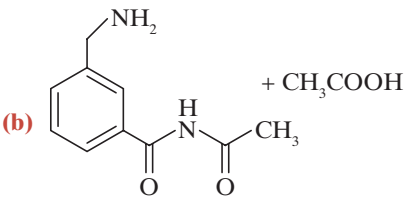
(a), (b), (c)

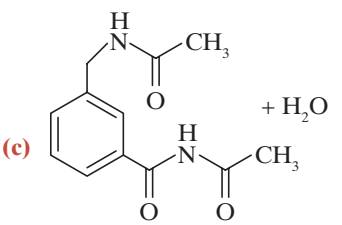


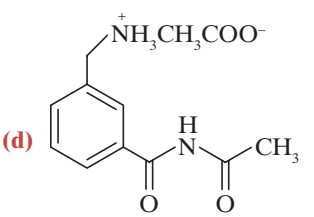
43. In the reaction shown below, the major product(s) formed is/are



(a) 

(b) 

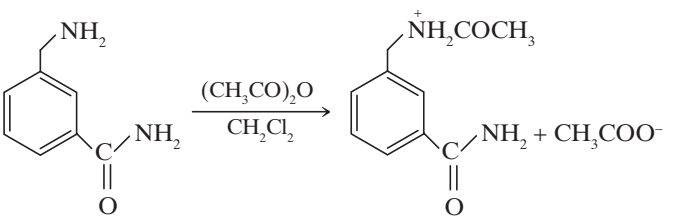
(c) 

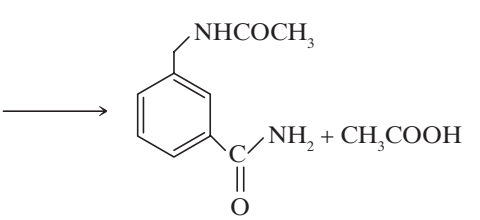
(d) 

(JEE Advanced 2014)

Solution

(a) The reaction involved is





44. Match the four starting materials (**P, Q, R, S**) given in **List I** with the corresponding reaction schemes (**I, II, III, IV**) provided in **List II** and select the correct answer using the code given below the lists.

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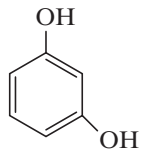
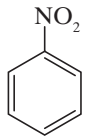
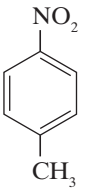
List-I	List-II
(P) H—≡—H	**1. Scheme I** ? $\xrightarrow[3.\ SOCl_2\ 4.\ NH_3]{1.\ KMnO_4,\ HO^-,\ heat\ 2.\ H^+,\ H_2O}$ $C_7H_6N_2O_3$
(Q) 	**2. Scheme II** ? $\xrightarrow[4.\ HNO_3\ 5.\ dil.\ H_2SO_4,\ heat\ 6.\ HO^-]{1.\ Sn/HCl\ 2.\ CH_3COCl\ 3.\ conc.\ H_2SO_4}$ $C_6H_6N_2O_2$
(R) 	**3. Scheme III** ? $\xrightarrow[3.\ H_2S.\ NH_3\ 4.\ NaNO_2,\ H_2SO_4\ 5.\ hydrolysis]{1.\ red\ hot\ iron,\ 873K\ 2.\ fuming\ HNO_3,\ H_2SO_4,\ heat}$ $C_6H_5NO_3$
(S) 	**4. Scheme IV** ? $\xrightarrow[2.\ conc.\ HNO_3,\ conc.\ H_2SO_4\ 3.\ dil.\ H_2SO_4,\ heat]{1.\ conc.\ H_2SO_4,\ 60°C}$ $C_6H_5NO_4$

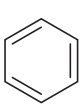
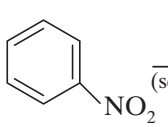
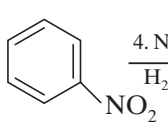
Code:

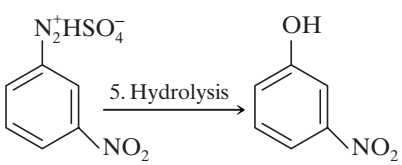
	P	Q	R	S
(a)	1	4	2	3
(b)	3	1	4	2
(c)	3	4	2	1
(d)	4	1	3	2

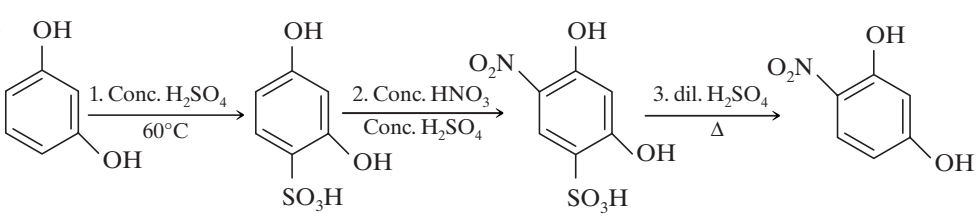
(JEE Advanced 2014)

Solution

(c) The reactions involved are as follows:

(P) $3CH{\equiv}CH \xrightarrow[\text{iron 873 K}]{\text{1. red hot}}$  $\xrightarrow[\Delta]{\text{2. fuming } HNO_3/H_2SO_4}$  $\xrightarrow[\text{(selective reduction)}]{\text{3. } H_2S,\ NH_3}$  $\xrightarrow[H_2SO_4]{\text{4. } NaNO_2}$



(Q) 

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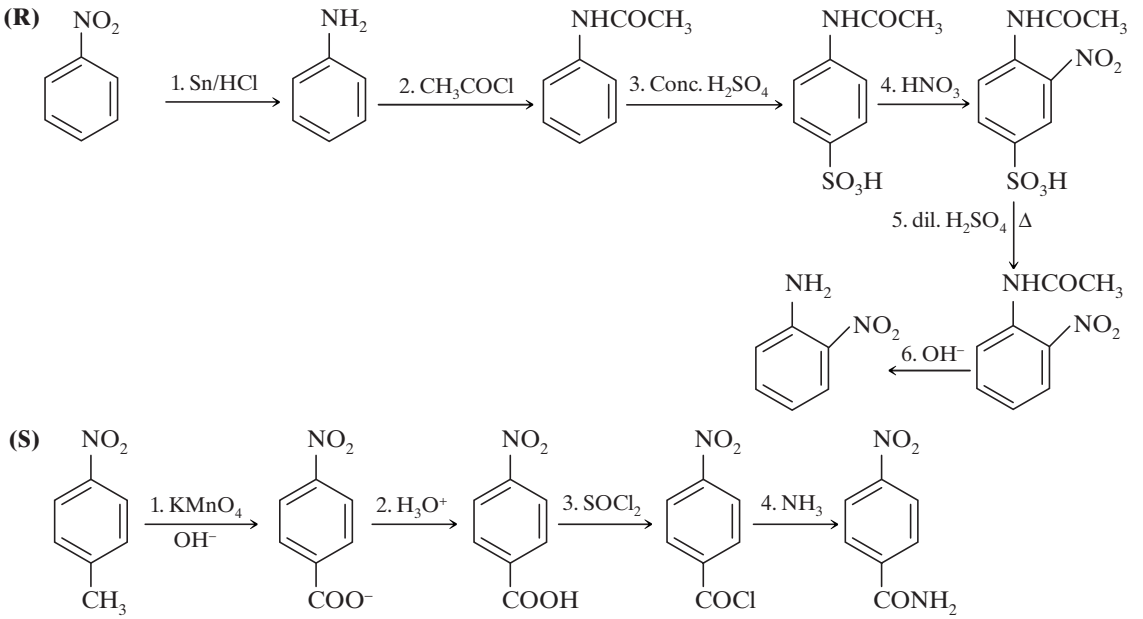
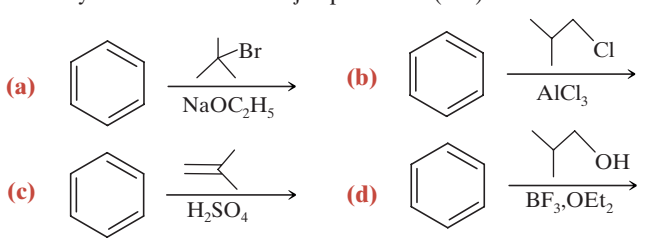


45. Among the following reaction(s) which gives (give) *tert*-butyl benzene as the major product is(are)

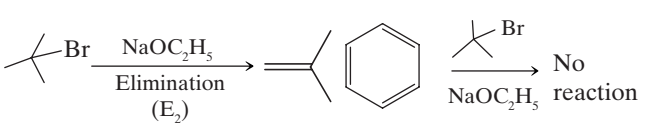


(JEE Advanced 2016)

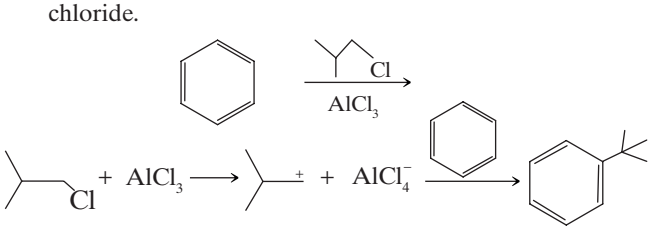
Solution

(b), (c), (d) The reactions of the given compounds are as follows:

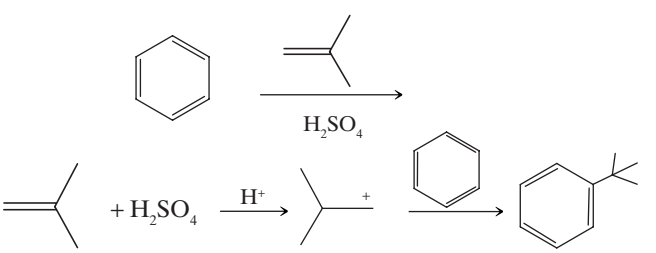
In the reaction given in option (a), *tert*-butyl benzene is not formed, instead *tert*-butyl bromide undergoes elimination reaction.



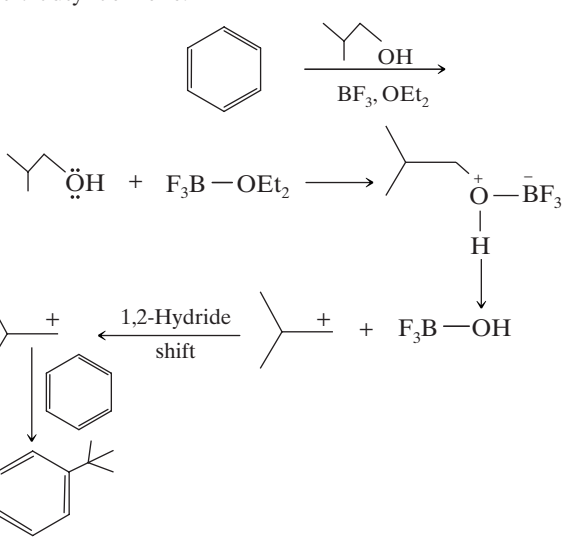
In the reaction given in option (b), *tert*-butyl benzene is obtained by Friedel-Crafts reaction with 2-methyl propyl chloride.



In the reaction given in option (c), the alkene undergoes electrophilic addition and the carbocation formed undergoes electrophilic substitution on the benzene ring to form *tert*-butyl benzene.



In the reaction given in option (d), the carbocation obtained undergoes 1,2-hydride shift and the resulting cation undergoes electrophilic substitution on the benzene ring to form *tert*-butyl benzene.



Chapter 15 Aldehydes and Ketones I. Nucleophilic Addition to the Carbonyl Group

46. Consider all possible isomeric ketones, including stereoisomers of MW = 100. All these isomers are independently

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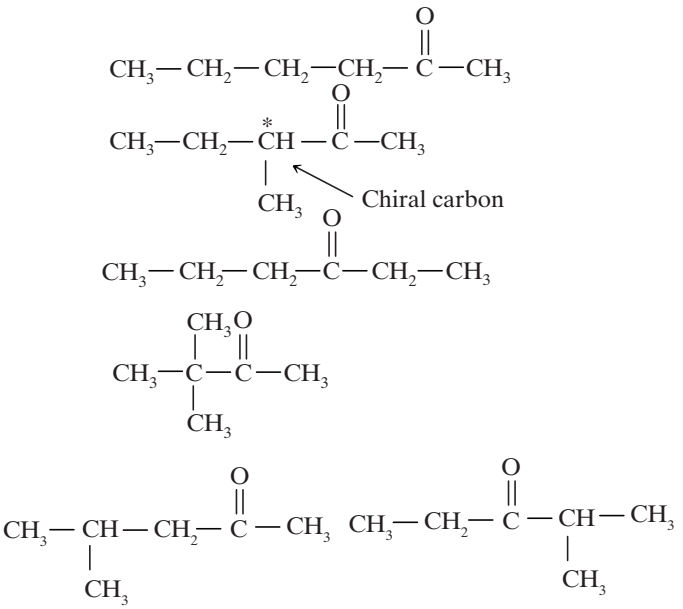
reacted with $NaBH_4$ (NOTE: Stereoisomers are also reacted separately). The total number of ketones that give a racemic product(s) is/are _____.

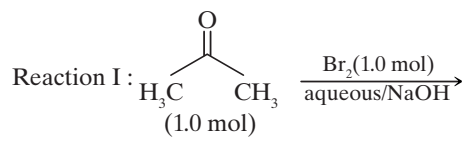
(JEE Advanced 2014)

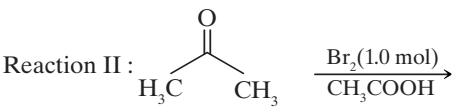
Solution

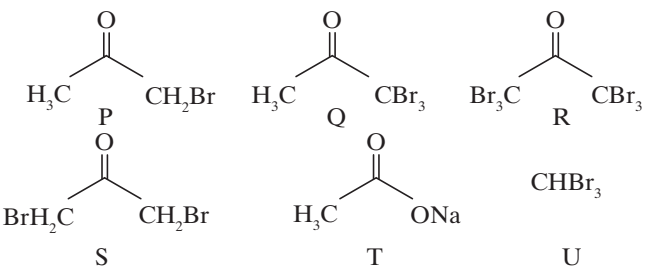
(5) The possible number of ketones with molecular formula $C_6H_{12}O$ is six. Out of these, the total number of ketones that give a racemic product(s) on reaction with $NaBH_4$ is 5. The structure with chiral carbon will not give racemic product on reduction.



47. After completion of the reactions (I and II), the organic compound(s) in the reaction mixtures is(are)





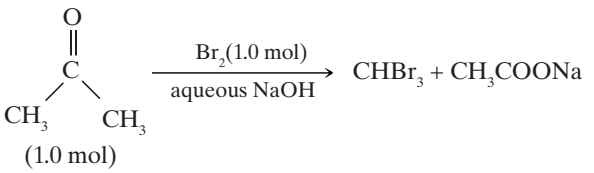


(a) Reaction I: P and Reaction II: P.
(b) Reaction I: U, acetone and Reaction II: Q, acetone.
(c) Reaction I: T, U, acetone and Reaction II: P.
(d) Reaction I: R, acetone and Reaction II: S, acetone.

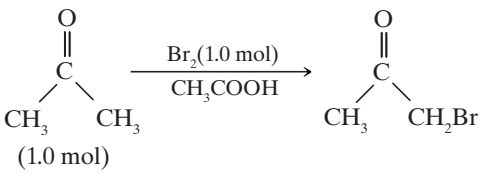
(JEE Advanced 2013)

Solution

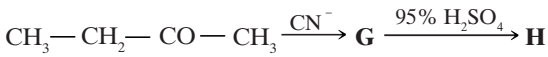
(c) In reaction I, in basic medium, with each α-halogenation the rate of reaction increases and the complete haloform reaction takes place.

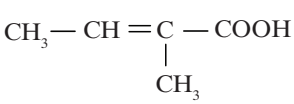


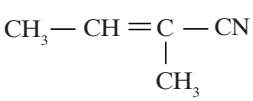
In reaction II, in acidic medium only 1 halogenated product is obtained with 1 mol of halogen.

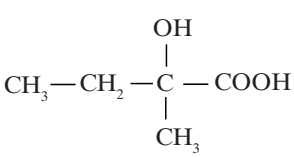


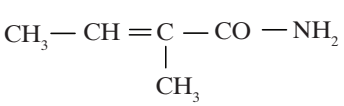
48. The major product **H** of the given reaction sequence is



(a) 

(b) 

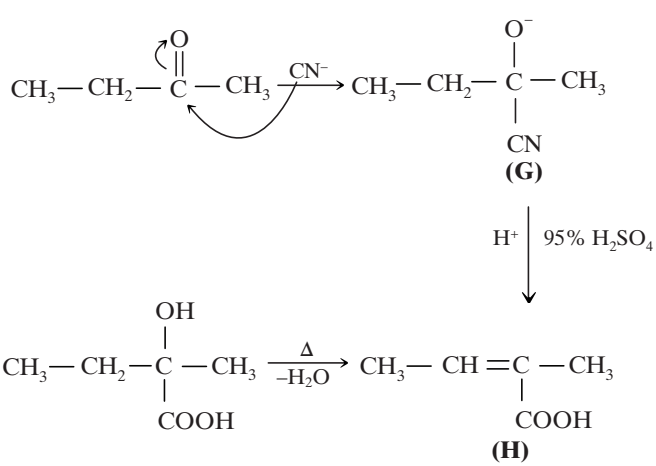
(c) 

(d) 

(IIT-JEE 2012)

Solution

(a) The reaction is



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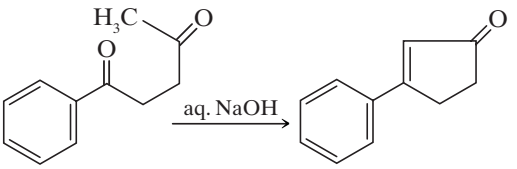
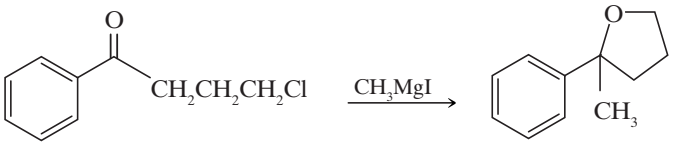
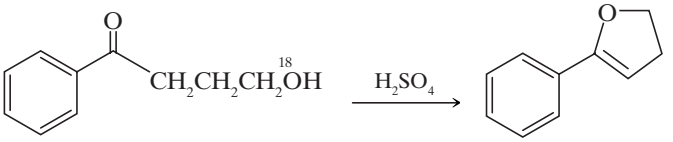
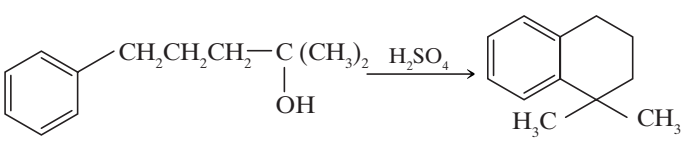
49. Match the reactions in **Column I** with appropriate types of steps/reactive intermediate involved in these reactions as given in **Column II**

Column I	Column II
(a) 	**(p)** Nucleophilic substitution
(b) 	**(q)** Electrophilic substitution
(c) 	**(r)** Dehydration
(d) 	**(s)** Nucleophilic
	(t) Carbanion

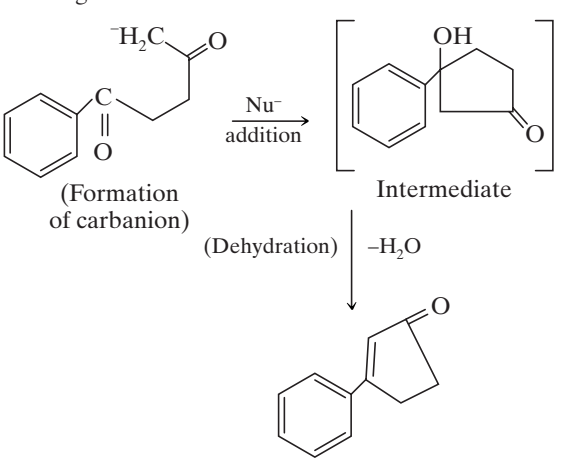
(IIT-JEE 2011)

Solution

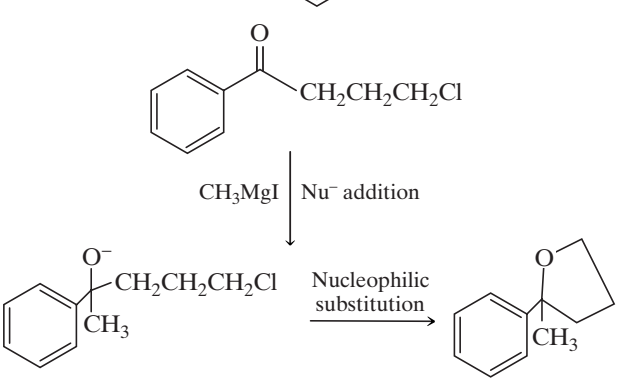
(a) → (r, s, t); (b) → (p, s); (c) →(r, s); (d) →(q, r)

In the given reactions

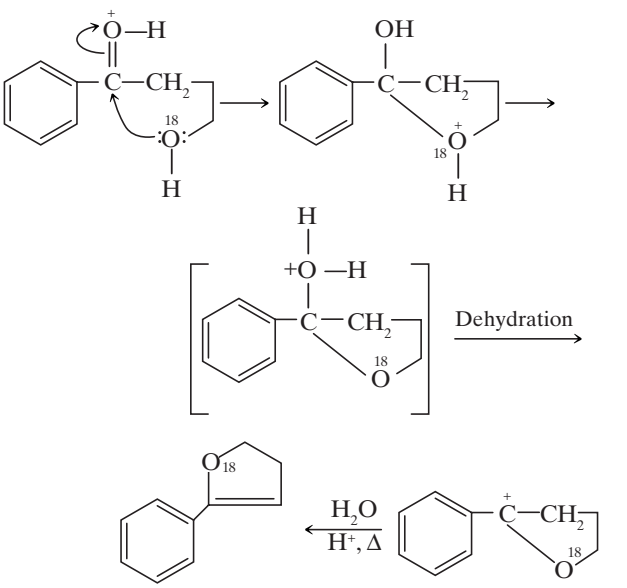
(a)



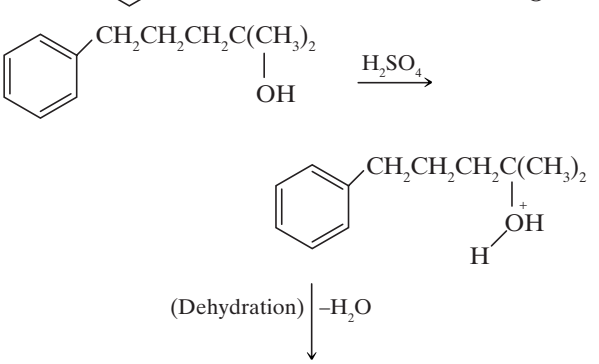
(b)



(c)



(d)



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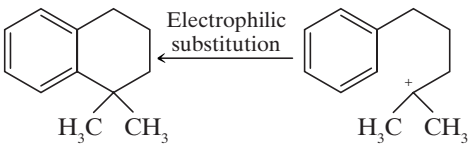
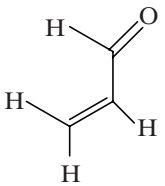
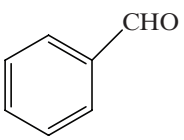


50. Positive Tollen's test is observed for

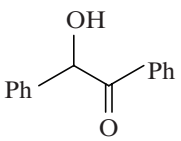
(a)



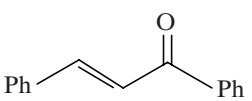
(b)



(c)



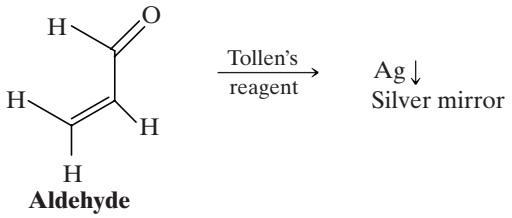
(d)



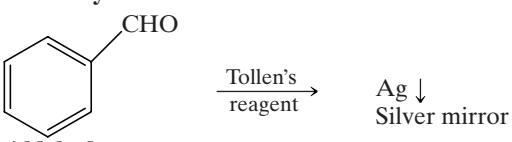
(JEE Advanced 2016)

Solution

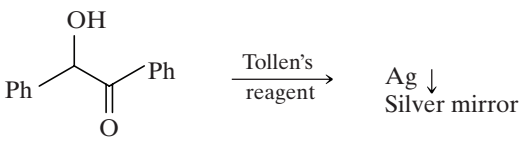
(a), (b), (c) Only aldehydes and α-hydroxyketones show positive test with Tollen's reagent containing $Ag(NH_3)_2^+$ ions. It is a weak oxidizing agent that oxidizes aldehydes to carboxylate ions and gets reduced to metallic silver Ag, depositing on the walls of test tube as silver mirror.



Aldehyde

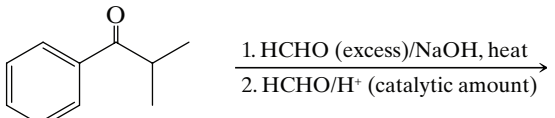


Aldehyde

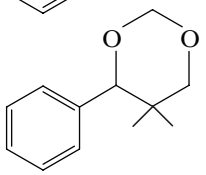


α–Hydroxy Ketone

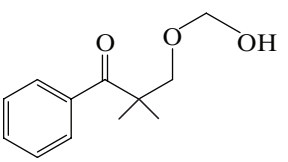
51. The major product of the following reaction sequence is:



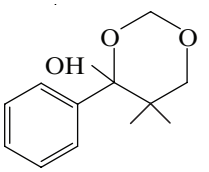
(a)



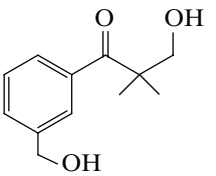
(b)



(c)



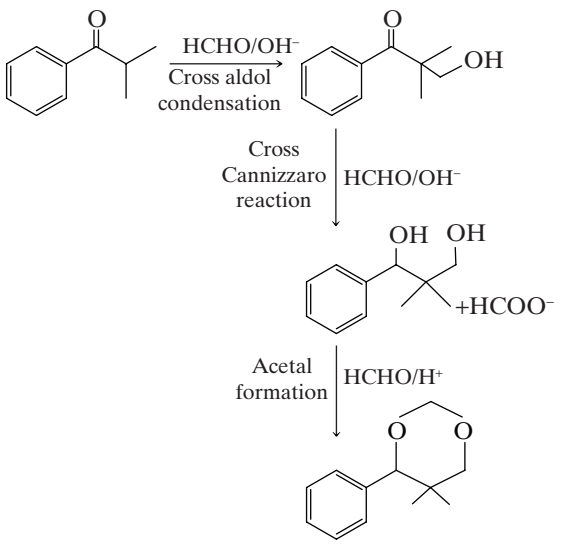
(d)



(JEE Advanced 2016)

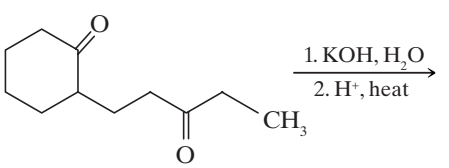
Solution

(a) The major product of the given reaction sequence is

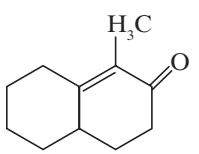


Chapter 16 Aldehydes and Ketones II. Aldol Reactions

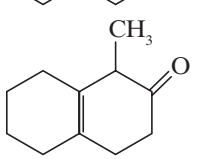
52. The major product of the following reaction is



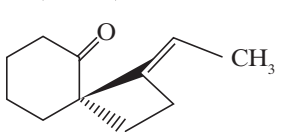
(a)



(b)



(c)



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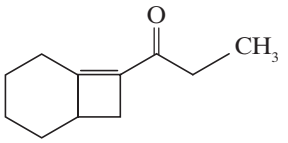
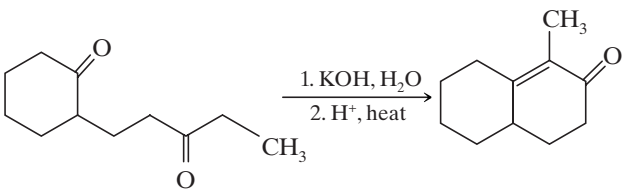
(d)



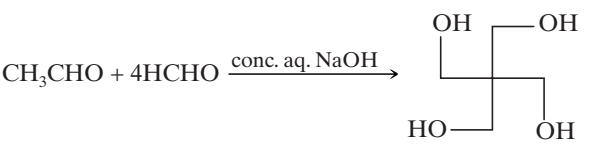
(JEE Advanced 2015)

Solution

(a) The reaction proceeds via intramolecular aldol condensation of the given diketone. The enolate formed on abstraction of proton adds to the second ketone group followed by cyclization to a six-membered ring.



53. The number of aldol reactions that occur in the given transformation are

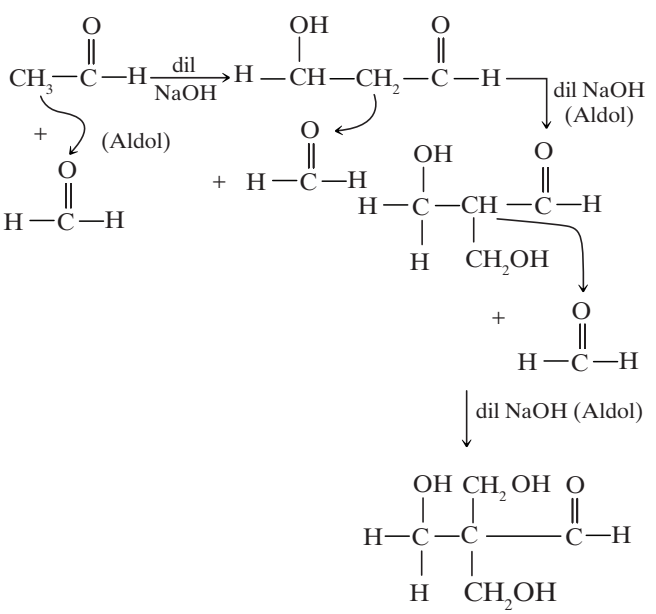


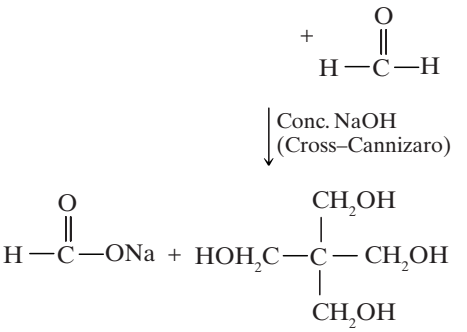
(a) 1 **(b)** 2
(c) 3 **(d)** 4

(IIT-JEE 2012)

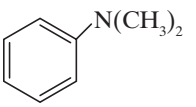
Solution

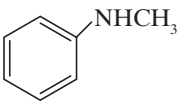
(c) The reactions involved in the transformation are:

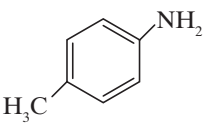


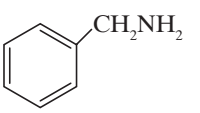


54. Amongst the compounds given, the one that would form a brilliant coloured dye on treatment with $NaNO_2$ in dil. HCl followed by addition to an alkaline solution of β-naphthol is

(a) 

(b) 

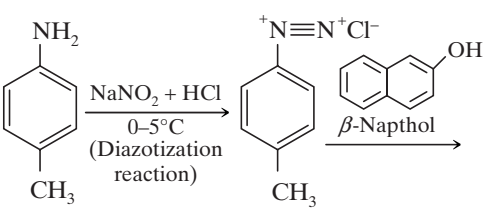
(c) 

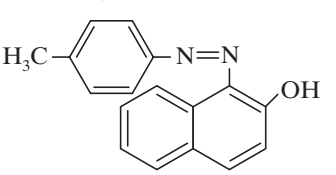
(d) 

(IIT-JEE 2011)

Solution

(c) Azo dye test is given by aromatic primary amines.





Red Azo dye

Chapter 17 Carboxylic Acids and their Derivatives

This section contains SIX questions of matching type. This section contains TWO tables (each having 3 columns and 4 rows) based on each table, there are three questions. Each question has four options (a), (b), (c) and (d). ONLY ONE of these four options is correct.

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Answer Q.55, Q.56 and Q.57 by appropriately matching the information given in the three columns of the following table.

Columns 1, 2 and 3 contain starting materials, reaction conditions, and type of reactions, respectively.

Column 1	Column 2	Column 3
(I) Toluene	(i) $NaOH/Br_2$	(P) Condensation
(II) Acetophenone	(ii) $Br_2/h\nu$	(Q) Carboxylation
(III) Benzaldehyde	(iii) $(CH_3CO)_2O/CH_3COOK$	(R) Substitution
(IV) Phenol	(iv) $NaOH/CO_2$	(S) Haloform

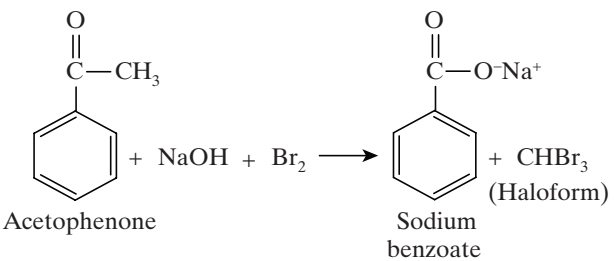
55. For the synthesis of benzoic acid, the only CORRECT combination is

(a) (II) (i) (S)
(b) (IV) (ii) (P)
(c) (I) (iv) (Q)
(d) (III) (iv) (R)

(JEE Advanced 2017)

Solution

(a) The synthesis involving benzoic acid is



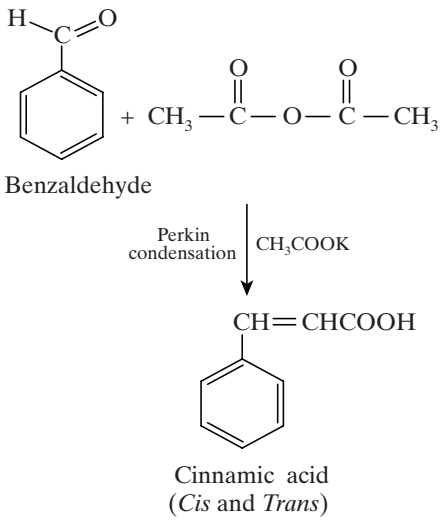
56. The only CORRECT combination that gives two different carboxylic acids is

(a) (II) (iv) (R)
(b) (IV) (iii) (Q)
(c) (III) (iii) (P)
(d) (I) (i) (S)

(JEE Advanced 2017)

Solution

(c)



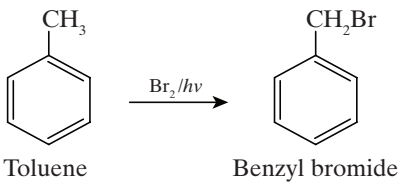
57. The only CORRECT combination in which the reaction proceeds through radical mechanism is

(a) (III) (ii) (P)
(b) (IV) (i) (Q)
(c) (II) (iii) (R)
(d) (I) (ii) (R)

(JEE Advanced 2017)

Solution

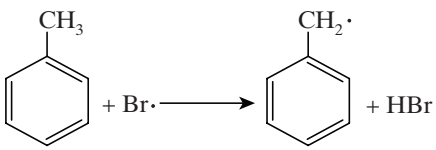
(d) The following reaction takes place by free radical mechanism:



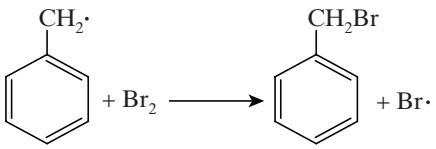
The mechanism is as follows:

Step 1: $Br_2 \xrightarrow{h\nu} 2Br\cdot$

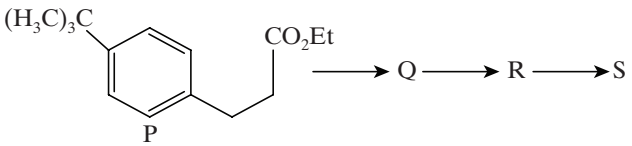
Step 2:



Step 3:



Paragraph for Questions 58 and 59: The reaction of compound **P** with CH_3MgBr (excess) in $(C_2H_5)_2O$ followed by addition of H_2O gives **Q**. The compound **Q** on treatment with H_2SO_4 at 0°C gives **R**. The reaction of **R** with CH_3COCl in the presence of anhydrous $AlCl_3$ in CH_2Cl_2 followed by treatment with H_2O produces compound S. [Et in compound **P** is ethyl group]



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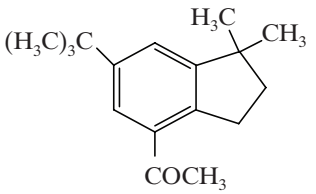
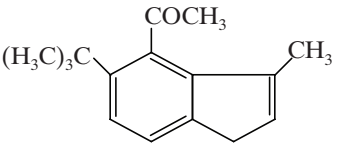
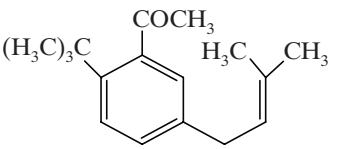
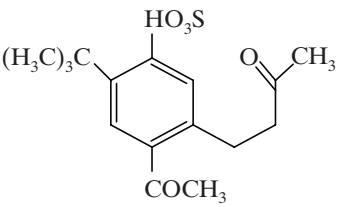
58. The product **S** is

(a) 

(b) 

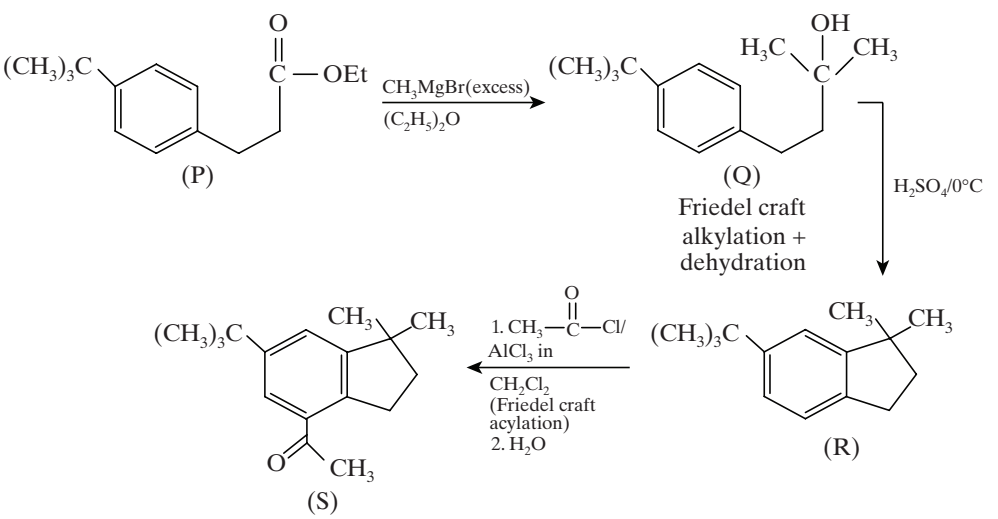
(c) 

(d) 

(JEE Advanced 2017)

Solution

(a) The reactions involved are as follows:



59. The reactions, **Q** to **R** and **R** to **S**, are

(a) dehydration and Friedel-Crafts acylation.
(b) aromatic sulfonation and Friedel-Crafts acylation.
(c) Friedel-Crafts alkylation, dehydration and Friedel-Crafts acylation.
(d) Friedel-Crafts alkylation and Friedel-Crafts acylation.

(JEE Advanced 2017)

Solution

(c) From the reaction scheme, Q to R is Friedel-Crafts alkylation, dehydration and R to S is Friedel-Crafts acylation.

60. The compound that does **NOT** liberate CO_2, on treatment with aqueous sodium bicarbonate solution, is

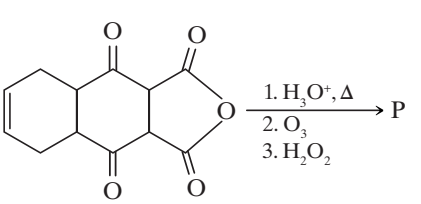
(a) benzoic acid.
(b) benzenesulphonic acid.
(c) salicylic acid.
(d) carbolic acid (Phenol).

(JEE Advanced 2013)

Solution

(d) Comparatively phenol is a weaker acidic than carbonic acid (H_2CO_3), and hence does not liberate CO_2 on treatment with aqueous $NaHCO_3$ solution. The rest are more acidic than H_2CO_3, and so liberate CO_2.

61. The total number of carboxylic acid groups in the product P is ___.



(JEE Advanced 2013)

Solution

(2) The reaction involved is

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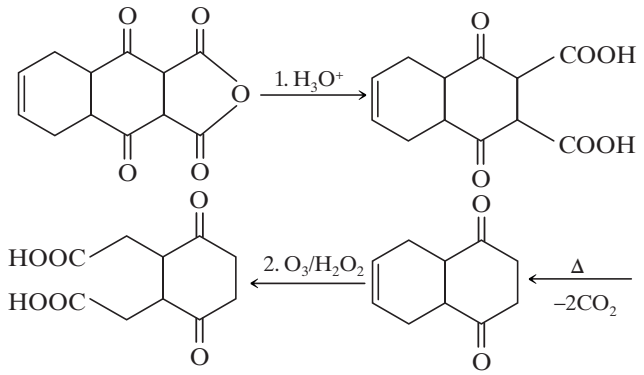
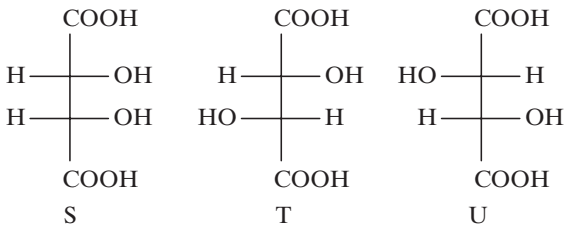


Paragraph for Questions 62 and 63: P and Q are isomers of dicarboxylic acid $C_4H_4O_4$. Both decolorize Br_2/H_2O. On heating, P forms the cyclic anhydride. Upon treatment with dilute alkaline $KMnO_4$, P as well as Q could produce one or more than one from S, T and U.



62. Compounds formed from P and Q are, respectively,

(a) Optically active S and optically active pair (T, U).

(b) Optically inactive S and optically inactive pair (T, U).

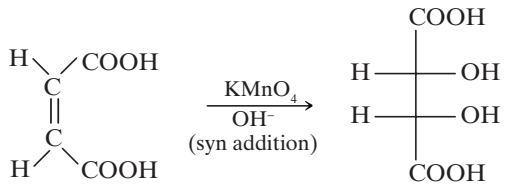
(c) Optically active pair (T, U) and optically active S.

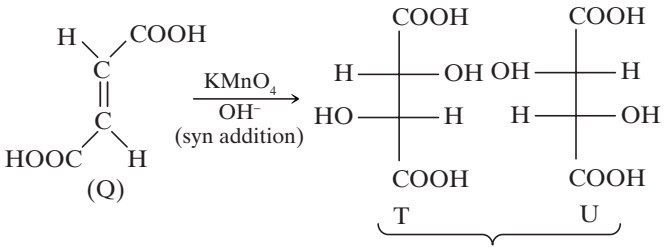
(d) Optically inactive pair (T, U) and optically inactive S.

(JEE Advanced 2013)

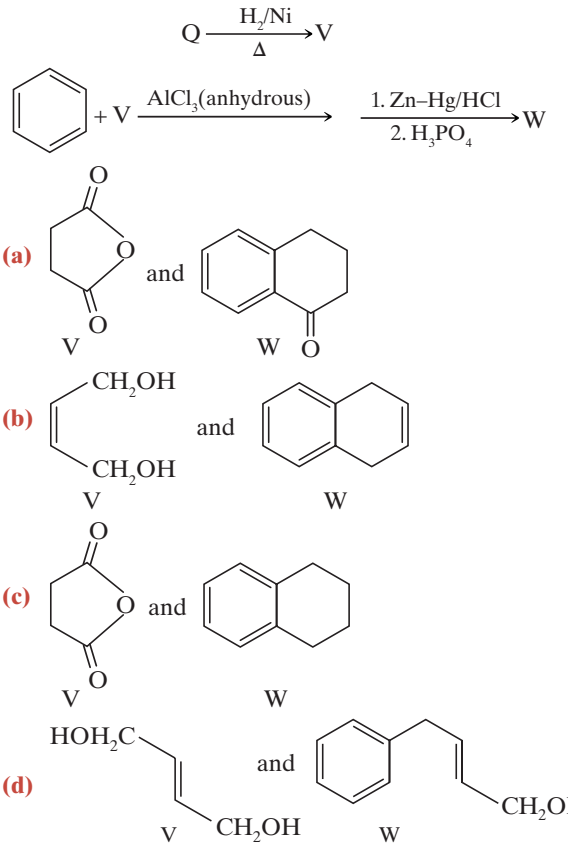
Solution

(b) The reactions involved are



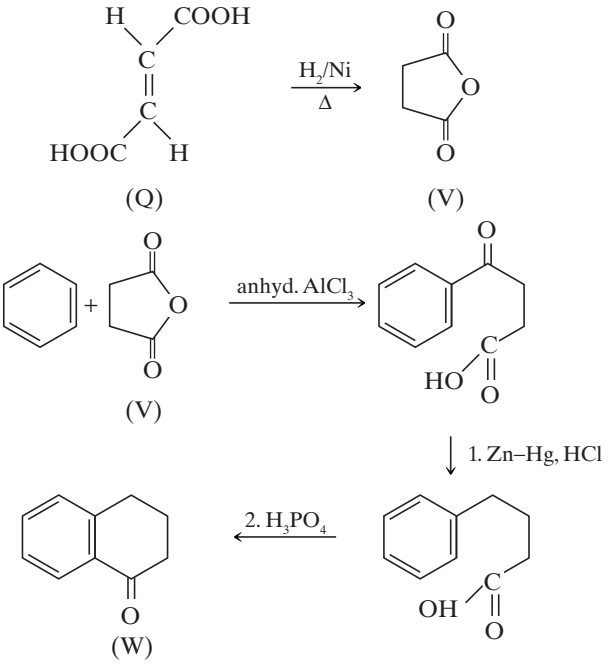


63. In the following reaction sequences V and W are, respectively,



Solution

(a) The reactions involved are



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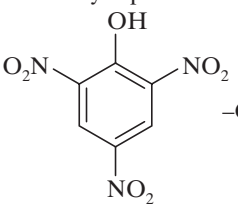
64. The carboxyl functional group (–COOH) is present in
(a) picric acid. **(b)** barbituric acid.
(c) ascorbic acid. **(d)** aspirin.

(IIT-JEE 2012)

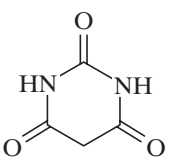
Solution

(d) The structures of the given compounds are as follows. Only aspirin has —COOH group.



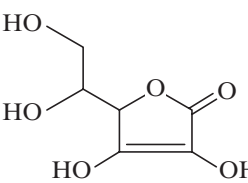
–Contains no –COOH gp

(Picric acid)



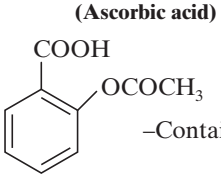
–Contains no –COOH gp

(Barbituric acid)



–Contains no –COOH gp

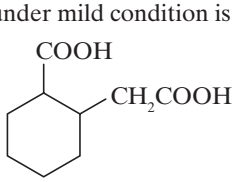
(Ascorbic acid)

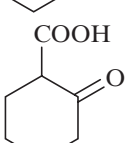


–Contains –COOH gp

(Aspirin)

65. The compound that undergoes decarboxylation most readily under mild condition is

(a)


(b)


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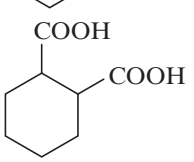
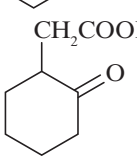
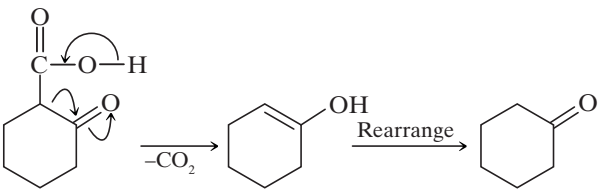


(d)


(IIT-JEE 2012)

Solution

(b) The β-keto acid given in option (b) undergoes decarboxylation most easily because it results in formation of stable product on rearrangement. The reaction taking place is



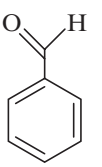
Paragraph for Questions 66 and 67: In the following reaction sequence, the compound **J** is an intermediate.

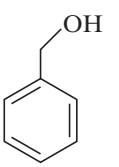
$$\mathbf{I} \xrightarrow[CH_3COONa]{(CH_3CO)_2O} \mathbf{J} \xrightarrow[2.\ SOCl_2\ \ 3.\ \text{anhyd. } AlCl_3]{1.\ H_2, Pd/C}$$

J($C_9H_8O_2$) gives effervescence on treatment with $NaHCO_3$ and a positive Baeyer's test.

(IIT-JEE 2012)

66. The compound **I** is

(a)


(b)


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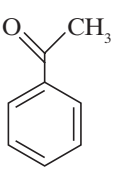
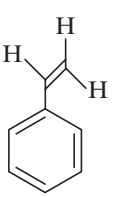


(d)


Solution

(a) In the given reaction, an aromatic aldehyde is condensed with an acid anhydride (Perkin condensation) in the presence of a base to form α,β-unsaturated acid (cinnamic acid). This gives effervescence on reaction with $NaHCO_3$ and positive test with Bayer's reagent (1% alkaline $KMnO_4$).

$$\underset{\textbf{(I)}}{Ph—CHO} \xrightarrow[CH_3COONa]{(CH_3CO)_2O}$$

$$\underset{\textbf{(J)}}{Ph—CH=CH—COOH} \xrightarrow{NaHCO_3} \text{Efferve-scence}$$

(Cinnamic acid)

$$\xrightarrow[\text{(Bayer's reagent)}]{1\%\ \text{Cold, alk; } KMnO_4} \text{Positive}$$

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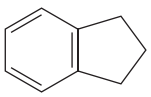
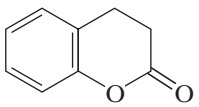
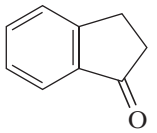
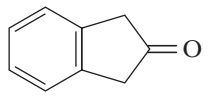
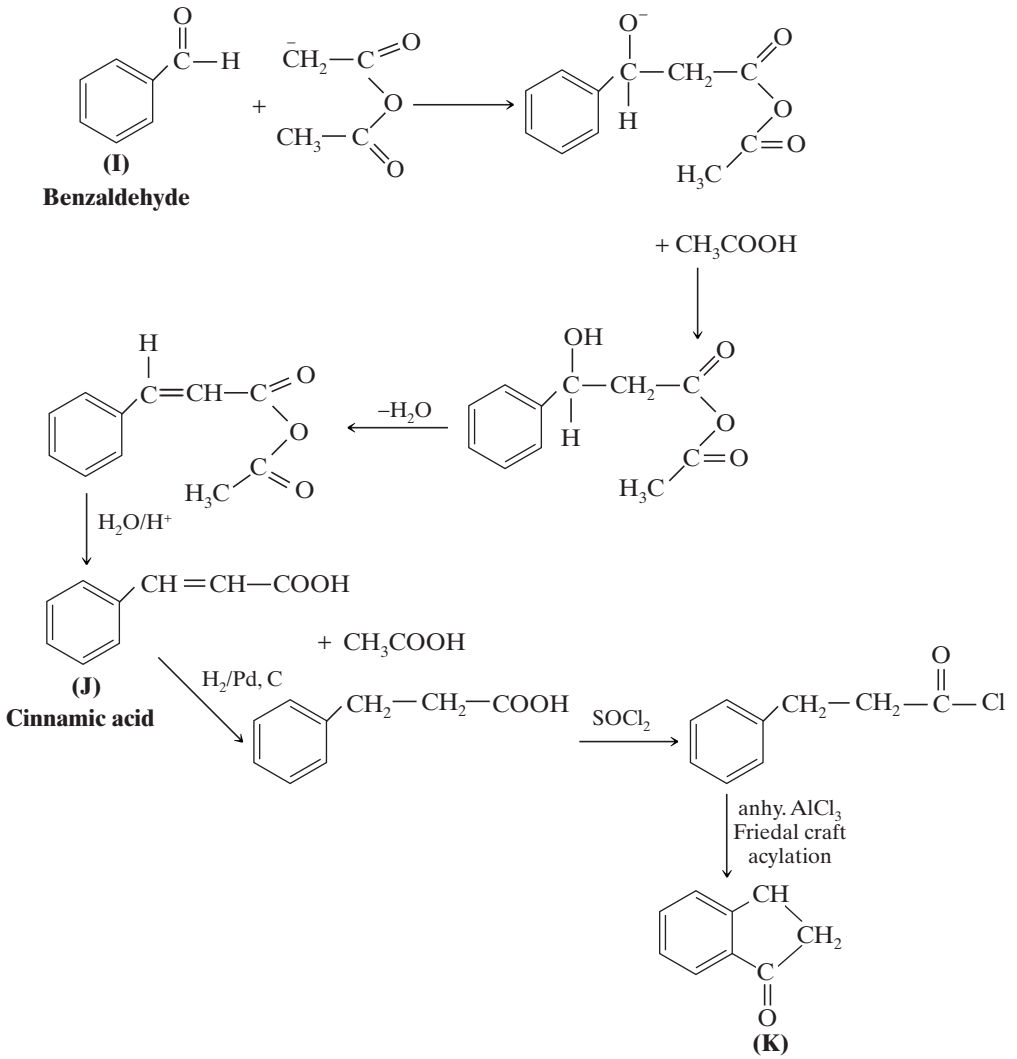
67. The compound **K** is

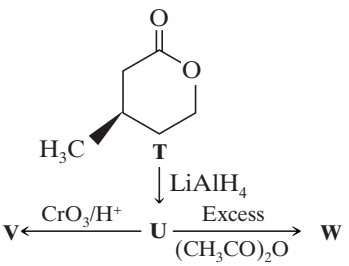
(a)  **(b)**  **(c)**  **(d)** 

Solution

(c) The reaction sequence is



68. With reference to the scheme given, which of the given statement(s) about **T**, **U**, **V** and **W** is (are) correct?



(a) **T** is soluble in hot aqueous NaOH.
(b) **U** is optically active.
(c) Molecular formula of **W** is $C_{10}H_{18}O_4$.
(d) **V** gives effervescence on treatment with aqueous $NaHCO_3$.

(IIT-JEE 2012)

Solution

(a), (c), (d) The reactions involved are:

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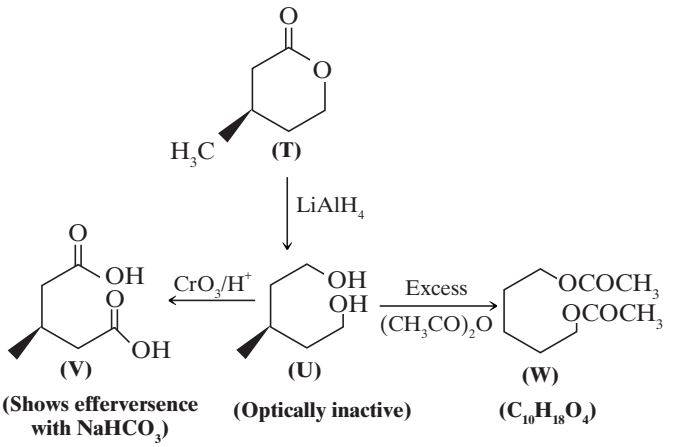


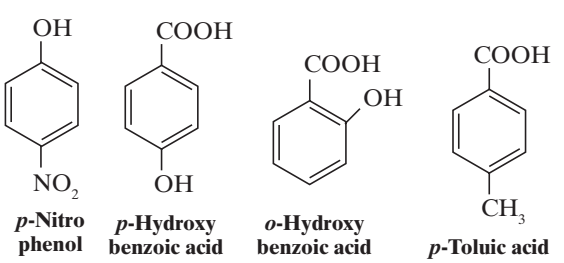
69. Among the following compounds, the most acidic is

(a) *p*-nitrophenol. **(b)** *p*-hydroxybenzoic acid.
(c) *o*-hydroxybenzoic acid. **(d)** *p*-toluic acid.

(IIT-JEE 2011)

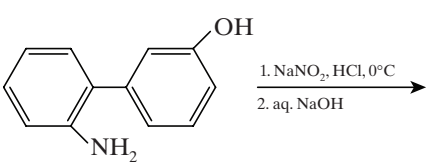
Solution

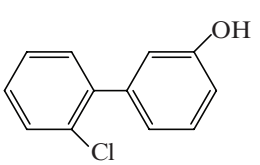
(c) The acidity of the acids can be measured in terms of its pK_a value, greater is the pK_a value, weaker is the acid. The decreasing order of pK_a values is *p*-nitrophenol (pK_a 7.15) > *p*-hydroxybenzoic acid (pK_a 4.58) > *p*-toluic acid (pK_a 4.37) >*o*-hydroxybenzoic acid (pK_a 2.98). The pK_a value for *o*-hydroxybenzoic acid is the least due to *ortho* effect. Here both the groups are *ortho* to each other so due to steric repulsions it is the strongest acid among these.

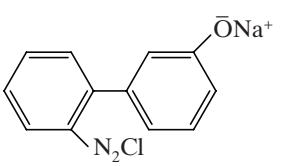


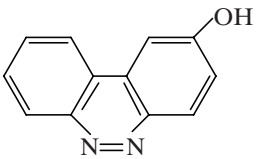
Chapter 18 Amines

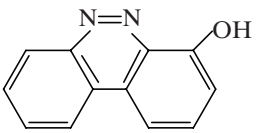
70. The major product of the following reaction is



(a) 

(b) 

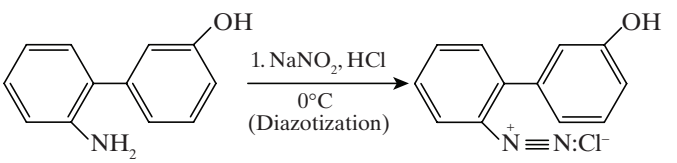
(c) 

(d) 

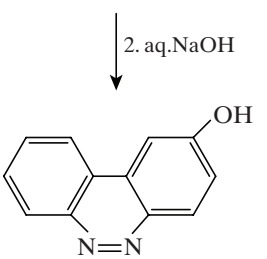
(JEE Advanced 2017)

Solution

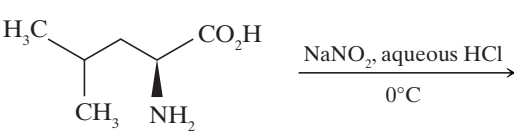
(c) The reaction involved is

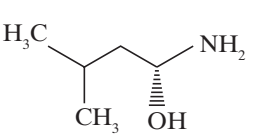


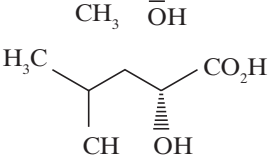
(Aromatic diazonium salt)
Highly unstable

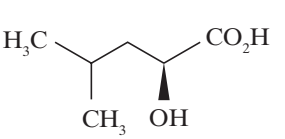


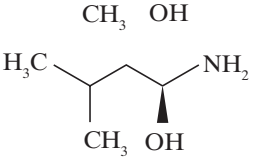
71. The major product of the reaction is



(a) 

(b) 

(c) 

(d) 

(JEE Advanced 2015)

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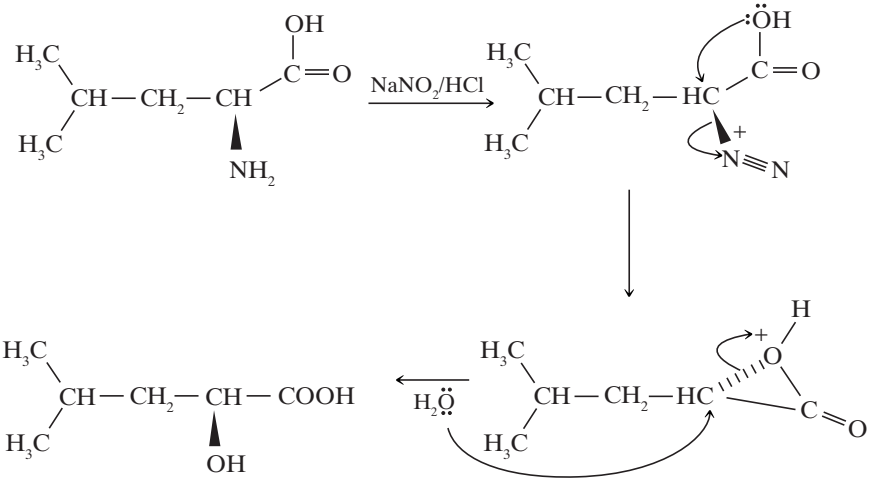
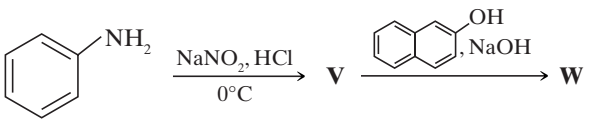
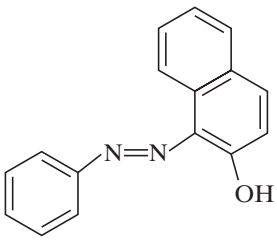
Solution



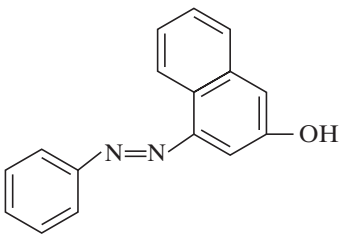
72. In the following reactions, the major product **W** is



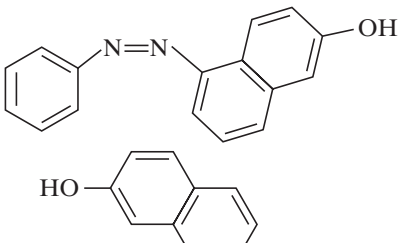
(a)



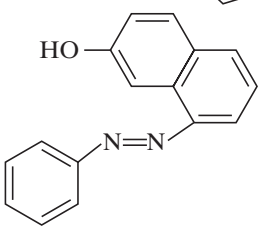
(b)



(c)



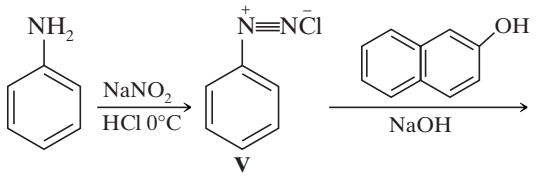
(d)

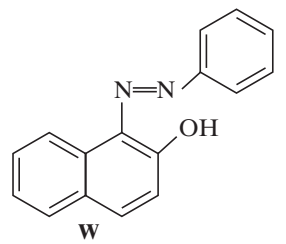


(JEE Advanced 2015)

Solution

(a) The reaction is





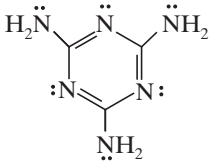
W

73. The total number of lone-pairs of electrons in melamine is ___.

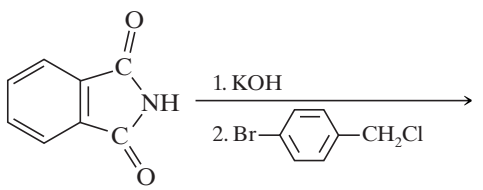
(JEE Advanced 2013)

Solution

(6) The structure of melamine is



74. The major product of the following reaction is



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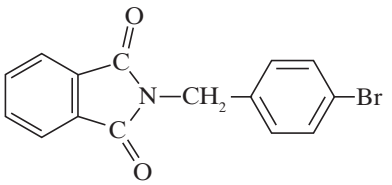
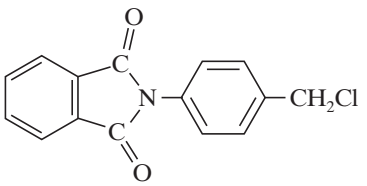
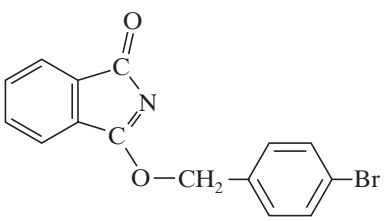
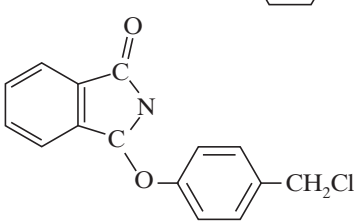
(a) 

(b) 

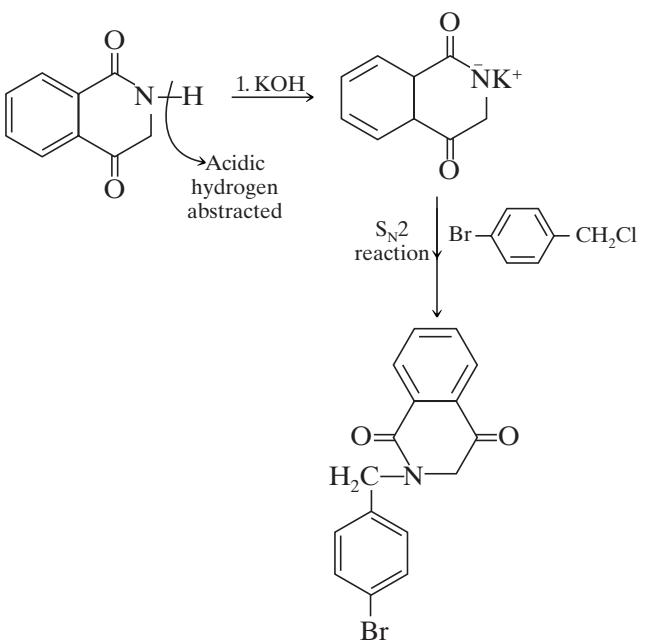
(c) 

(d) 

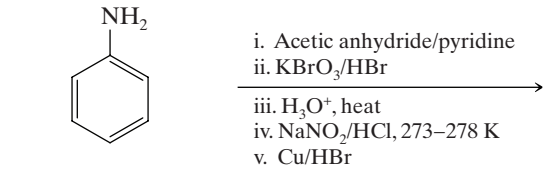
(IIT-JEE 2011)

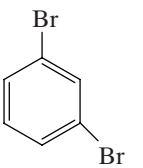
Solution

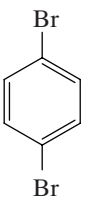
(a) This is an example of Gabriel pthalamide type of reaction. The benzylic carbon is the preferred site for S_N2 reaction in comparison to the phenylic carbon.

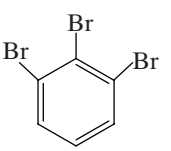


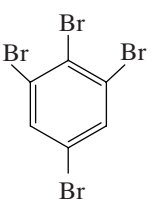
75. The product(s) of the following reaction sequence is(are)



(a) 

(b) 

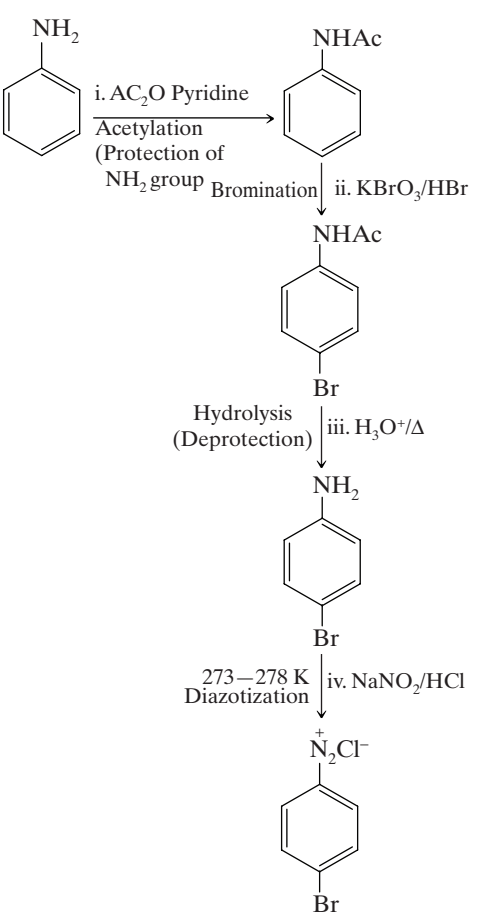
(c) 

(d) 

(JEE Advanced 2016)

Solution

(b) The reaction sequence is as follows:



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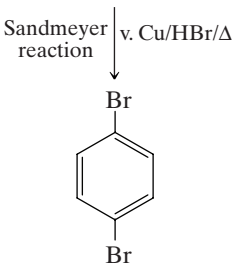


Chapter 19 Phenols and Aryl Halides: Nucleophilic Aromatic Substitution

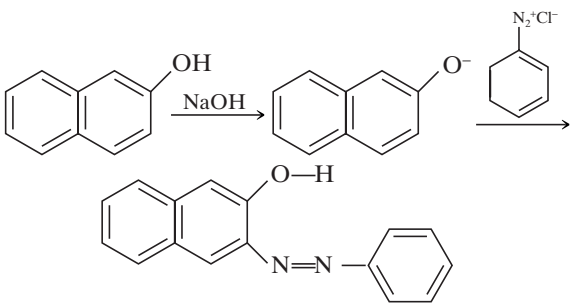
76. For the identification of β-naphthol using dye test, it is necessary to use

(a) dichloromethane solution of β-naphthol.
(b) acidic solution of β-naphthol.
(c) neutral solution of β-naphthol.
(d) alkaline solution of β-naphthol.

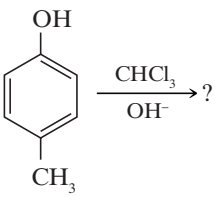
(JEE Advanced 2014)

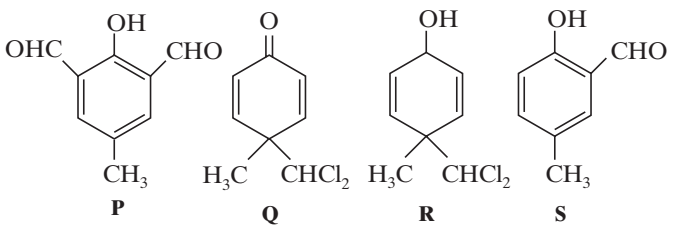
Solution

(d) The reaction involved is



77. In the following reaction, the product(s) formed is (are)



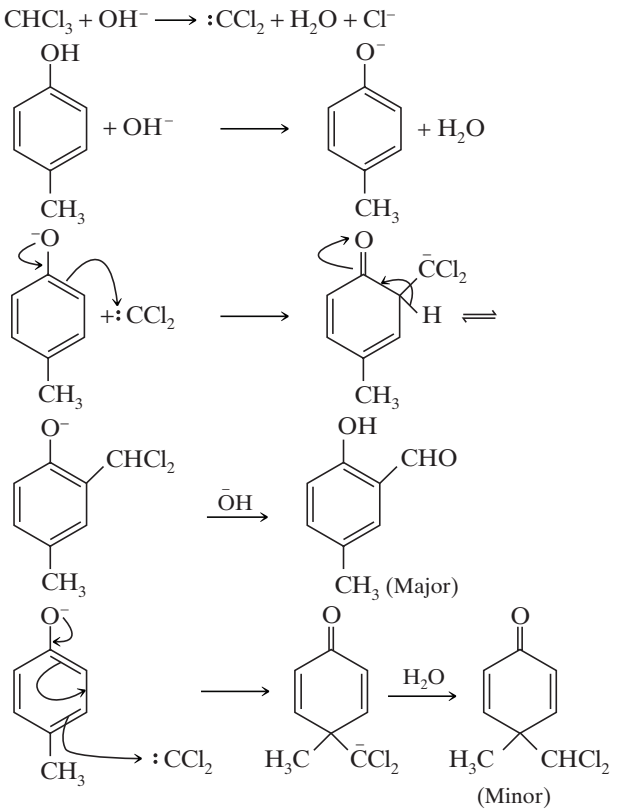


(a) P (major) **(b)** Q (minor)
(c) R (minor) **(d)** S (major)

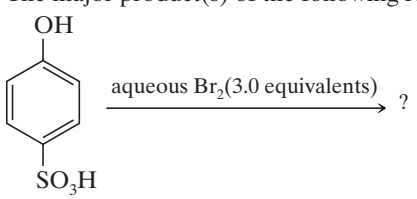
(JEE Advanced 2013)

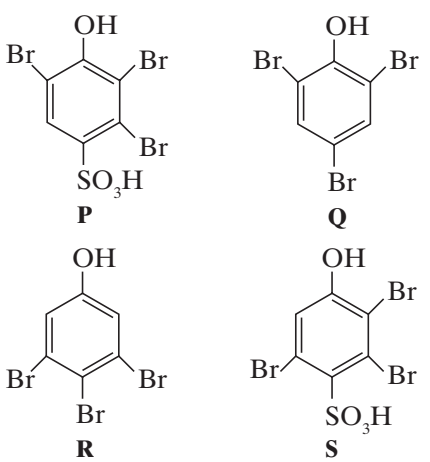
Solution

(b), (d) The mechanism involved is



78. The major product(s) of the following reaction is(are)





(a) P **(b)** Q
(c) R **(d)** S

(JEE Advanced 2013)

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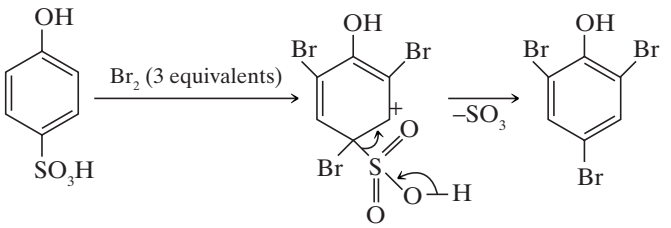
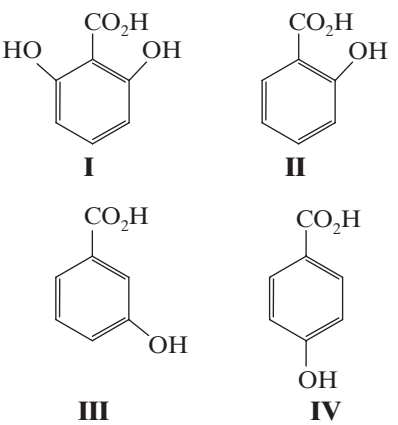
Solution

(b) The reaction involved is



79. The correct order of acidity for the following compounds is:

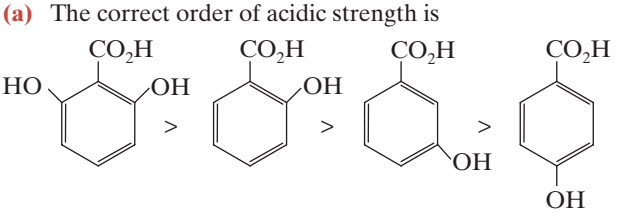


(a) I > II > III > IV **(b)** III > I > II > IV
(c) III > IV > II > I **(d)** I > III > IV > II

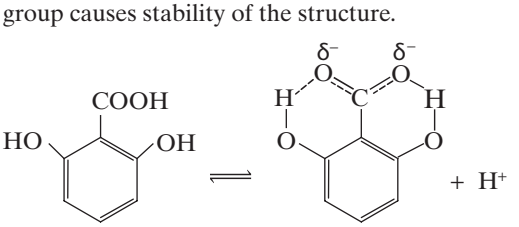
(JEE Advanced 2016)

Solution

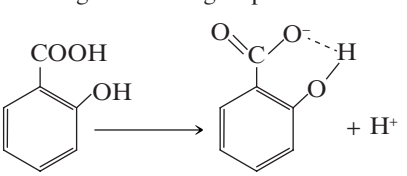
(a) The correct order of acidic strength is



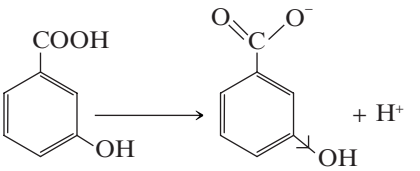
o,*o*-Dihydroxy benzoic acid is the most acidic, as after losing H^+, chelation of two –OH group with –COO group causes stability of the structure.



It is followed by *o*-hydroxy benzoic acid in which on losing H^+, the COO– group is stabilized by hydrogen bonding with –OH group.



The inductive effect (–I) of –OH group increases the acidic strength of *m*-hydroxy benzoic acid.



p-Hydroxy benzoic acid is least acidic as +M effect of –OH group at para position decreases its acidic character.

80. The correct statement(s) about of the following reaction sequence is(are)

$$\text{Cumene}(C_9H_{12}) \xrightarrow[\text{(ii) } H_3O^+]{\text{(i) } O_2} P \xrightarrow{CHCl_3/NaOH} Q(\text{major}) + R(\text{minor})$$

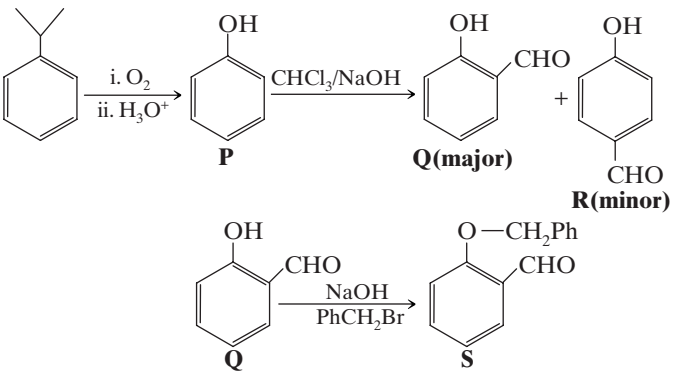
$$Q \xrightarrow[PhCH_2Br]{NaOH} S$$

(a) R is steam volatile.
(b) Q gives dark violet coloration with 1% aqueous $FeCl_3$ solution.
(c) S gives yellow precipitate with 2,4,-dinitrophenylhydrazine.
(d) S gives dark violet coloration with 1% aqueous $FeCl_3$ solution.

(JEE Advanced 2016)

Solution

(b), (c)



Q (2-hydroxybenzaldehyde) is steam volatile and not **R** (4-hydroxybenzaldehyde). This is due to the presence of hydrogen bonding in the ortho-substituted isomer, resulting from close proximity of –OH and CHO groups. This kind of hydrogen bonding is not possible in para-substituted isomer because the two groups are far apart. The boiling point of ortho-isomer is thus lower.

Q and **R** both show positive test (dark violet coloration) with 1% aqueous $FeCl_3$ solution due to the presence of phenol group.
S does not give dark violet coloration with 1% aqueous $FeCl_3$ solution because the phenol group is protected and not free.
Q, **R** and **S** show positive test with 2,4-dinitrophenylhydrazine due to the formation of yellow precipitate of phenyl hydrazones.

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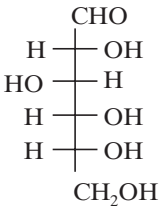
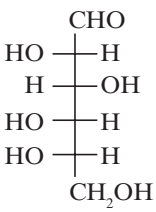
Chapter 20 Carbohydrates

81. The structure of D-(+)-glucose is

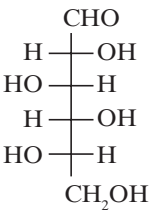


The structure of L-(–)-glucose is

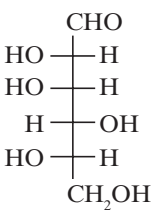
(a)



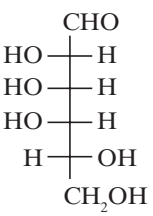
(b)



(c)



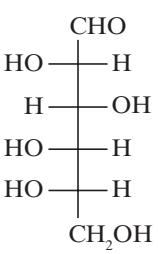
(d)



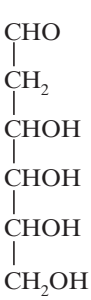
(JEE Advanced 2015)

Solution

(a) In D-(+)-glucose the OH group attached to the last stereocentre is on the right hand side while in L-(–)-glucose it is on left hand side. The structure of L-(–)-glucose is



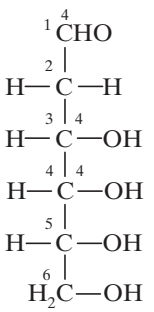
82. When the following aldohexose exists in its D-configuration, the total number of stereoisomers in its pyranose form is ___.

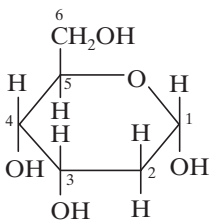


(IIT-JEE 2012)

Solution

(8) The structure of aldohexose in D-configuration can be represented as

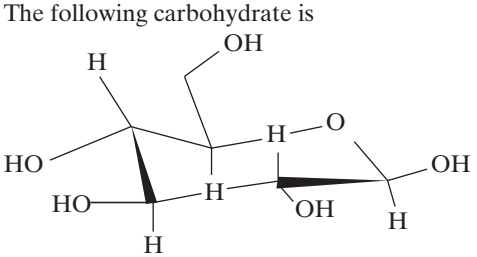




3 Chiral carbons

Since there are three chiral centres, so the total number of stereoisomers are $2^n = 2^3 = 8$ where n is the number of chiral centres.

83. The following carbohydrate is



(a) a ketohexose. **(b)** an aldohexose.
(c) an α–furanose. **(d)** an α–pyransose.

(IIT-JEE 2011)

Solution

(b) The given structure represents an aldohexose. These are the monosaccarides with six carbon atoms, containing aldehyde (—CHO) group.

84. For 'invert sugar', the correct statement(s) is (are) (Given: specific rotations of (+) sucrose, (+) maltose, L(–)–glucose and L–(+)–fructose in aqueous solution are +66°, +140°, –52° and +92°, respectively)

(a) 'invert sugar' is prepared by acid catalyzed hydrolysis of maltose.
(b) 'invert sugar' is an equimolar mixture of D-(+) glucose and D-(–)-fructose.
(c) specific rotation of 'invert sugar' is –20°.
(d) on reaction with Br_2 water, 'invert sugar' forms saccharic acid as one of the products.

(JEE Advanced 2016)

Solution

(b), (c) Invert sugar is prepared by acid hydrolysis of sucrose and is an equimolar mixture of D(+) glucose ($\alpha = +52°$) and D(–) fructose ($\alpha = -92°$). The specific rotation is given by

$$[\alpha] = \frac{\alpha}{c \cdot l}$$

where α is the observed rotation, c is the concentration of the solution in g mL^{-1} and l is the length of the cell in decimetre. So, the specific rotation of the mixture is

$$[\alpha]_{mix} = 0.5 \times (52) + 0.5 \times (-92) = -20°$$

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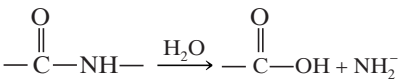
Chapter 21 Amino Acids and Proteins

85. A decapeptide (mol. wt. 796) on complete hydrolysis gives glycine (mol. wt. 75), alanine and phenylalanine. Glycine contributes 47.0% to the total weight of the hydrolysed products. The number of glycine units present in the decapeptide is ———

(IIT-JEE 2012)

Solution

(6) The hydrolysis reaction of peptide linkage is



Let n glycine units be present in the compound, then the total weight of the product will be

$796 + 9 \times 18 = 958$ (since there are 9 water molecules)

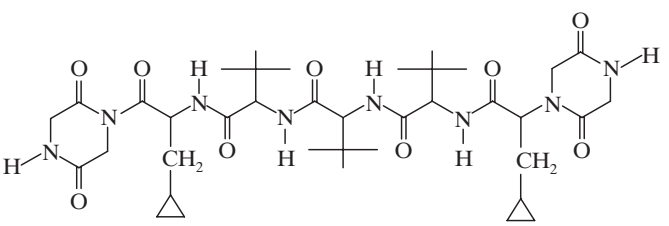
Percent weight of glycine in the given weight of product

$$\frac{75n}{958} \times 100 = 47\,\%$$

Therefore,

$$n = 47 \times \frac{958}{75} \times 100 = 6$$

86. The total number of **distinct naturally occurring amino acids** obtained by complete acidic hydrolysis of the peptide shown below is _____.

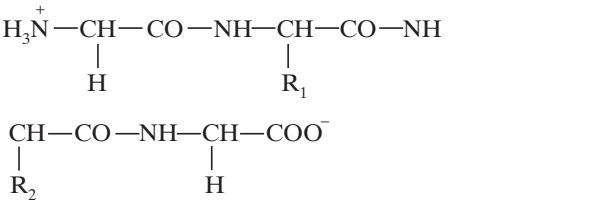


(JEE Advanced 2014)

Solution

(1) Only glycine is formed as natural amino acid, that is, $HOOC{-}CH_2{-}NH_2$.

87. The substituents R_1 and R_2 for nine peptides are listed in the table given below. How many of these peptides are positively charged at pH = 7.0?



Peptide	R_1	R_2
I	H	H
II	H	CH_3
III	CH_2COOH	H
IV	CH_2CONH_2	$(CH_2)_4NH_2$
V	CH_2CONH_2	CH_2CONH_2
VI	$(CH_2)_4NH_2$	$(CH_2)_4NH_2$
VII	CH_2COOH	CH_2CONH_2
VIII	CH_2OH	$(CH_2)_4NH_2$
IX	$(CH_2)_4NH_2$	CH_3

(IIT-JEE 2012)

Solution

(4) For basic amino acids with pH > 7, peptides will exist as cations. For example, when the substituents are basic, that is, $R_1 = CH_2CONH_2$ and $R_2 = (CH_2)_4NH_2$ or when $R_1 = (CH_2)_4NH_2$ and $R_2 = (CH_2)_4NH_2$ or when $R_1 = CH_2OH$ and $R_2 = (CH_2)_4NH_2$ or when $R_1 = (CH_2)_4NH_2$ and $R_2 = CH_3$.

88. A tetrapeptide has —COOH group on alanine. This produces glycine (Gly), valine (Val), phenyl alanine (Phe) and alanine (Ala), on complete hydrolysis. For this tetrapeptide, the number of possible sequences (primary structures) with $-NH_2$ group attached to a chiral center is ___.

(JEE Advanced 2013)

Solution

(4) The possible combinations with C-terminal as alanine and N-terminal with chiral carbon (i.e., excluding glycine) are:

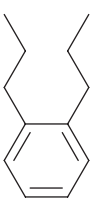
Val–Phe–Gly–Ala

Val–Gly–Phe–Ala

Phe–Val–Gly–Ala

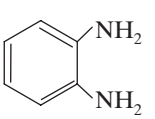
Phe–Gly–Val–Ala

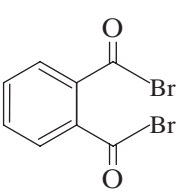
Paragraph for Questions 89 and 90: Treatment of compound O with $KMnO_4/H^+$ gave P, which on heating with ammonia gave Q. The compound Q on treatment with Br_2/NaOH produced R. On strong heating, Q gave S, which on further treatment with ethyl 2-bromopropanoate in the presence of KOH following by acidification, gave a compound T.

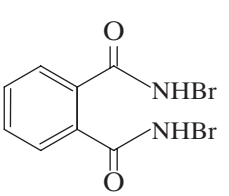


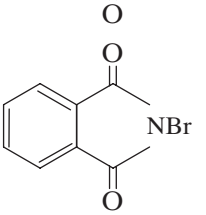
(JEE Advanced 2016)

89. The compound R is

(a) 

(b) 

(c) 

(d) 

Solution

(a)

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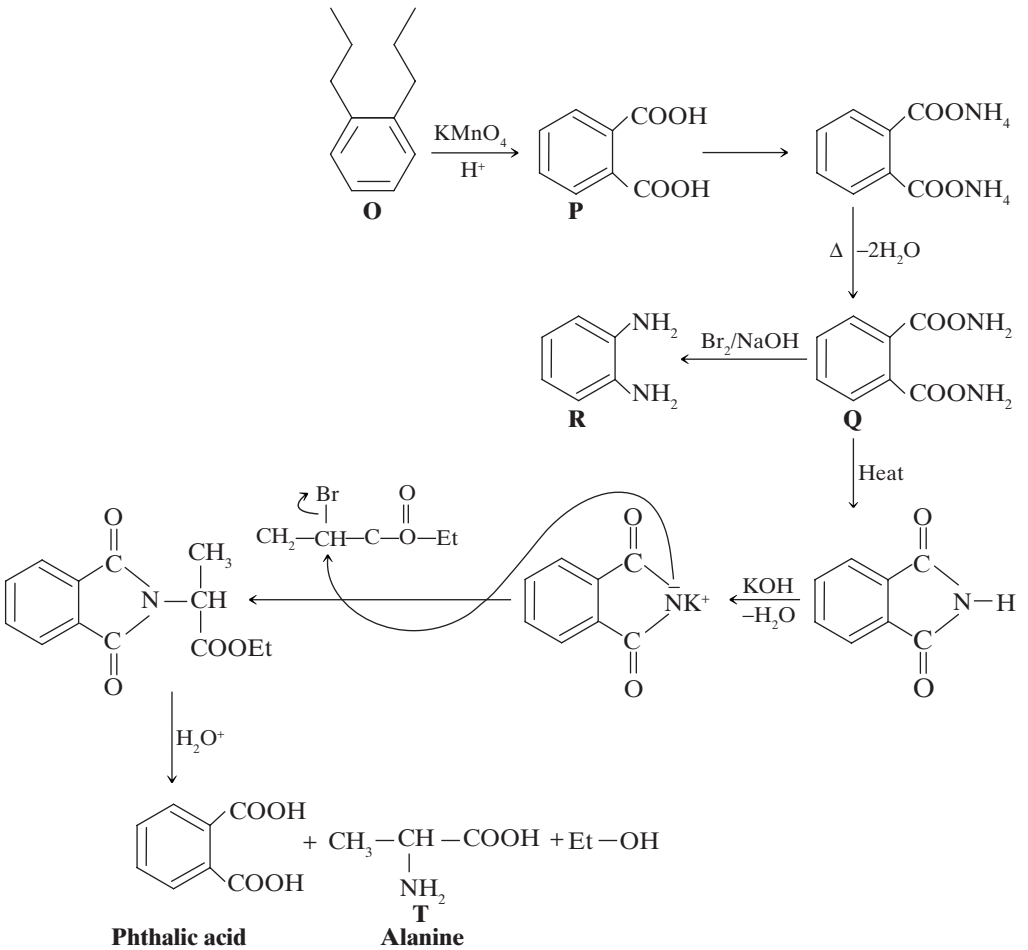
90. The compound T is
- **(a)** glycine.
- **(b)** alanine.
- **(c)** valine.
- **(d)** serine.

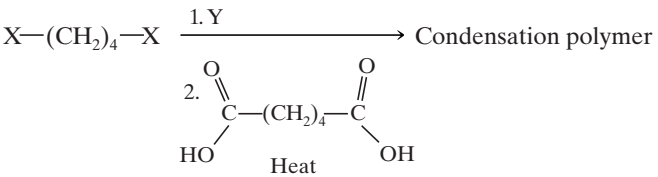
Solution

(b) **Explanation for 89 and 90**



Chapter 24 Polymers

91. The correct functional group **X** and the reagent/reaction condition **Y** in the following scheme are



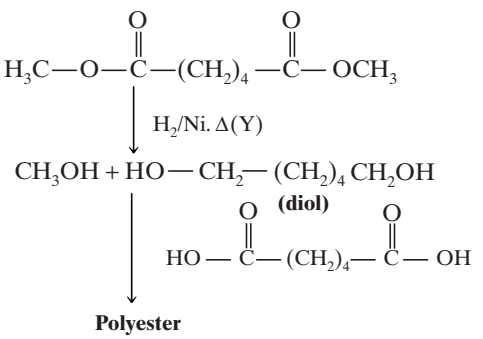
- **(a)** X = $COOCH_3$, Y = H_2/Ni/heat.
- **(b)** X = $CONH_2$, Y = H_2/Ni/heat.
- **(c)** X = $CONH_2$, Y = Br_2/NaOH.
- **(d)** X = CN, Y = H_2/Ni/heat.

(IIT-JEE 2011)

Solution

(a), (b), (c), (d) Both diols and diamines form condensation polymers with carboxylic acids. Diamines form polyamides with dicarboxylic acids, whereas, diols form polyesters with dicarboxylic acid.

(a)



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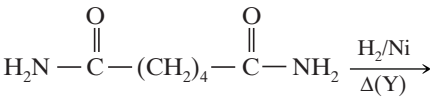
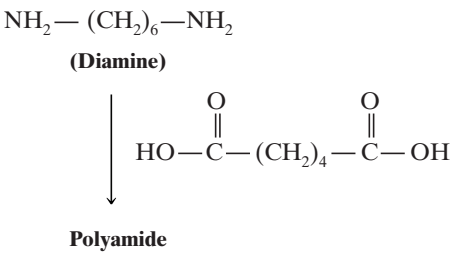
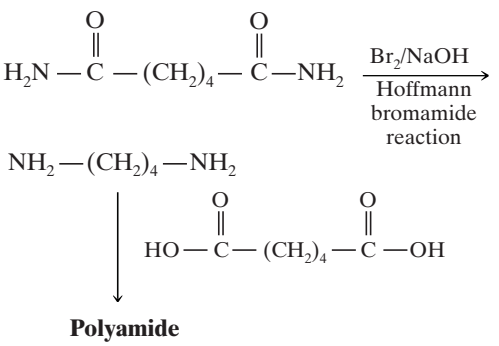


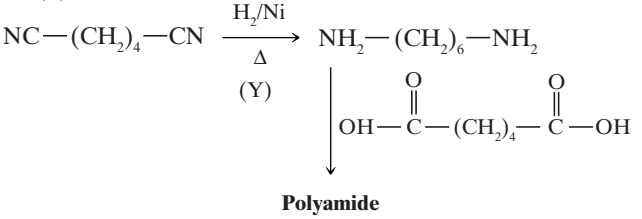
(b)



(c)



(d)



92. On complete hydrogenation, natural rubber produces

(a) ethylene-propylene copolymer.

(b) vulcanized rubber.

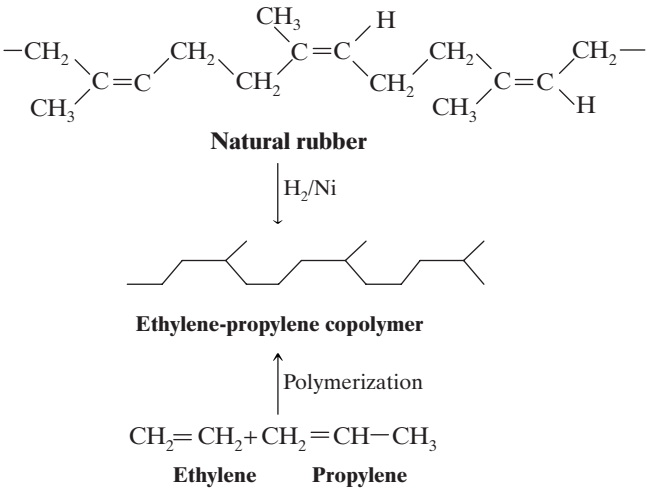
(c) polypropylene.

(d) polybutylene.

(JEE Advanced 2016)

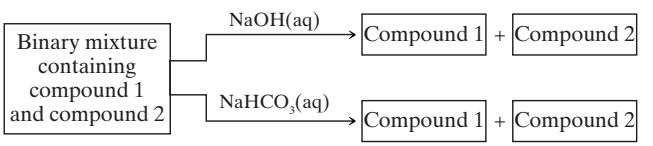
Solution

(a) Hydrogenation of natural rubber leads to formation of ethylene-propylene copolymer.



Miscellaneous

93. Identify the binary mixture(s) that can be separated into individual compounds, by differential extraction, as shown in the given scheme.



(a) C_6H_5OH and C_6H_5COOH

(b) C_6H_5COOH and $C_6H_5CH_2OH$

(c) $C_6H_5CH_2OH$ and C_6H_5OH

(d) $C_6H_5CH_2OH$ and $C_6H_5CH_2COOH$

(IIT-JEE 2012)

Solution

(b), (d) Both phenol and benzoic acid are soluble in NaOH, so they cannot be separated

$$C_6H_5OH + NaOH \rightarrow C_6H_5ONa + H_2O$$

$$C_6H_5COOH + NaOH \rightarrow C_6H_5COONa + H_2O$$

Benzyl alcohol $C_6H_5CH_2OH$ is not soluble in NaOH and $NaHCO_3$, while benzoic acid is soluble in both, so these can be separated. Both C_6H_5OH and $C_6H_5CH_2OH$ are insoluble in $NaHCO_3$, so they cannot be separated. $C_6H_5CH_2COOH$ is soluble in NaOH and $NaHCO_3$, whereas benzyl alcohol is not soluble in NaOH and $NaHCO_3$. So they can be separated.

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JEE (ADVANCED) 2018
PAPER I (CHEMISTRY)

SECTION 1

- This section contains **SIX (06)** questions.
- Each question has **FOUR** options for correct answer(s). **ONE OR MORE THAN ONE** of these four option(s) is (are) correct option(s).

1. The compound(s) which generate(s) N_2 gas upon thermal decomposition below 300°C is (are)
(A) NH_4NO_3 (B) $(NH_4)_2Cr_2O_7$ (C) $Ba(N_3)_2$ (D) Mg_3N_2

Solution

(B) (C) Ammonium salts decompose quite readily on heating. If the anion is more oxidizing (e.g. NO_3^- , $Cr_2O_7^{2-}$) then NH_4^+ gets oxidized to N_2 or N_2O.

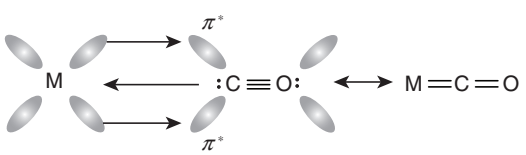
$$NH_4NO_3 \xrightarrow{\text{Heat}} N_2O + 2H_2O$$
$$(NH_4)_2Cr_2O_7 \xrightarrow{\text{Heat}} N_2 + 4H_2O + Cr_2O_3$$
$$Ba(N_3)_2 \xrightarrow{\text{Heat}} Ba + 3N_2$$

Mg_3N_2 is an ionic compound, therefore, will not decompose at 300°C.

2. The correct statement(s) regarding the binary transition metal carbonyl compounds is (are) (Atomic numbers: Fe = 26, Ni = 28)
(A) Total number of valence shell electrons at metal centre in $Fe(CO)_5$ or $Ni(CO)_4$ is 16.
(B) These are predominantly low spin in nature.
(C) Metal–carbon bond strengthens when the oxidation state of the metal is lowered.
(D) The carbonyl C—O bond weakens when the oxidation state of the metal is increased.

Solution

(B) (C) Option (A): Incorrect. Total number of valence shell electrons in $Fe(CO)_5$ [$8 + 5 \times 2 = 18$] and $Ni(CO)_4$ [$10 + 4 \times 2 = 18$] is 18.
Option (B): Correct. CO being a strong field ligand cause pairing of electrons. Hence, both the complexes formed are low spin in nature.
Option (C): Correct. CO ligand not only donates the lone pair of electrons to the central atom but also accept the electron cloud from the central atom in their low-lying vacant orbitals. This kind of back donation is known as 'synergic effect' or 'synergic bonding. In case of CO, the back donation to the π^* orbital of central atom may be depicted as:



Greater the electron density on the metal atom, that is, lower the oxidation state of the metal, greater will be the back donation hence stronger will be the M—C bond.
Option (D): Incorrect. When the oxidation state of metal increases its tendency to accept the electrons from C of CO increases but tendency to donate the electrons from M to C decreases consequently M—C bond strength decreases and C—O bond strength increases.

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3. Based on the compounds of group 15 elements, the correct statement(s) is (are)

(A) Bi_2O_5 is more basic than N_2O_5.

(B) NF_3 is more covalent than BiF_3.

(C) PH_3 boils at lower temperature than NH_3.

(D) The N—N single bond is stronger than the P—P single bond.

Solution

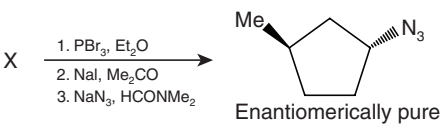
(A) (B) (C) Option (A): Correct. The basicity of oxides usually increases on descending a group. Therefore, Bi_2O_5 is more basic than N_2O_5.

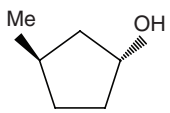
Option (B): Correct. Covalent nature of a molecule depends on the electronegativity difference between bonded atoms.

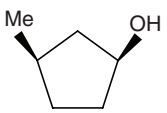
Option (C): Correct. Boiling point of NH_3 is more than that of PH_3 due to hydrogen bonding.

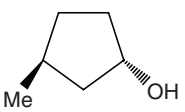
Option (D): Incorrect. P—P single bond is stronger than N—N single bond. This is due to the fact that N is small in size, due to smaller size of atoms lone pair of repulsion will be more.

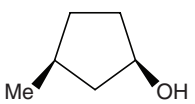
4. In the following reaction sequence, the correct structure(s) of **X** is (are)



(A) 

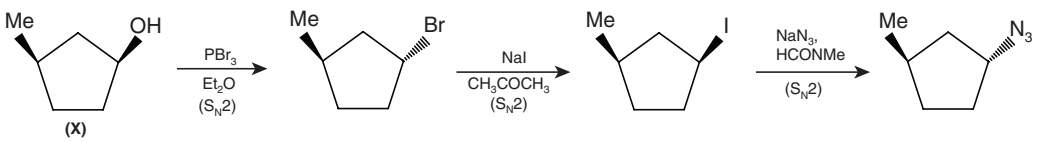
(B) 

(C) 

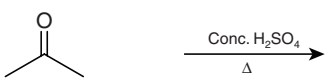
(D) 

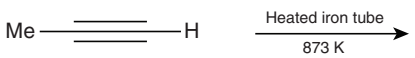
Solution

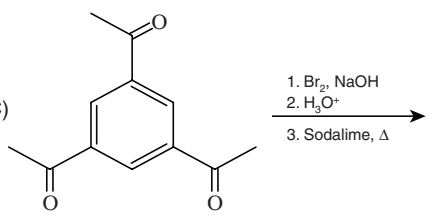
(B)

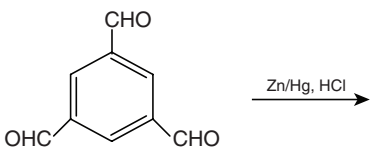


5. The reaction(s) leading to the formation of 1, 3, 5-trimethylbenzene is (are)

(A) 

(B) 

(C) 

(D) 

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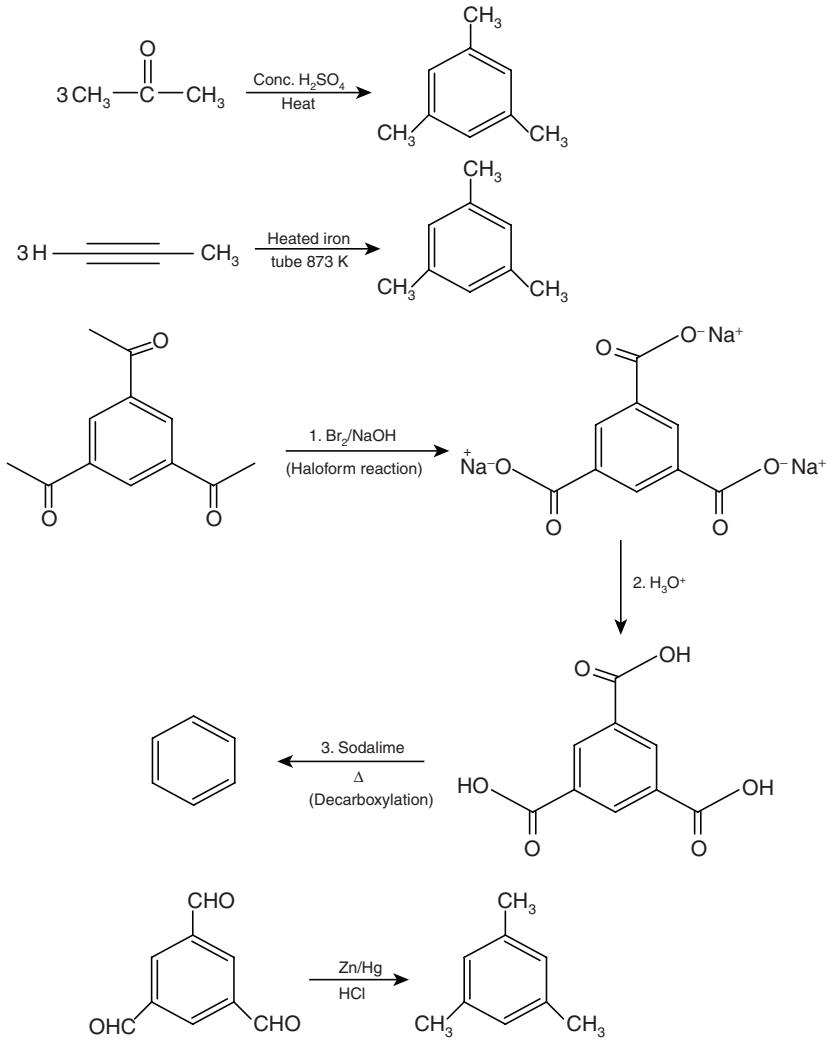
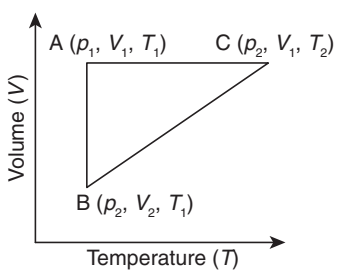
Solution

(A) (B) (D)



6. A reversible cyclic process for an ideal gas is shown below. Here p, V, and T are pressure, volume and temperature, respectively. The thermodynamic parameters q, w, H and U are heat, work, enthalpy and internal energy, respectively.



The correct option(s) is (are)

(A) $q_{AC} = \Delta U_{BC}$ and $w_{AB} = p_2(V_2 - V_1)$

(B) $w_{BC} = p_2(V_2 - V_1)$ and $q_{BC} = \Delta H_{AC}$

(C) $\Delta H_{CA} < \Delta U_{CA}$ and $q_{AC} = \Delta U_{BC}$

(D) $q_{BC} = \Delta H_{AC}$ and $\Delta H_{CA} > \Delta U_{CA}$

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Solution

(B) (C) We know $\Delta U = q + w$ and $w = -p\Delta V$

In the above figure, A-C is isochoric, A-B is isothermal and B-C is isobaric process. Therefore, for an isochoric process AC, we have

$$q_{AC} = \Delta U_{AC} = nC_{V,m}(T_2 - T_1) = \Delta U_{BC}$$

For an isobaric process BC, we have

$$q_{BC} = \Delta H_{BC} = nC_{p,m}(T_2 - T_1) = \Delta H_{AC}$$
$$w_{BC} = -p_2(V_1 - V_2) = p_2(V_2 - V_1)$$
$$\Delta H_{CA} = nC_{p,m}(T_1 - T_2) \text{ and } \Delta U_{CA} = nC_{V,m}(T_1 - T_2)$$

Since, $T_2 > T_1$, therefore, ΔH_{CA} and ΔU_{CA} are negative.

$$\Delta H_{CA} = \Delta U_{CA} + V\,\Delta p$$

As $\Delta p < 0$, therefore, $\Delta H_{CA} < \Delta U_{CA}$.

SECTION 2

- This section contains **EIGHT (08)** questions. The answer to each question is a **NUMERICAL VALUE**.

---

7. Among the species given below, the total number of diamagnetic species is _____.
H atom, NO_2 monomer, O_2^- (superoxide), dimeric sulphur in vapor phase, Mn_3O_4, $(NH_4)_2[FeCl_4]$, $(NH_4)_2[NiCl_4]$, K_2MnO_4, K_2CrO_4

Solution

(1) The paramagnetic species are H atom, NO_2 monomer, O_2^- (superoxide), dimeric sulphur in vapor phase, Mn_3O_4, $(NH_4)_2[FeCl_4]$, $(NH_4)_2[NiCl_4]$ and K_2MnO_4.
The diamagnetic species is K_2CrO_4.

8. The ammonia prepared by treating ammonium sulphate with calcium hydroxide is completely used by $NiCl_2 \cdot 6H_2O$ to form a stable coordination compound. Assume that both the reactions are 100% complete. If 1584 g of ammonium sulphate and 952 g of $NiCl_2 \cdot 6H_2O$ are used in the preparation, the combined weight (in grams) of gypsum and the nickel–ammonia coordination compound thus produced is _____.
(Atomic weights in g mol^{-1}: H = 1, N = 14, O = 16, S = 32, Cl = 35.5, Ca = 40, Ni = 59)

Solution

The reactions involved are as follows:

$$(NH_4)_2SO_4 + Ca(OH)_2 \rightarrow CaSO_4 \cdot 2H_2O + 2NH_3$$

$$NiCl_2 \cdot 6H_2O + 6NH_3 \rightarrow [Ni(NH_3)_6]Cl_2 + 6H_2O$$

From the above reactions we can see that
132 g of $(NH_4)_2SO_4$ will produce 172 g of gypsum

1584 g of $(NH_4)_2SO_4$ will produce $\frac{172}{132} \times 1584 = 2064$ g of gypsum

Therefore, number of moles of gypsum produced $\frac{2064}{172} = 12$ mol

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238 g of $NiCl_4 \cdot 6H_2O$ will produce 314 g of Ni-complex

952 g of $NiCl_4 \cdot 6H_2O$ will produce $\frac{314}{238} \times 952 = 1256\,g$ of Ni-complex

Therefore, number of moles of Ni-complex produced $\frac{1256}{314} = 4\,mol$

So, total mass of products is $12 \times 172\ (gypsum) + 4 \times 232\ ([Ni(NH_3)_6]Cl_2) = 2992\ g$

9. Consider an ionic solid **MX** with NaCl structure. Construct a new structure (**Z**) whose unit cell is constructed from the unit cell of **MX** following the sequential instructions given below. Neglect the charge balance.

(i) Remove all the anions (**X**) except the central one
(ii) Replace all the face centered cations (**M**) by anions (**X**)
(iii) Remove all the corner cations (**M**)
(iv) Replace the central anion (**X**) with cation (**M**)

The value of $\left(\frac{\text{number of anions}}{\text{number of cations}}\right)$ in ***Z*** is _____.

Solution

(3) Given that MX is an ionic solid having NaCl type structure having ccp. So, the anion X^- occupies all octahedral voids. The changes (i)-(iv) cause the following effects:

(i) No. of anions left = 1
(ii) No. of anions added by replacing face centered cations M = 3; No. of cations left = 1
(iii) No. of cations left = 0
(iv) No. of cations added = 1; No. of anions left = 3

Finally, the unit cell contains 1 cation and 3 anions. So,

The value of $\left(\frac{\text{number of anions}}{\text{number of cations}}\right)$ in ***Z*** is 3.

10. For the electrochemical cell,

$$Mg(s) \mid Mg^{2+}(aq, 1\ M) \parallel Cu^{2+}(aq, 1\ M) \mid Cu(s)$$

the standard emf of the cell is 2.70 V at 300 K. When the concentration of Mg^{2+} is changed to x M, the cell potential changes to 2.67 V at 300 K. The value of x is _____.

(Given, $\frac{F}{R} = 11500\ K\ V^{-1}$, where F is the Faraday constant and R is the gas constant, ln (10) = 2.30)

Solution

(10) The cell reaction is

$$Mg(s) + Cu^{2+}(aq, 1\ M) \rightarrow Mg^{2+}(aq, x\ M) + Cu(s)$$

$$E_{cell} = E^{o}_{cell} - 2.303 \times \frac{RT}{2F} \log \frac{[Mg^{2+}]}{[Cu^{2+}]}$$

$$2.67 = 2.70 - 2.303 \times \frac{300}{2 \times 11500} \log(x)$$

$$0.03 = \frac{2.303 \times 3}{115 \times 2} \log x \Rightarrow \log x = 1 \Rightarrow x = 10$$

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11. A closed tank has two compartments **A** and **B**, both filled with oxygen (assumed to be ideal gas). The partition separating the two compartments is fixed and is a perfect heat insulator (Figure 1). If the old partition is replaced by a new partition which can slide and conduct heat but does **NOT** allow the gas to leak across (Figure 2), the volume (in m^3) of the compartment **A** after the system attains equilibrium is _____.

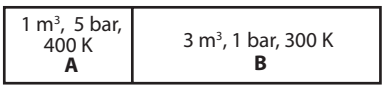

Figure 1

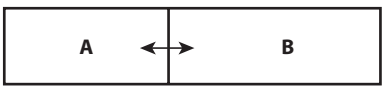

Figure 2

Solution

(2.22) Using $pV = nRT$, we have
In Figure 1,

$$n_A = \frac{p_A V_A}{RT} = \frac{5}{400R} \text{ and } n_B = \frac{p_B V_B}{RT} = \frac{1}{100R}$$

In Figure 2, after equilibrium is attained, we have

$$p_A = p_B \text{ and } T_A = T_B = T, \text{ so}$$

$$\frac{n_A RT}{V_A} = \frac{n_B RT}{V_B} \Rightarrow \frac{5}{400R \cdot V_A} = \frac{1}{100R \cdot V_B}$$

$$\Rightarrow 4V_A = 5V_B$$

Now,

$$V_A + V_B = 4 \text{ m}^3, \text{ so } V_A + \frac{4}{5}V_A = 4 \Rightarrow V_A = \frac{20}{9} = 2.22 \text{ m}^3$$

12. Liquids **A** and **B** form ideal solution over the entire range of composition. At temperature T, equimolar binary solution of liquids **A** and **B** has vapor pressure 45 torr. At the same temperature, a new solution of **A** and **B** having mole fractions x_A and x_B, respectively, has vapor pressure of 22.5 torr. The value of x_A/x_B in the new solution is
(Given that the vapor pressure of pure liquid **A** is 20 torr at temperature T)

Solution

(19)

$$p_A^\circ x_A + p_B^\circ x_B = p_T = 45$$

For equimolar binary solution, $x_A = x_B = 0.5$, so

$$20 \times 0.5 + p_B \times 0.5 = 45 \Rightarrow 70 \text{ torr}$$

For the new solution,

$$p_B^\circ + (p_A^\circ - p_B^\circ)x_A = 22.5 \Rightarrow 70 + (20 - 70)x_A \Rightarrow 22.5 \Rightarrow x_A = 47.5/50$$

Now,

$$\frac{x_A}{x_B} = \frac{x_A}{1 - x_A} = \frac{47.5/50}{1 - (47.5/50)} = \frac{47.5}{2.5} = 19$$

13. The solubility of a salt of weak acid (AB) at pH 3 is $Y \times 10^{-3}$ mol L^{-1}. The value of Y is _____.
(Given that the value of solubility product of AB (K_{sp}) = 2×10^{-10} and the value of ionization constant of HB (K_a) = 1×10^{-8})

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Solution

(4.47) The reactions are

$$\underset{}{AB(s)} \rightleftharpoons \underset{S}{A^+(aq)} + \underset{S-x}{B^-(aq)}$$

$$\underset{S-x}{B^-(aq)} + \underset{10^{-3}}{H^+(aq)} \rightleftharpoons HB$$

Now, for HB,

$$K_a = \frac{[H^+][B^-]}{[HB]} \Rightarrow \frac{(s-x)\times 10^{-3}}{x} = 10^{-8}$$

$$\Rightarrow s - x = x \times 10^{-5}$$

$$K_{sp} = [A^+][B^-] = S(S-x) = 2\times 10^{-10}$$

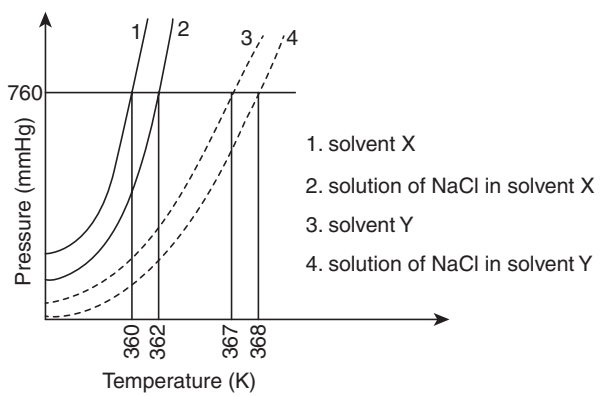
Putting $Sx = 2\times 10^{-5}$ in $S^2 - Sx - 2\times 10^{-10} = 0$, we get

$$S \approx \sqrt{(2\times 10^{-5})} = 4.47\times 10^{-3}\ \text{M}$$

Alternate solution

$$S = \sqrt{K_{sp}\left(\frac{[H^+]}{K_a}+1\right)} = \sqrt{20\times 10^{-10}\left(\frac{10^{-3}}{10^{-8}}+1\right)} \approx \sqrt{(2\times 10^{-5})} = 4.47\times 10^{-3}\ \text{M}$$

14. The plot given below shows $p - T$ curves (where p is the pressure and T is the temperature) for two solvents **X** and **Y** and isomolal solutions of NaCl in these solvents. NaCl completely dissociates in both the solvents.



On addition of equal number of moles of a non–volatile solute **S** in equal amount (in kg) of these solvents, the elevation of boiling point of solvent **X** is three times that of solvent **Y**. Solute S is known to undergo dimerization in these solvents. If the degree of dimerization is 0.7 in solvent **Y**, the degree of dimerization in solvent **X** is

Solution

(0.05) For solvent X, $\Delta T_{bX} = K_{bX}\, m \Rightarrow 2 = 2K_{bX}\, m$ (1)

For solvent Y, $\Delta T_{bY} = K_{bY}\, m \Rightarrow 1 = 2K_{bY}\, m$ (2)

Dividing Eq. (1) by Eq. (2), we get

$$\frac{K_{bX}}{K_{bY}} = 2$$

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After adding solute S, molality is the same for both solutions. So, we have

For solvent X, van't Hoff factor $i = 1 - \frac{\alpha}{2}$

$$\Delta T_{bX} = iK_{bX}\, m = \left(1 - \frac{\alpha}{2}\right) K_{bX}\, m \tag{3}$$

For solvent Y, van't Hoff factor $i = 1 - \frac{0.7}{2} = \frac{1.3}{2}$

$$\Delta T_{bY} = iK_{bY}\, m \Rightarrow \left(\frac{1.3}{2}\right) K_{bY}\, m \tag{4}$$

Given that $\Delta T_{bX} = 3\Delta T_{bY}$. Dividing Eq. (3)/(4), we have

$$\frac{\Delta T_{bX}}{\Delta T_{bY}} = \frac{\left(1 - \frac{\alpha}{2}\right) K_{bX}\, m}{\left(\frac{1.3}{2}\right) K_{bY}\, m} \Rightarrow \frac{1}{3} = \frac{2(2-\alpha)}{1.3} \Rightarrow \alpha = 0.05$$

SECTION 3

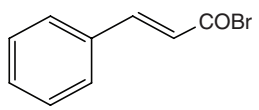
- This section contains **TWO (02)** paragraphs. Based on each paragraph, there are **TWO (02)** questions.
- Each question has **FOUR** options. **ONLY ONE** of these four options corresponds to the correct answer.

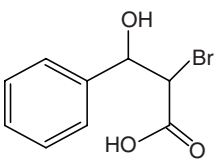
PARAGRAPH "X"

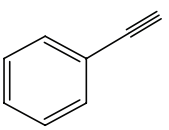
Treatment of benzene with CO/HCl in the presence of anhydrous $AlCl_3$/CuCl followed by reaction with Ac_2O/NaOAc gives compound **X** as the major product. Compound **X** upon reaction with Br_2/Na_2CO_3, followed by heating at 473 K with moist KOH furnishes **Y** as the major product. Reaction of **X** with H_2/Pd-C, followed by H_3PO_4 treatment gives **Z** as the major product.

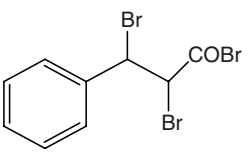
(***There are two questions based on PARAGRAPH "X", the question given below is one of them***)

15. The compound **Y** is

(A) 

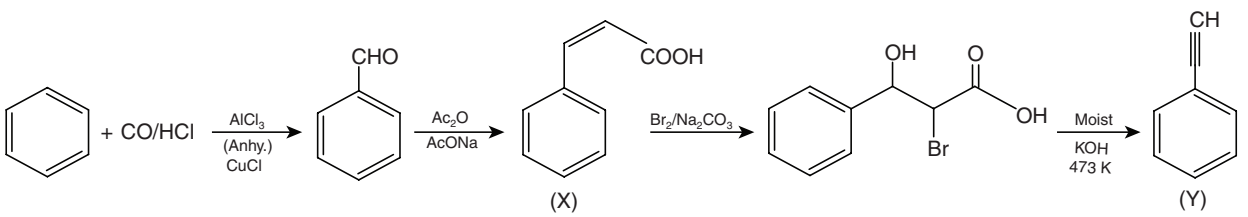
(B) 

(C) 

(D) 

Solution

(C)



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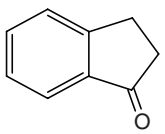
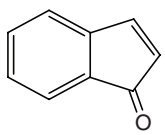
PARAGRAPH "X"

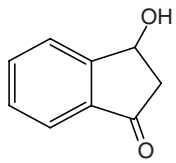
Treatment of benzene with CO/HCl in the presence of anhydrous $AlCl_3$/CuCl followed by reaction with Ac_2O/NaOAc gives compound **X** as the major product. Compound **X** upon reaction with Br_2/Na_2CO_3, followed by heating at 473 K with moist KOH furnishes **Y** as the major product. Reaction of **X** with H_2/Pd-C, followed by H_3PO_4 treatment gives **Z** as the major product.

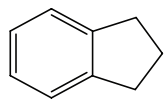
(***There are two questions based on PARAGRAPH "X", the question given below is one of them***)

16. The compound **Z** is

(A) 

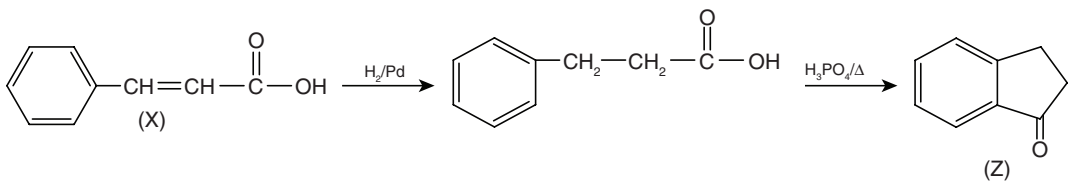
(B) 

(C) 

(D) 

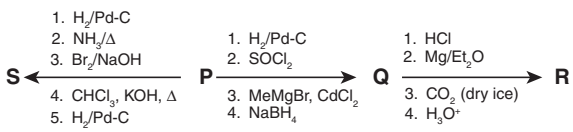
Solution

(A)



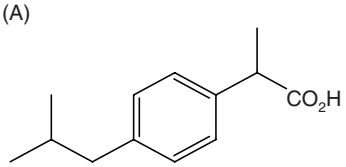
PARAGRAPH "A"

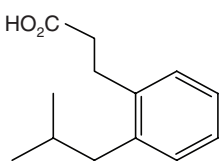
An organic acid **P** ($C_{11}H_{12}O_2$) can easily be oxidized to a dibasic acid which reacts with ethylene glycol to produce a polymer dacron. Upon ozonolysis, **P** gives an aliphatic ketone as one of the products. **P** undergoes the following reaction sequences to furnish **R** *via* **Q**. The compound **P** also undergoes another set of reactions to produce **S**.

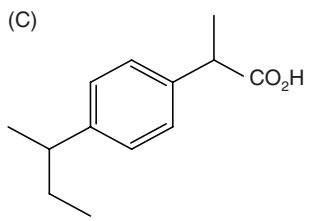


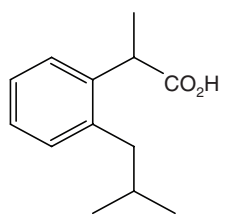
(***There are two questions based on PARAGRAPH "A", the question given below is one of them***)

17. The compound **R** is

(A) 

(B) 

(C) 

(D) 

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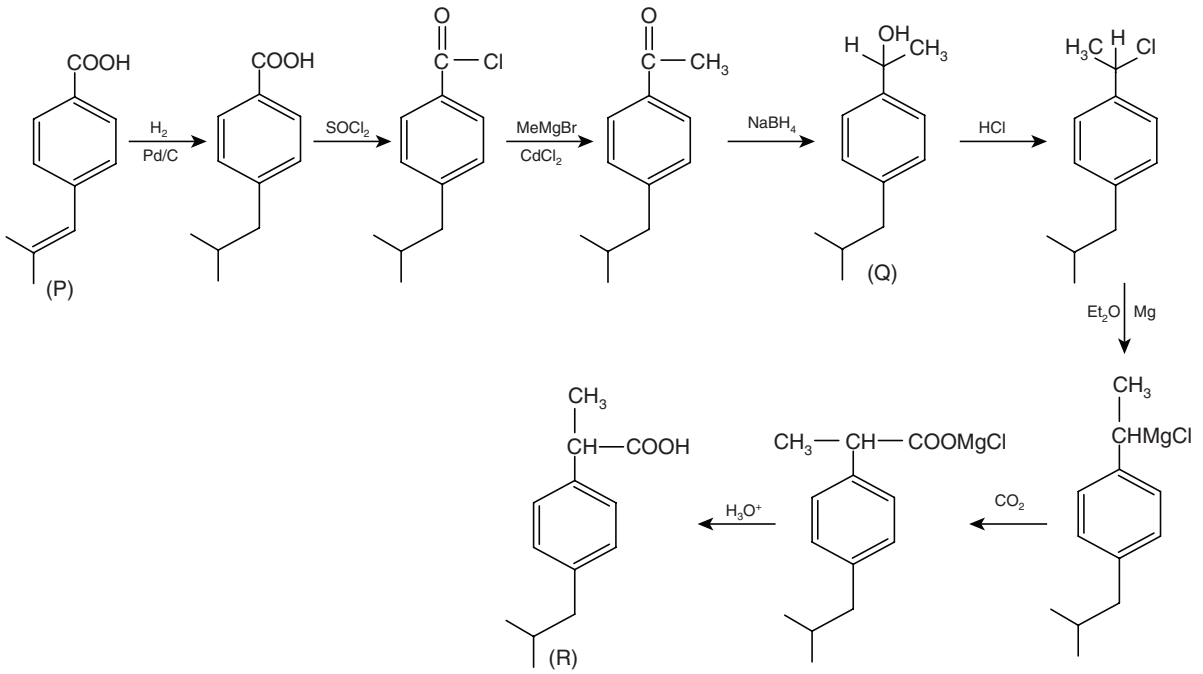
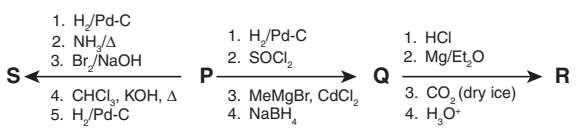
Solution

(A)



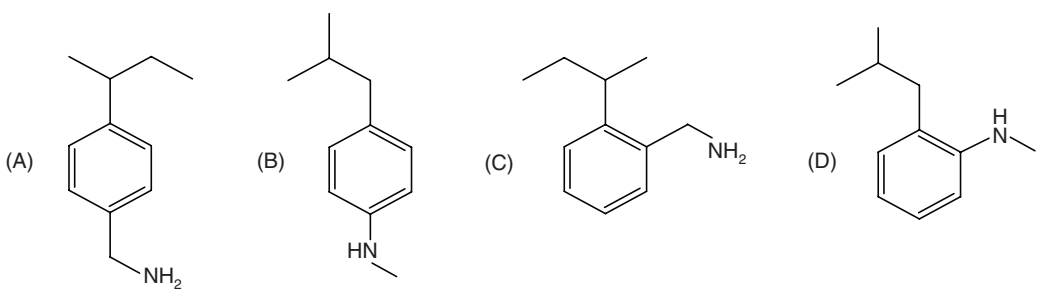
PARAGRAPH "A"

An organic acid **P** ($C_{11}H_{12}O_2$) can easily be oxidized to a dibasic acid which reacts with ethylene glycol to produce a polymer dacron. Upon ozonolysis, **P** gives an aliphatic ketone as one of the products. **P** undergoes the following reaction sequences to furnish **R** *via* **Q**. The compound P also undergoes another set of reactions to produce **S**.



(***There are two questions based on PARAGRAPH "A", the question given below is one of them***)

18. The compound **S** is



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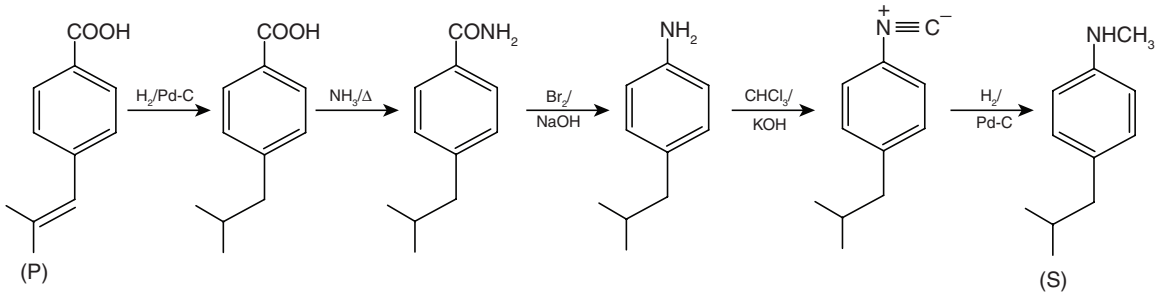
Solution

(B)



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JEE (ADVANCED) 2018
PAPER II (CHEMISTRY)

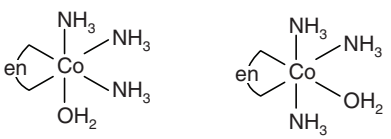
SECTION 1

- This section contains **SIX (06)** questions.
- Each question has **FOUR** options for correct answer(s). **ONE OR MORE THAN ONE** of these four option(s) is (are) correct option(s).

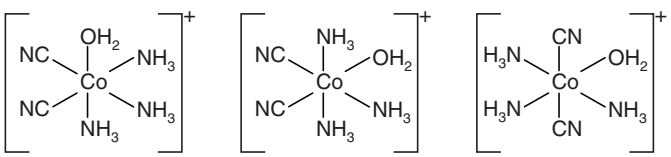
1. The correct option(s) regarding the complex $[Co(en)(NH_3)_3(H_2O)]^{3+}$ ($en = H_2NCH_2CH_2NH_2$) is (are)
(A) It has two geometrical isomers.
(B) It will have three geometrical isomers if bidentate 'en' is replaced by two cyanide ligands.
(C) It is paramagnetic.
(D) It absorbs light at longer wavelength as compared to $[Co(en)(NH_3)_4]^{3+}$.

Solution

(A) (B) (D) Option (A): Correct. The complex $[Co(en)(NH_3)_3(H_2O)]^{3+}$ has two following isomers:



Option (B): Correct. When bidentate 'en' is replaced by two cyanide ligands complex $[Co(CN)_2(NH_3)_3(H_2O)]^{+}$ will have three following isomers:



Option (C): Incorrect. In complex $[Co(en)(NH_3)_3(H_2O)]^{3+}$, Co is in +3 oxidation, that is, $[Ar]d^6$. In the presence given ligands the complex will have low spin, hence, diamagnetic.
Option (D): Correct. In complex $[Co(en)(NH_3)_4]^{3+}$ there is larger gap between t_{2g} and e_g than in complex $[Co(en)(NH_3)_3(H_2O)]^{3+}$. Hence $[Co(en)(NH_3)_3(H_2O)]^{3+}$ will absorb light at longer wavelength as compared to $[Co(en)(NH_3)_4]^{3+}$.

2. The correct option(s) to distinguish nitrate salts of Mn^{2+} and Cu^{2+} taken separately is (are)
(A) Mn^{2+} shows the characteristic green color in the flame test.
(B) Only Cu^{2+} shows the formation of precipitate by passing H_2S in acidic medium.
(C) Only Mn^{2+} shows the formation of precipitate by passing H_2S in faintly basic medium.
(D) Cu^{2+}/Cu has higher reduction potential than Mn^{2+}/Mn (measured under similar conditions).

Solution

(B) (D) Option (A): Incorrect. Mn^{2+} shows purple color in the flame test.
Option (B): Correct. When H_2S gas is passed through a solution containing Cu^{2+} in the acidic medium, black ppt. is obtained.

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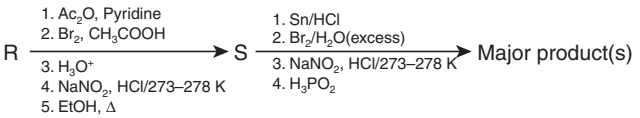
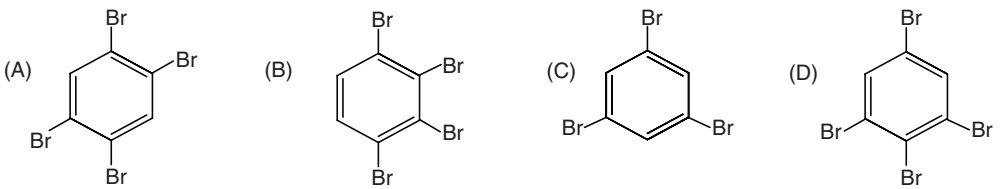
$$Cu^{2+} \xrightarrow[HCl]{H_2S} \underset{\text{(Black ppt.)}}{CuS}$$

Option (C): Incorrect. Both Mn^{2+} and Cu^{2+}can form precipitate by passing H_2S in faintly basic medium.
Option (D): Correct. Higher reduction potential indicates higher tendency of Cu^{2+} to gain the electrons. Cu^{2+} ion on accepting the electrons gain stability due to fully filled *d*-orbital.

$$\underset{(d^9s^0)}{Cu^{2+}} \rightarrow \underset{(d^{10}s^1)}{Cu} \qquad \underset{(d^5s^0)}{Mn^{2+}} \rightarrow \underset{(d^5s^2)}{Mn}$$

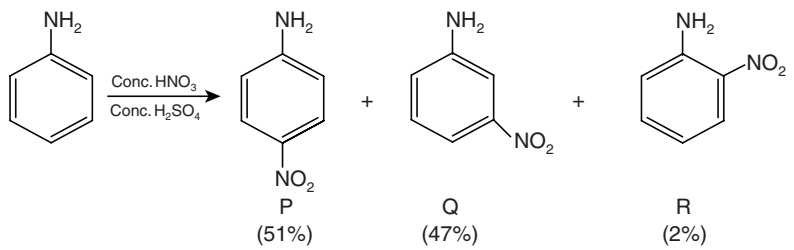
3. Aniline reacts with mixed acid (conc. HNO_3 and conc. H_2SO_4) at 288 K to give **P** (51%), **Q** (47%) and **R** (2%). The major product(s) of the following reaction sequence is (are)

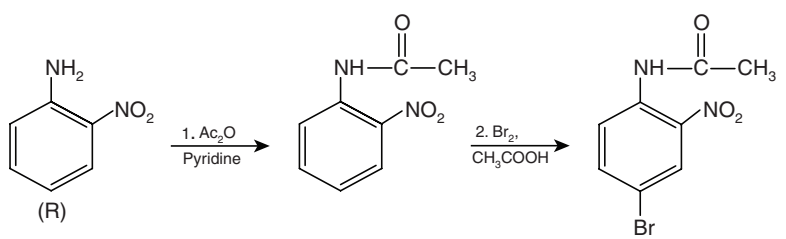


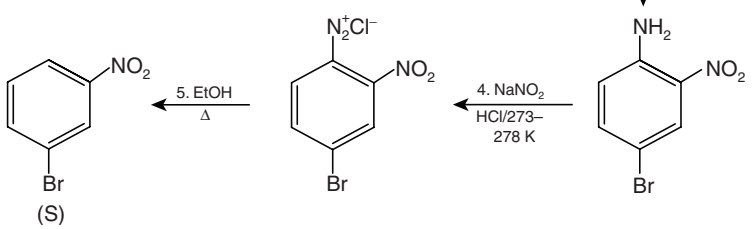


Solution

(D)







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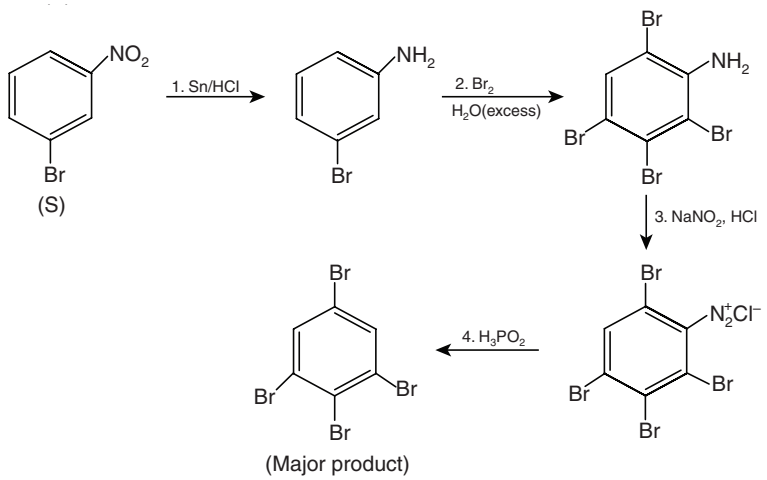
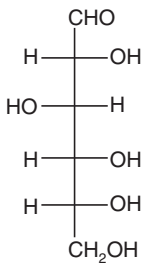
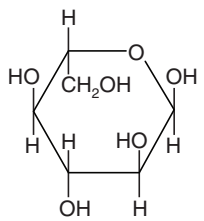


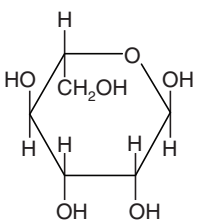
4. The Fischer presentation of D-glucose is given below.

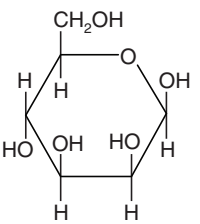


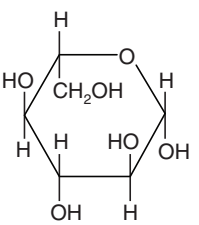
D-glucose

The correct structure(s) of β-L-glucopyranose is (are)

(A) 

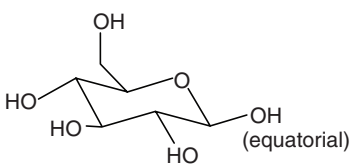
(B) 

(C) 

(D) 

Solution

(D) The structure of β-L-glucopyranose is as follows:



β– D–(+)– Glucopyranose

5. For a first order reaction A(g) $\rightarrow$ 2B(g) + C(g) at constant volume and 300 K, the total pressure at the beginning ($t = 0$) and at time t are p_0 and p_t, respectively. Initially, only A is present with concentration $[A]_0$, and $t_{1/3}$ is the time required for the partial pressure of A to reach 1/3rd of its initial value. The correct option(s) is (are)
(Assume that all these gases behave as ideal gases)

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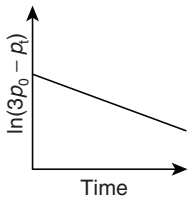
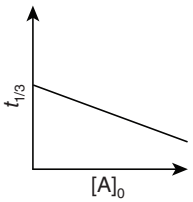
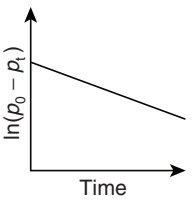
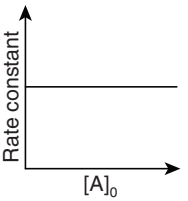
(A)


(B)


(C)


(D)


Solution

(A) (D) The reaction can be represented as

$$\begin{array}{lccc} & A(g) & \rightarrow & 2B(g)+C(g) \\ \text{At } t=0 & p_0 & & 0 \quad 0 \\ \text{At } t=t_{1/3} & p_0-\dfrac{2p_0}{3} & & 0 \quad 0 \\ \text{At } t=t & p_0-x & & 2x \quad x \end{array}$$

Now, $$p_t = p_0 - x + 2x + x \Rightarrow x = \frac{p_t - p_0}{2}$$

Substituting in the expression $t = \frac{1}{k}\ln\left(\frac{p_0}{p_0 - x}\right)$, we get

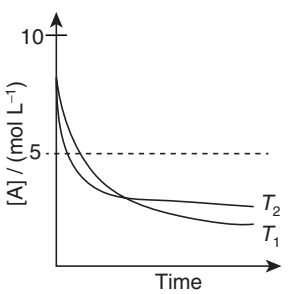
$$t = \frac{1}{k}\ln\left(\frac{p_0}{p_0 - \frac{p_t - p_0}{2}}\right) = \frac{1}{k}\ln\left(\frac{2p_0}{3p_0 - p_t}\right)$$

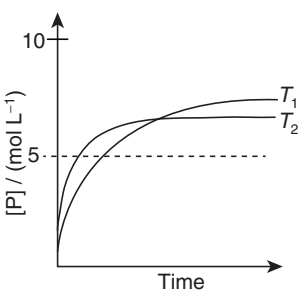
which can be rearranged as

$$\ln(3p_0 - p_t) = -kt + \ln 2p_0$$

Thus, the graph of $\ln(3p_0 - p_t)$ vs t is a straight line having negative slope $-k$ and intercept $\ln 2p_0$ as shown in (A). Also, as rate is independent of initial concentration, so the plot in option (D) is also correct.

6. For a reaction, A $\rightleftharpoons$ P, the plots of [A] and [P] with time at temperatures T_1 and T_2 are given below.





If $T_2 > T_1$, the correct statement(s) is (are)
(Assume ΔH^θ and ΔS^θ are independent of temperature and ratio of ln$K$ at T_1 to ln$K$ at T_2 is greater than T_2/T_1 Here H, S, G and K are enthalpy, entropy, Gibbs energy and equilibrium constant, respectively)

(A) $\Delta H^\theta < 0, \Delta S^\theta < 0$
(B) $\Delta G^\theta < 0, \Delta H^\theta > 0$
(C) $\Delta G^\theta < 0, \Delta S^\theta < 0$
(D) $\Delta G^\theta < 0, \Delta S^\theta > 0$

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Solution

(A) (C) As we increase the temperature, the concentration of the product reduces. This implies that the reaction is exothermic, and $\Delta H^{\theta} < 0$.

$$\frac{\ln K_{T_1}}{\ln K_{T_2}} > 1 \Rightarrow \ln K_{T_1} > \ln K_{T_2} \Rightarrow K_{T_1} > K_{T_2}$$

But

$$\frac{\ln K_{T_1}}{\ln K_{T_2}} > \frac{T_2}{T_1}$$

As $\Delta G = -RT \ln K$, $\Delta G^{\theta}_{T_1} < \Delta G^{\theta}_{T_2} \Rightarrow \Delta H^{\theta}_{T_1} - T\Delta S^{\theta}_{T_1} < \Delta H^{\theta}_{T_2} - T\Delta S^{\theta}_{T_2}$

This is only possible if $\Delta S^{\theta} < 0$

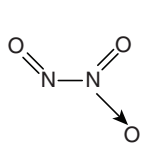
SECTION 2

This section contains **EIGHT (08)** questions. The answer to each question is a **NUMERICAL VALUE**.

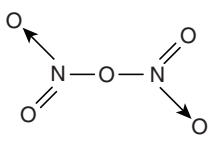
7. The total number of compounds having at least one bridging oxo group among the molecules given below is _____.
N_2O_3, N_2O_5, P_4O_6, P_4O_7, $H_4P_2O_5$, $H_5P_3O_{10}$, $H_2S_2O_3$, $H_2S_2O_5$

Solution

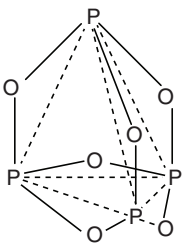
(5)



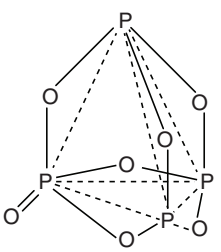
N_2O_3



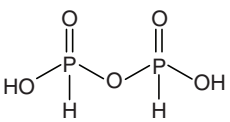
N_2O_5



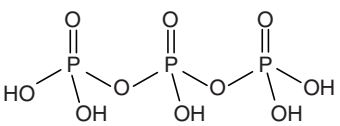
P_4O_6



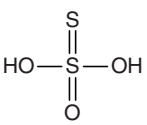
P_4O_7



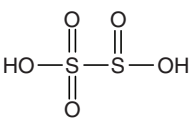
$H_4P_2O_5$



$H_5P_3O_{10}$



$H_2S_2O_3$



$H_2S_2O_5$

8. Galena (an ore) is partially oxidized by passing air through it at high temperature. After some time, the passage of air is stopped, but the heating is continued in a closed furnace such that the contents undergo self-reduction. The weight (in kg) of Pb produced per kg of O_2 consumed is _____.
(Atomic weights in g mol^{-1}: O = 16, S = 32, Pb = 207)

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Solution

(6.47) The steps involved in the oxidation of galena (PbS) are as follows:

$$2PbS + 3O_2 \rightarrow 2PbO + 2SO_2$$
$$2PbO + PbS \rightarrow 3Pb + SO_2$$

As per the above reactions, we can conclude that
3 mol of O_2 produces 3 mol of lead
96 kg of O_2 produces 621 kg of lead

Therefore, 1 kg of O_2 will produce $\frac{621}{96} \times 1 = 6.47\,\text{kg}$ of Pb.

9. To measure the quantity of $MnCl_2$ dissolved in an aqueous solution, it was completely converted to $KMnO_4$ using the reaction,
$MnCl_2 + K_2S_2O_8 + H_2O \rightarrow KMnO_4 + H_2SO_4 + HCl$ (equation not balanced).
Few drops of concentrated HCl were added to this solution and gently warmed. Further, oxalic acid (225 mg) was added in portions till the color of the permanganate ion disappeared. The quantity of $MnCl_2$ (in mg) present in the initial solution is _____.
(Atomic weights in g mol^{-1}: Mn = 55, Cl = 35.5)

Solution

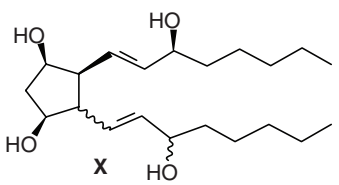
(126) The balanced equation can be written as

$$2MnCl_2 + 5K_2S_2O_8 + 8H_2O \rightarrow 2KMnO_4 + 4K_2SO_4 + 6H_2SO_4 + 4HCl$$
$$2KMnO_4 + 5H_2C_2O_4 + 3H_2SO_4 \rightarrow K_2SO_4 + 2MnSO_4 + 8H_2O + 10CO_2$$

$$\text{Millimoles of } KMnO_4 = \text{Millimoles of } H_2C_2O_4$$
$$\text{Millimole } MnCl_2 \times 5 = \left(\frac{225}{90}\right) \times 2$$

So, millimole of $MnCl_2$ = 1 = 126 mg.

10. For the given compound **X**, the total number of optically active stereoisomers is _____.



This type of bond indicates that the configuration at the specific carbon and the geometry of the double bond is fixed.

This type of bond indicates that the configuration at the specific carbon and the geometry of the double bond is not fixed.

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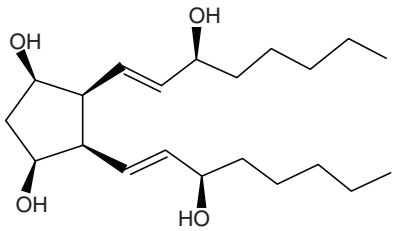
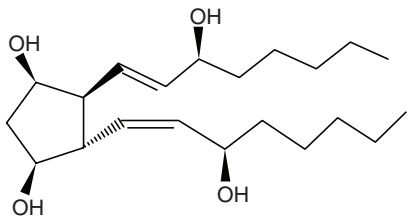
Solution

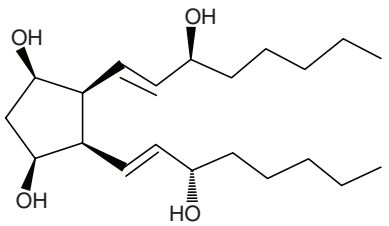
(7) There are total 7 optically active stereoisomers. Their structures are as follows:



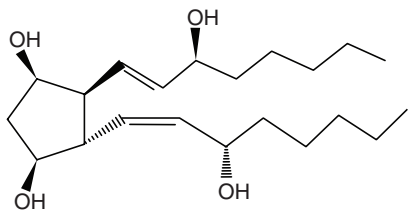
(optically inactive)



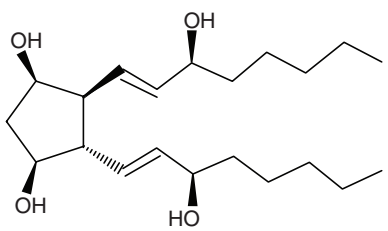
(optically active)



(optically active)



(optically active)



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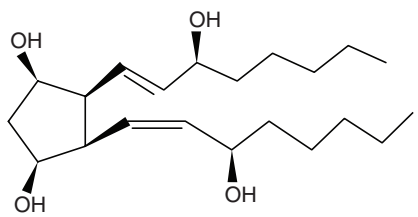

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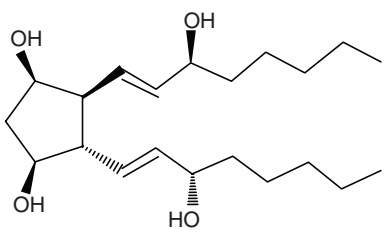

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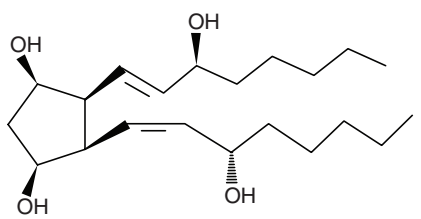
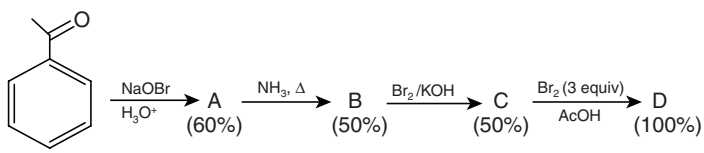


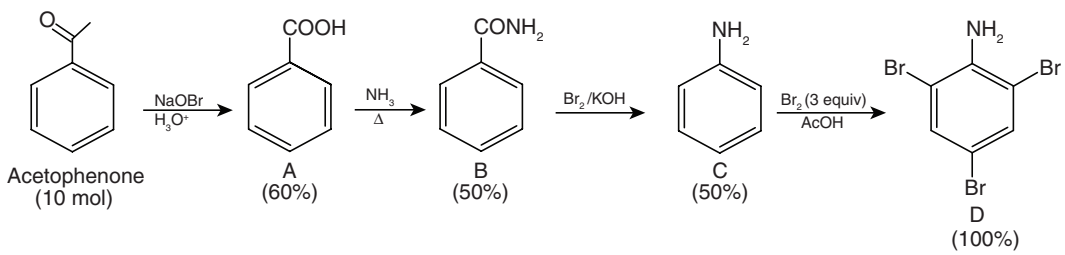
(optically active)

11. In the following reaction sequence, the amount of **D** (in g) formed from 10 mol of acetophenone is _____. (Atomic weights in g mol^{-1}: H = 1, C = 12, N = 14, O = 16, Br = 80. The yield (%) corresponding to the product in each step is given in the parenthesis)



Solution

(495)



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The amount of D formed in mol is $\frac{60}{100}\times\frac{50}{100}\times\frac{50}{100}\times 10 = 1.5\,\text{mol}$

Amount of D in grams is = 1.5×330 g = 495 g

12. The surface of copper gets tarnished by the formation of copper oxide. N_2 gas was passed to prevent the oxide formation during heating of copper at 1250 K. However, the N_2 gas contains 1 mole % of water vapor as impurity. The water vapor oxidizes copper as per the reaction given below:

$$2Cu(s) + H_2O(g) \rightarrow Cu_2O(s) + H_2(g)$$

p_{H_2} is the minimum partial pressure of H_2 (in bar) needed to prevent the oxidation at 1250 K. The value of $\ln(p_{H_2})$ is _____.

(Given: total pressure = 1 bar, R (universal gas constant) = 8 J K^{-1} mol^{-1}, ln(10) = 2.3. Cu(s) and Cu_2O(s) are mutually immiscible.

At 1250 K: $2Cu(s) + \frac{1}{2}O_2(g) \rightarrow Cu_2O(s)$; $\Delta G^\circ = -78{,}000$ J mol^{-1}

$H_2(g) + \frac{1}{2}O_2(g) \rightarrow H_2O(g)$; $\Delta G^\circ = -1{,}78{,}000$ J mol^{-1}; G is the Gibbs energy)

Solution

(–14.6)

$$2Cu(s)+\frac{1}{2}O_2(g)\rightarrow Cu_2O(s);\quad \Delta G^\circ = -78{,}000\ \text{J mol}^{-1} \tag{1}$$

$$H_2(g)+\frac{1}{2}O_2(g)\rightarrow H_2O(g);\quad \Delta G^\circ = -1{,}78{,}000\ \text{J mol}^{-1} \tag{2}$$

Subtracting Eq. (1) – Eq. (2), we get

$$2Cu(s)+H_2O(g)\rightarrow Cu_2O(s)+H_2(g);\quad \Delta G^\circ = +100000\ \text{J mol}^{-1} \tag{3}$$

Now,
$$\Delta G = \Delta G^\circ + RT\ln\left(\frac{p_{H_2}}{p_{H_2O}}\right)$$

For the reaction (3) to not occur,

$$\Delta G > 0 \text{ or } \Delta G^\circ + RT\ln\left(\frac{p_{H_2}}{p_{H_2O}}\right) > 0$$

$$\Rightarrow 100000 + 8\times 1250\ln\left(\frac{p_{H_2}}{p_{H_2O}}\right) > 0$$

$$\Rightarrow 100000 + 8\times 1250\ln\left(\frac{p_{H_2}}{p_{H_2O}}\right) > \frac{-100000}{8\times 1250}$$

$$\Rightarrow \ln\left(\frac{p_{H_2}}{p_{H_2O}}\right) > -10$$

$$\ln p_{H_2} > -10 + \ln p_{H_2O}$$

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Now, $p_{H_2O} = x_{H_2O} \times p_T = 0.01 \times 1 = 10^{-2}$

So, $\ln p_{H_2} > -10 - 2\ln 10 \Rightarrow p_{H_2} > -14.6$ bar

13. Consider the following reversible reaction,

$$A(g) + B(g) \rightleftharpoons AB(g).$$

The activation energy of the backward reaction exceeds that of the forward reaction by $2RT$ (in J mol^{-1}). If the pre-exponential factor of the forward reaction is 4 times that of the reverse reaction, the absolute value of ΔG^θ (in J mol^{-1}) for the reaction at 300 K is _____.
(Given; ln(2) = 0.7, RT = 2500 J mol^{-1} at 300 K and G is the Gibbs energy)

Solution

(–8466 J mol^{-1})

$$\Delta G^\theta = -RT \ln K$$

where

$$K = \frac{K_f}{K_b} = \frac{A_f e^{-E_{a_f}/RT}}{A_b e^{-E_{a_b}/RT}}$$

Now, given that $A_f = 4A_b$ and $E_{a_b} - E_{a_f} = 2RT$. Substituting, we get

$$K = \frac{K_f}{K_b} = 4e^{(E_{a_b} - E_{a_f})/RT} = 4e^2$$

Therefore, $\Delta G^\theta = -RT \ln(4e^2) = -2500 \times [\ln(4) + 2] = -8466$ J mol^{-1}

14. Consider an electrochemical cell: A(s) | A^{n+} (aq, 2 M) || B^{2n+} (aq, 1 M) | B(s). The value of ΔH^θ for the cell reaction is twice that of ΔG^θ at 300 K. If the emf of the cell is zero, the ΔS^θ (in J K^{-1} mol^{-1}) of the cell reaction per mole of B formed at 300 K is _____.
(Given: ln(2) = 0.7, R (universal gas constant) = 8.3 J K^{-1} mol^{-1}. H, S and G are enthalpy, entropy and Gibbs energy, respectively)

Solution

(–11.62 JK^{-1}mol^{-1}) The half-cell reactions are

$$A(s) \rightarrow A^{n+}(aq) + ne^- \quad (1)$$

$$B^{2n+}(aq) + 2ne^- \rightarrow B(s) \quad (2)$$

Adding Eq. (1) and Eq. (2), we get

$$2A(s) + B^{2n+}(aq) \rightarrow 2A^{n+}(aq) + B(s)$$

Given that $\Delta H^\theta = 2\Delta G^\theta$ and $E_{cell} = 0$, so

$$\Delta G^\theta = \Delta H^\theta - T\Delta S^\theta \Rightarrow \Delta S^\theta = \frac{\Delta G^\theta}{T} = \frac{-RT \ln K}{T}$$

$$\Rightarrow \Delta S^\theta = -R \ln \frac{[A^{n+}]^2}{[B^{2n+}]} = -8.3 \times \ln 4 = -11.5 \text{ J K}^{-1} \text{ mol}^{-1}$$

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SECTION 3

- This section contains **FOUR (04)** questions.
- Each question has **TWO (02)** matching lists: **LIST-I** and **LIST-II**.
- FOUR options are given representing matching of elements from **LIST-I** and **LIST-II. ONLY ONE** of these four options corresponds to a correct matching.

---

15. Match each set of hybrid orbitals from LIST-I with complex(es) given in LIST-II.

LIST-I	LIST-II
P. dsp^2	**1.** $[FeF_6]^{4-}$
Q. sp^3	**2.** $[Ti(H_2O)_3Cl_3]$
R. sp^3d^2	**3.** $[Cr(NH_3)_6]^{3+}$
S. d^2sp^3	**4.** $[FeCl_4]^{2-}$
	5. $[Ni(CO)]_4$
	6. $[Ni(CN)_4]^{2-}$

The correct option is

(A) P → 5; Q → 4, 6; R → 2, 3; S → 1

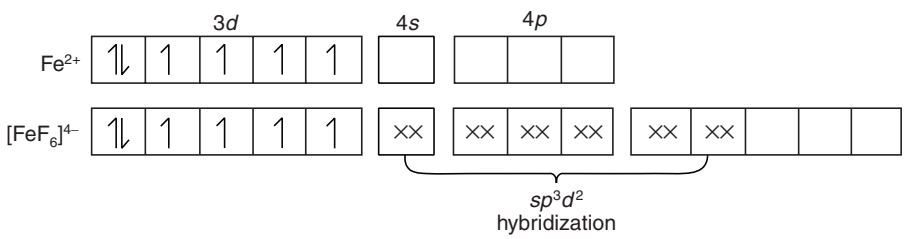
(B) P → 5, 6; Q → 4; R → 3; S → 1, 2

(C) P → 6; Q → 4, 5; R → 1; S → 2, 3

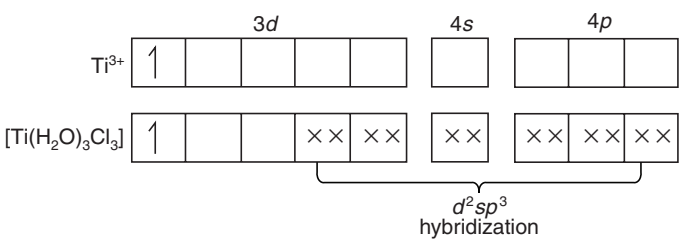
(D) P → 4, 6; Q → 5, 6; R → 1, 2; S → 3

Solution

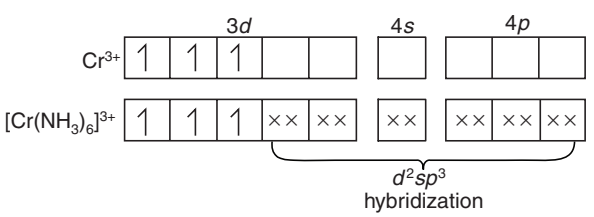
(C) $[FeF_6]^{4-}$: The arrangement of electrons in Fe^{2+} ($3d^6$) will be



$[Ti(H_2O)_3Cl_3]$: The arrangement of electrons in Ti^{3+} ($3d^1$) will be



$[Cr(NH_3)_6]^{3+}$: The arrangement of electrons in Cr^{3+} ($3d^3$) will be



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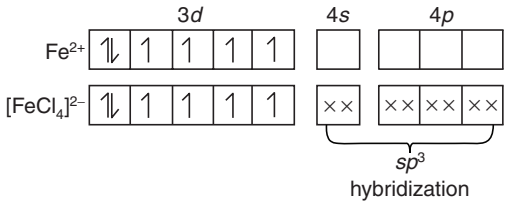
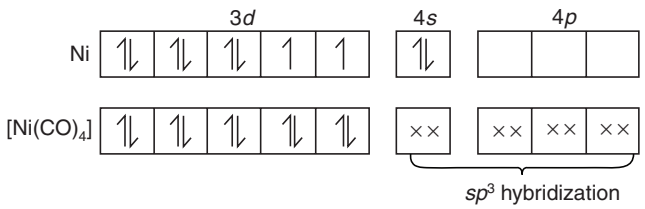
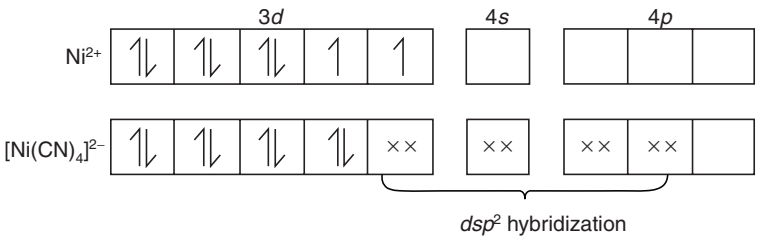
$[FeCl_4]^{2-}$: The arrangement of electrons in Fe^{2+} ($3d^6$) will be



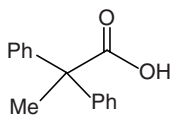
$[Ni(CO)_4]$: The arrangement of electrons in Ni^0 ($3d^8 4s^2$) will be



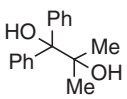
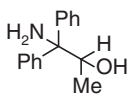
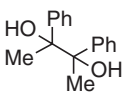
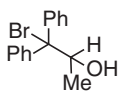
$[Ni(CN)_4]^{2-}$: The arrangement of electrons in Ni^{2+} ($3d^8$) will be



16. The desired product **X** can be prepared by reacting the major product of the reactions in LIST-I with one or more appropriate reagents in LIST-II.
(Given, order of migratory aptitude: aryl > alkyl > hydrogen)



X

LIST-I		LIST-II
P. 	+ H_2SO_4	**1.** I_2, NaOH
Q. 	+ HNO_2	**2.** $[Ag(NH_3)_2]OH$
R. 	+ H_2SO_4	**3.** Fehling solution
S. 	+ $AgNO_3$	**4.** HCHO, NaOH
		5. NaOBr

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The correct option is

(A) P → 1; Q → 2, 3; R → 1, 4; S → 2, 4

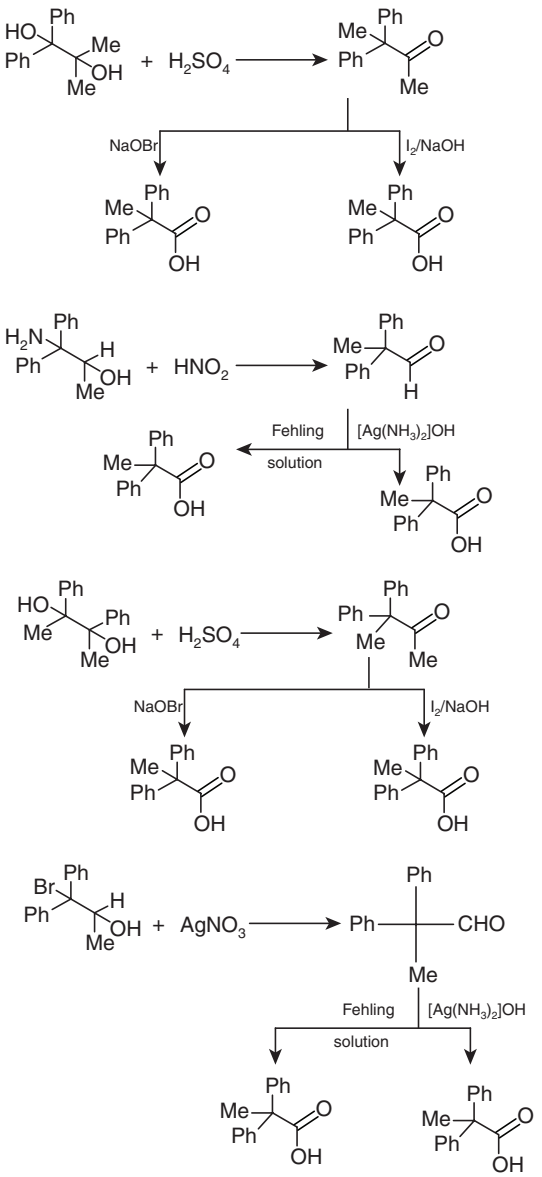
(B) P → 1, 5; Q → 3, 4; R → 4, 5; S → 3

(C) P → 1, 5; Q → 3, 4; R → 5; S → 2, 4

(D) P → 1, 5; Q → 2, 3; R → 1, 5; S → 2, 3

Solution

(D) The reactions are as follows:



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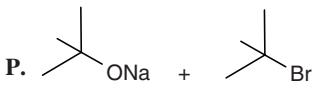
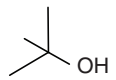
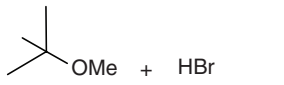
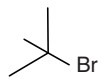
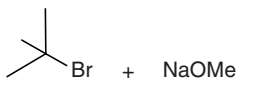
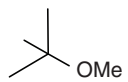
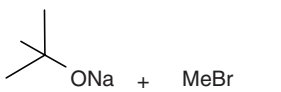
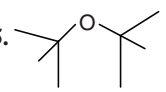
17. LIST-I contains reactions and LIST-II contains major products.

LIST-I	LIST-II
P. 	**1.** 
Q. 	**2.** 
R. 	**3.** 
S. 	**4.** 
	5. 

Match each reaction in LIST-I with one or more products in LIST-II and choose the correct option.

(A) P → 1, 5; Q → 2; R → 3; S → 4

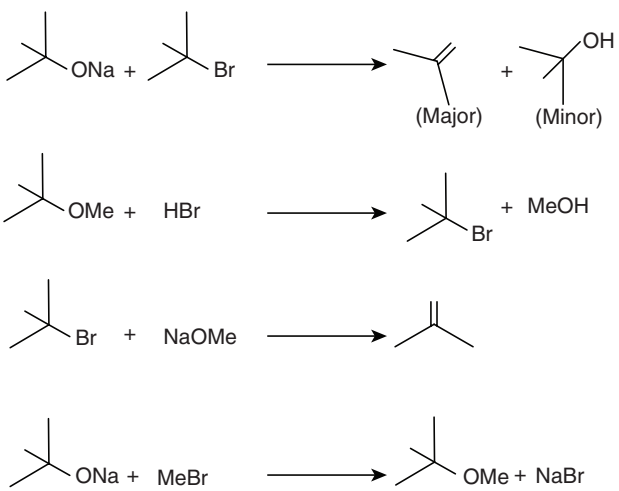
(B) P → 1, 4; Q → 2; R → 4; S → 3

(C) P → 1, 4; Q → 1, 2; R → 3, 4; S → 4

(D) P → 4, 5; Q → 4; R → 4; S → 3, 4

Solution

(B) With *tertiary* halides, steric hindrance in the substrate is severe, thus, elimination is highly favored, especially when the reaction is carried out at higher temperatures.



18. Dilution processes of different aqueous solutions, with water, are given in LIST-I. The effects of dilution of the solutions on $[H^+]$ are given in

(**Note:** Degree of dissociation (α) of weak acid and weak base is << 1; degree of hydrolysis of salt << 1; $[H^+]$ represents the concentration of H^+ ions)

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LIST-I	LIST-II
P. (10 mL of 0.1 M NaOH + 20 mL of 0.1 M acetic acid) diluted to 60 mL	**1.** the value of $[H^+]$ does not change on dilution
Q. (20 mL of 0.1 M NaOH + 20 mL of 0.1 M acetic acid) diluted to 80 mL	**2.** the value of $[H^+]$ changes to half of its initial value on dilution
R. (20 mL of 0.1 M HCl + 20 mL of 0.1 M ammonia solution) diluted to 80 mL	**3.** the value of $[H^+]$ changes to two times of its initial value on dilution
S. 10 mL saturated solution of $Ni(OH)_2$ in equilibrium with excess solid $Ni(OH)_2$ is diluted to 20 mL (solid $Ni(OH)_2$ is still present after dilution).	**4.** the value of $[H^+]$ changes to $\frac{1}{\sqrt{2}}$ times of its initial value on dilution
	5. the value of $[H^+]$ changes to $\sqrt{2}$ times of its initial value on dilution

Match each process given in LIST-I with one or more effect(s) in LIST-II. The correct option is

(A) P → 4; Q → 2; R → 3; S → 1 (B) P → 4; Q → 3; R → 2; S → 3

(C) P → 1; Q → 4; R → 5; S → 3 (D) P → 1; Q → 5; R → 4; S → 1

Solution

(D)

$$NaOH + CH_3COOH \rightarrow CH_3COONa + H_2O$$

$$10 \times 0.1 = 1 \text{ mmol} \quad 20 \times 0.1 = 2 \text{ mmol}$$

$$\left[CH_3COO^-\right] = \frac{20 \times 0.1 - 10 \times 0.1}{30} = \frac{1}{30}$$

Since it is a buffer solution, with 1 mmol of CH_3COOH and 1 mmol of CH_3COONa in solution. So, (P) → (1).

$$NaOH + CH_3COOH \rightarrow CH_3COONa + H_2O$$

$$20 \times 0.1 = 2 \text{ mmol} \quad 20 \times 0.1 = 2 \text{ mmol}$$

Since the solution contains 2 mmol of CH_3COONa in 40 ml solution. So, for a salt of weak acid and strong base, we have

$$[H^+]_{\text{initial}} = \sqrt{\frac{K_w K_a}{C}}$$

On dilution to 80 ml, C becomes $C/2$, so $[H^+]_{\text{new}} = \sqrt{\frac{K_w K_a}{C/2}} = [H^+]_{\text{initial}} \times \sqrt{2}$. So, (Q) → (5)

$$HCl + NH_3 \rightarrow NH_4Cl$$

$$20 \times 0.1 = 2 \text{ mmol} \quad 20 \times 0.1 = 2 \text{ mmol}$$

Since the solution contains 2 mmol of CH_3COONa in 40 mL solution. So, for a salt of strong acid and weak base, we have

$$[H^+]_{\text{initial}} = \sqrt{\frac{K_w C}{K_b}}$$

On dilution to 80 mL, C becomes $C/2$, so $[H^+]_{\text{new}} = \sqrt{\frac{K_w C}{2K_b}} = [H^+]_{\text{initial}} / \sqrt{2}$. So, (R) → (4)

$$Ni(OH)_2(s) \rightarrow Ni^{2+}(aq) + 2OH^-(aq)$$

As it is a sparingly soluble salt, there is no change in $[OH^-]$ on dilution. So, (S) → (1)

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JEE Main 2019 (January 9, Shift 1)

CHEMISTRY

1. Two complexes $[Cr(H_2O)_6]Cl_3$ (A) and $[Cr(NH_3)_6]Cl_3$ (B) are violet and yellow coloured, respectively. The incorrect statement regarding them is:

(1) Δ_o values of (A) and (B) are calculated from the energies of violet and yellow light, respectively.

(2) both are paramagnetic with three unpaired electrons.

(3) both absorb energies corresponding to their complementary colors.

(4) Δ_o values for (A) is less than that of (B).

2. The correct decreasing order for acid strength is:

(1) $NO_2CH_2COOH > FCH_2COOH > CNCH_2COOH > ClCH_2COOH$

(2) $FCH_2COOH > NCCH_2COOH > NO_2CH_2COOH > ClCH_2COOH$

(3) $CNCH_2COOH > O_2NCH_2COOH > FCH_2COOH > ClCH_2COOH$

(4) $NO_2CH_2COOH > NCCH_2COOH > FCH_2COOH > ClCH_2COOH$

3. The major product of following reaction is:

$$R-C\equiv N \xrightarrow[(ii)\ H_2O]{(i)\ AlH(i-Bu)_2} ?$$

(1) RCOOH (2) $RCONH_2$

(3) RCHO (4) RCH_2NH_2

4. The highest value of the calculated spin-only magnetic moment (in BM) among all the transition metal complexes is:

(1) 5.92 (2) 6.93

(3) 3.87 (4) 4.90

5. 0.5 moles of gas A and x moles of gas B exert a pressure of 200 Pa in a container of volume 10 m^3 at 1000 K. Given R is the gas constant in $JK^{-1}\ mol^{-1}$, x is:

(1) $\frac{2R}{4+R}$ (2) $\frac{2R}{4-R}$

(3) $\frac{4+R}{2R}$ (4) $\frac{4-R}{2R}$

6. The one that is extensively used as a piezoelectric material is:

(1) tridymite (2) amorphous silica

(3) quartz (4) mica

7. Correct statements among a to d regarding silicones are:

(a) They are polymers with hydrophobic character.

(b) They are biocompatible.

(c) In general, they have high thermal stability and low dielectric strength.

(d) Usually, they are resistant to oxidation and used as greases.

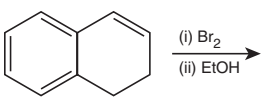
(1) (a), (b), (c) and (d)

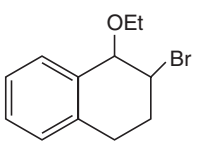
(2) (a), (b) and (c) only

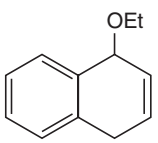
(3) (a) and (b) only

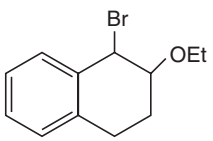
(4) (a), (b) and (d) only

8. The major product of the following reaction is:



(1) 

(2) 

(3) 

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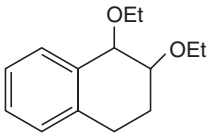
(4) 

9. In general, the properties that decrease and increase down a group in the periodic table, respectively, are:

(1) atomic radius and electronegativity.

(2) electron gain enthalpy and electronegativity.

(3) electronegativity and atomic radius.

(4) electronegativity and electron gain enthalpy.

10. A solution of sodium sulfate contains 92 g of Na^+ ions per kilogram of water. The molality of Na^+ ions in that solution in mol kg^{-1} is:

(1) 12 (2) 4

(3) 8 (4) 16

11. The correct match between Item-I and Item-II is:

Item-I (drug)	**Item-II** (test)
(A)Chloroxylenol	(P) Carbylamine test
(B) Norethindron	(Q) Sodium hydrogen-carbonate test
(C) Sulphapyridine	(R) Ferric chloride test
(D) Penicillin	(S) Baeyer's test

(1) A → R; B → P; C → S; D → Q

(2) A → Q; B → S; C → P; D → R

(3) A → R; B → S; C → P; D → Q

(4) A → Q; B → P; C → S; D → R

12. A water sample has ppm level concentration of the following metals: Fe = 0.2; Mn = 5.0, Cu = 3.0; Zn = 5.0. The metal that makes the water sample unsuitable for drinking is:

(1) Cu (2) Mn

(3) Fe (4) Zn

13. The anodic half-cell of lead-acid battery is recharged using electricity of 0.05 Faraday. The amount of $PbSO_4$ electrolyzed in g during the process is : (Molar mass of $PbSO_4$ = 303 g mol^{-1})

(1) 22.8 (2) 15.2

(3) 7.6 (4) 11.4

14. Which one of the following statements regarding Henry's law is not correct?

(1) Higher the value of K_H at a given pressure, higher is the solubility of the gas in the liquids.

(2) Different gases have different K_H (Henry's law constant) values at the same temperature.

(3) The partial pressure of the gas in vapour phase is proportional to the mole fraction of the gas in the solution.

(4) The value of K_H increases with increase of temperature and K_H is function of the nature of the gas

15. The following results were obtained during kinetic studies of the reaction;

$$2A + B \rightarrow \text{Products}$$

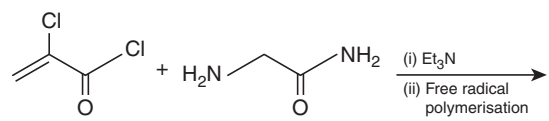
Experiment	**[A] (in mol L^{-1})**	**[B] (in mol L^{-1})**	**Initial Rate of Reaction (in mol L^{-1} min^{-1})**
I	0.10	0.20	6.93×10^{-3}
II	0.10	0.25	6.93×10^{-3}
III	0.20	0.30	1.386×10^{-2}

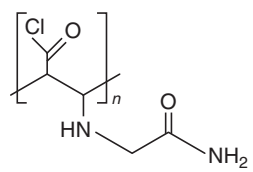
The time (in minutes) required to consume half of A is:

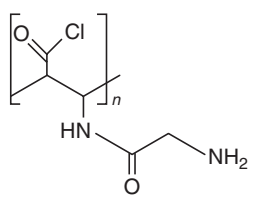
(1) 5 (2) 10

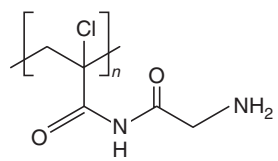
(3) 1 (4) 100

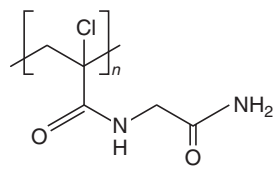
16. Major product of the following reaction is:



(1) 

(2) 

(3) 

(4) 

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17. The alkaline earth metal nitrate that does not crystallise with water molecules, is:

(1) $Mg(NO_3)_2$ (2) $Sr(NO_3)_2$

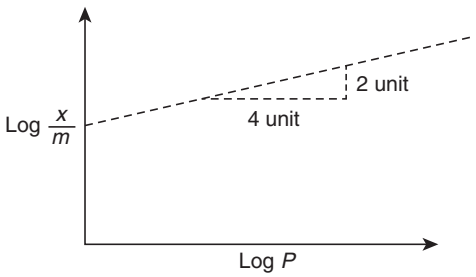
(3) $Ca(NO_3)_2$ (4) $Ba(NO_3)_2$

18. 20 mL of 0.1 M H_2SO_4 solution is added to 30 mL of 0.2 M NH_4OH solution. The pH of the resultant mixture is : [pK_b of NH_4OH = 4.7].

(1) 5.2 (2) 9.0

(3) 5.0 (4) 9.4

19. Adsorption of a gas follows Freundlich adsorption isotherm. In the given plot, x is the mass of the gas adsorbed on mass m of the adsorbent at pressure p. $\frac{x}{m}$ is proportional to:



(1) p^2 (2) $p^{1/4}$

(3) $p^{1/2}$ (4) p

20. Which amongst the following is the strongest acid?

(1) $CHBr_3$ (2) CHI_3

(3) $CH(CN)_3$ (4) $CHCl_3$

21. The ore that contains both iron and copper is:

(1) copper pyrites (2) malachite

(3) dolomite (4) azurite

22. For emission line of atomic hydrogen from $n_i = 8$ to $n_f = n$, the plot of wave number $(\bar{\nu})$ against $\left(\frac{1}{n^2}\right)$ will be (The Rydberg constant, R_H is in wave number unit)

(1) Linear with intercept – R_H

(2) Non linear

(3) Linear with slope R_H

(4) Linear with slope – R_H

23. The isotopes of hydrogen are:

(1) Tritium and protium only

(2) Protium and deuterium only

(3) Protium, deuterium and tritium

(4) Deuterium and tritium only

24. According to molecular orbital theory, which of the following is true with respect to Li_2^+ and Li_2^-?

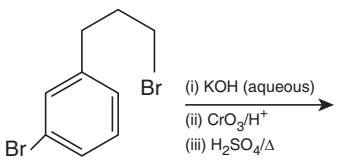
(1) Li_2^+ is unstable and Li_2^- is stable

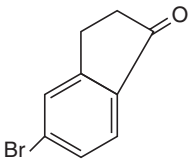
(2) Li_2^+ is stable and Li_2^- is unstable

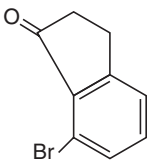
(3) Both are stable

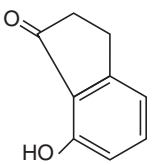
(4) Both are unstable

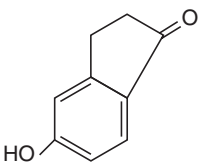
25. The major product of the following reaction is:



(1) 

(2) 

(3) 

(4) 

26. Aluminium is usually found in +3 oxidation state. In contrast, thallium exists in +1 and +3 oxidation states. This is due to:

(1) inert pair effect

(2) diagonal relationship

(3) lattice effect

(4) lanthanoid contraction

27. The increasing order of pK_a of the following amino acids in aqueous solution is:

Gly Asp Lys Arg

(1) Asp < Gly < Arg < Lys

(2) Gly < Asp < Arg < Lys

(3) Asp < Gly < Lys < Arg

(4) Arg < Lys < Gly < Asp

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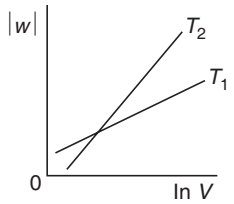
28. Consider the reversible isothermal expansion of an ideal gas in a closed system at two different temperatures T_1 and T_2 ($T_1 < T_2$). The correct graphical depiction of the dependence of work done (w) on the final volume (V) is:

(1)



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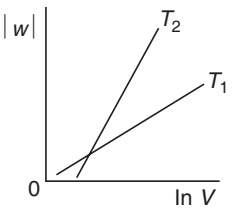

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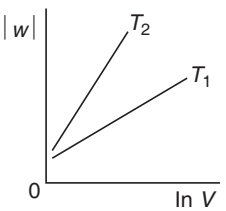

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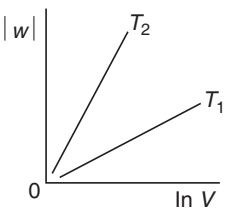
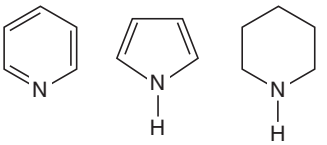


29. Arrange the following amines in the decreasing order of basicity:



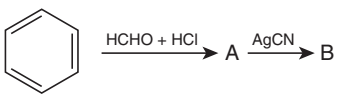
(1) I > II > III

(2) III > I > II

(3) III > II > I

(4) I > III > II

30. The compounds A and B in the following reaction are, respectively:



(1) A = Benzyl alcohol, B = Benzyl cyanide

(2) A = Benzyl chloride, B = Benzyl cyanide

(3) A = Benzyl alcohol, B = Benzyl isocyanide

(4) A = Benzyl chloride, B = Benzyl isocyanide

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JEE Main 2019 (January 9, Shift 2)

CHEMISTRY

1. The entropy change associated with the conversion of 1 kg of ice at 273 K to water vapours at 383 K is:

(Specific heat of water liquid and water vapour are 4.2 kJ K^{-1} kg^{-1} and 2.0 kJ K^{-1} kg^{-1}; heat of liquid fusion and vapourisation of water are 334 kJ kg^{-1} and 2491 kJ kg^{-1}, respectively). (log 273 = 2.436, log 373 = 2.572, log 383 = 2.583)

(1) 7.90 kJ kg^{-1} K^{-1} (2) 2.64 kJ kg^{-1} K^{-1}

(3) 8.49 kJ kg^{-1} K^{-1} (4) 9.26 kJ kg^{-1} K^{-1}

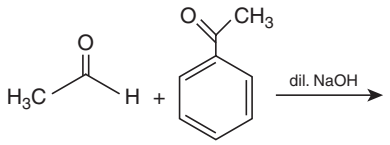
2. For the following reaction, the mass of water produced from 445 g of $C_{57}H_{110}O_6$ is:

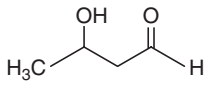
$$2C_{57}H_{110}O_6(s) + 163\ O_2(g) \rightarrow 114\ CO_2(g) + 110\ H_2O(l)$$

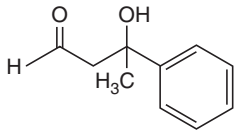
(1) 490 g (2) 445 g

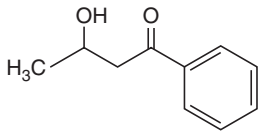
(3) 495 g (4) 890 g

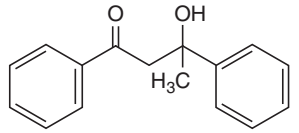
3. The major product formed in the following reaction is:



(1) 

(2) 

(3) 

(4) 

4. Which of the following conditions in drinking water causes methemoglobinemia?

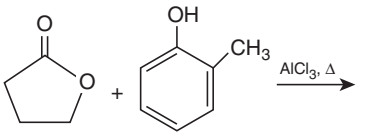
(1) >50 ppm of lead

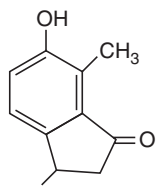
(2) >50 ppm of chloride

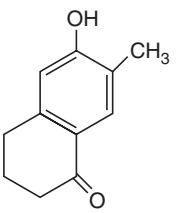
(3) >50 ppm of nitrate

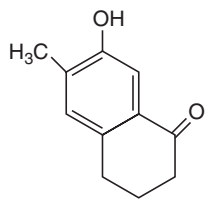
(4) >100 ppm of sulphate

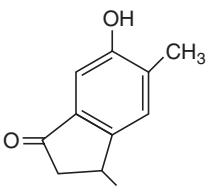
5. The major product of the following reaction is:



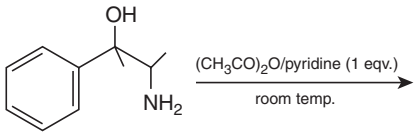
(1) 

(2) 

(3) 

(4) 

6. The major product obtained in the following reaction is:



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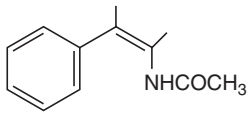
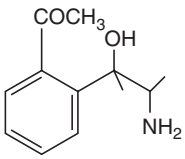
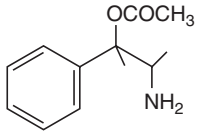
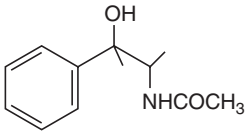
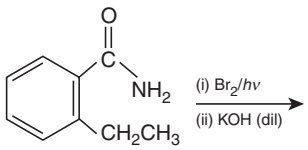
(1) 

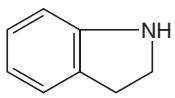
(2) 

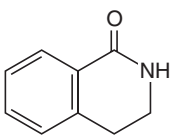
(3) 

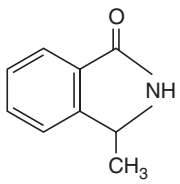
(4) 

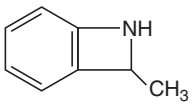
7. The major product of the following reaction is:



(1) 

(2) 

(3) 

(4) 

8. The correct match between Item I and Item II is:

Item I	Item II
(A) Benzaldehyde	(P) Mobile phase
(B) Alumina	(Q) Adsorbent
(C) Acetonitrile	(R) Adsorbate

(1) (A) → (Q); (B) → (P); (C) → (R)

(2) (A) → (R); (B) → (Q); (C) → (P)

(3) (A) → (Q); (B) → (R); (C) → (P)

(4) (A) → (P); (B) → (R); (C) → (Q)

9. The metal that forms nitride by reacting directly with N_2 of air, is:

(1) K (2) Li

(3) Rb (4) Cs

10. For coagulation of arsenious sulphide sol, which one of the following salt solution will be most effective?

(1) $BaCl_2$ (2) $AlCl_3$

(3) NaCl (4) Na_3PO_4

11. The complex that has highest crystal field splitting energy (Δ), is:

(1) $[Co(NH_3)_5(H_2O)]Cl_3$ (2) $K_2[CoCl_4]$

(3) $[Co(NH_3)_5Cl]Cl_2$ (4) $K_3[Co(CN)_6]$

12. The pH of rain water, is approximately:

(1) 5.6 (2) 7.5

(3) 7.0 (4) 6.5

13. Consider the following reversible chemical reactions:

$$A_2(g) + B_2(g) \overset{K_1}{\rightleftharpoons} 2AB(g) \quad ...(1)$$

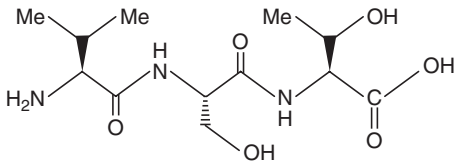
$$6AB(g) \overset{K_2}{\rightleftharpoons} 3A_2(g) + 3B_2(g) \quad ...(2)$$

The relation between K_1 and K_2 is:

(1) $K_1K_2 = \frac{1}{3}$ (2) $K_2 = K_1^3$

(3) $K_2 = K_1^{-3}$ (4) $K_1K_2 = 3$

14. The correct sequence of amino acids present in the tripeptide given below is:



(1) Val – Ser – Thr (2) Thr – Ser – Val

(3) Leu – Ser – Thr (4) Thr – Ser – Leu

15. For the reaction, 2A + B → products, when the concentrations of A and B both were doubled, the rate of the reaction increased from 0.3 mol L^{-1} s^{-1} to 2.4 mol L^{-1} s^{-1}. When the concentration of A alone is doubled, the rate increased from 0.3 mol L^{-1} s^{-1} to 0.6 mol L^{-1} s^{-1}.

Which one of the following statements is correct?

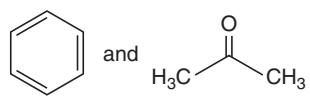
(1) Total order of the reaction is 4

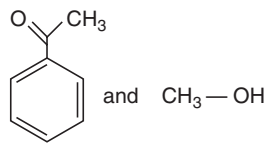
(2) Order of the reaction with respect to B is 2

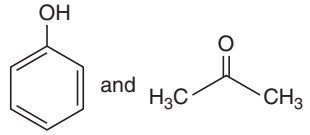
(3) Order of the reaction with respect to B is 1

(4) Order of the reaction with respect to A is 2

16. The products formed in the reaction of cumene with O_2 followed by treatment with dil. HCl are:

(1) 

(2) 

(3) 

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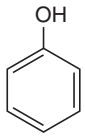
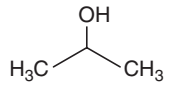
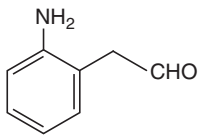
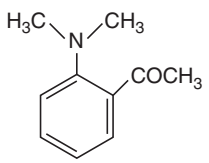
(4)  and 

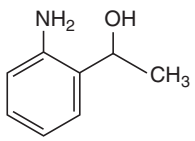
17. The tests performed on compound X and their inferences are:

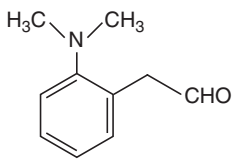
Test	Inference
(a) 2, 4-DNP test	Coloured precipitate
(b) Iodoform test	Yellow precipitate
(c) Azo-dye test	No dye formation

Compound 'X' is:

(1) 

(2) 

(3) 

(4) 

18. If the standard electrode potential for a cell is 2 V at 300 K, the equilibrium constant (K) for the reaction

$Zn(s) + Cu^{2+}(aq) \rightleftharpoons Zn^{2+}(aq) + Cu(s)$ at 300 K is approximately

(R = 8 JK^{-1} mol^{-1}, F = 96000 C mol^{-1})

(1) e^{-80} (2) e^{-160}

(3) e^{320} (4) e^{160}

19. The temporary hardness of water is due to:

(1) Na_2SO_4 (2) NaCl

(3) $Ca(HCO_3)_2$ (4) $CaCl_2$

20. In which of the following processes, the bond order has increased and paramagnetic character has charged to diamagnetic?

(1) $NO \rightarrow NO^+$ (2) $N_2 \rightarrow N_2^+$

(3) $O_2 \rightarrow O_2^+$ (4) $O_2 \rightarrow O_2^{2-}$

21. Which of the following combination of statements is true regarding the interpretation of the atomic orbitals?

(a) An electron in an orbital of high angular momentum stays away from the nucleus than an electron in the orbital of lower angular momentum.

(b) For a given value of the principal quantum number, the size of the orbit is inversely proportional to the azimuthal quantum number.

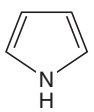
(c) According to wave mechanics, the ground state angular momentum is equal to $\frac{h}{2\pi}$.

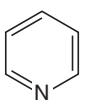
(d) The plot of ψ Vs r for various azimuthal quantum numbers, shows peak shifting towards higher r value.

(1) (a), (d) (2) (a), (b)

(3) (a), (c) (4) (b), (c)

22. Which of the following compounds is not aromatic?

(1)  (2) 

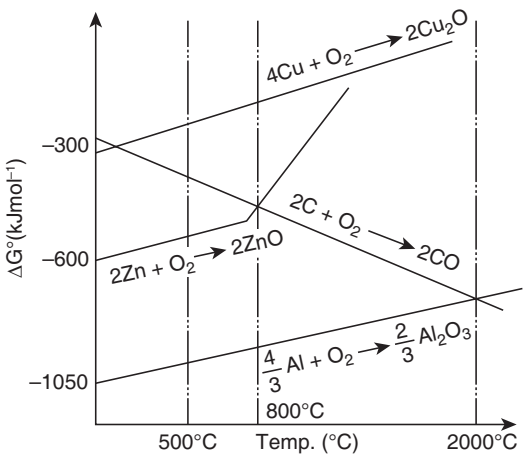
(3)  (4) 

23. Good reducing nature of H_3PO_2 is attributed to the presence of:

(1) Two P – OH bonds (2) One P – H bond

(3) Two P – H bonds (4) One P – OH bond

24. The correct statement regarding the given Ellingham diagram is:



(1) At 1400°C, Al can be used for the extraction of Zn from ZnO.

(2) At 500°C, coke can be used for the extraction of Zn from ZnO.

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(3) Coke cannot be used for the extraction of Cu from Cu_2O.

(4) At 800°C, Cu can be used for the extraction of Zn from ZnO.

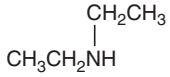
25. The transition element that has lowest enthalpy of atomization, is:

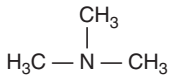
(1) Fe (2) Cu

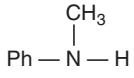
(3) V (4) Zn

26. The increasing basicity order of the following compounds is:

(A) $CH_3CH_2NH_2$

(B) 

(C) 

(D) 

(1) (D) < (C) < (B) < (A)

(2) (D) < (C) < (A) < (B)

(3) (A) < (B) < (C) < (D)

(4) (A) < (B) < (D) < (C)

27. When the first electron gain enthalpy ($\Delta_{eg}H$) of oxygen is −141 kJmol^{-1}, its second electron gain enthalpy is:

(1) a more negative value than the first

(2) almost the same as that of the first

(3) negative, but less negative than the first

(4) a positive value

28. At 100°C, copper (Cu) has FCC unit cell structure with cell edge length of x Å. What is the approximate density of Cu (in g cm^{-3}) at this temperature?

[Atomic Mass of Cu = 63.55 u]

(1) $\frac{205}{x^3}$ (2) $\frac{105}{x^3}$

(3) $\frac{211}{x^3}$ (4) $\frac{422}{x^3}$

29. A solution containing 62 g ethylene glycol in 250 g water is cooled to −10°C. If K_f for water is 1.86 K kg mol^{-1}, the amount of water (in g) separated as ice is:

(1) 48 (2) 32

(3) 64 (4) 16

30. Homoleptic octahedral complexes of a metal ion 'M^{3+}' with three monodentate ligands L_1, L_2 and L_3 absorb wavelengths in the region of green, blue and red respectively. The increasing order of the ligand strength is:

(1) $L_3 < L_1 < L_2$ (2) $L_3 < L_2 < L_1$

(3) $L_1 < L_2 < L_3$ (4) $L_2 < L_1 < L_3$

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JEE Main 2019 (January 10, Shift 1)

CHEMISTRY

1. The total number of isomers for a square planar complex [M(F)(Cl)(SCN)(NO_2)] is:

(1) 16 (2) 8

(3) 4 (4) 12

2. A process has $\Delta H = 200$ J mol^{-1} and $\Delta S = 40$ JK^{-1} mol^{-1}. Out of the values given below, choose the minimum temperature above which the process will be spontaneous:

(1) 20 K (2) 12 K

(3) 5 K (4) 4 K

3. The values of K_p/K_C for the following reactions at 300 K are, respectively : (At 300 K, $RT = 24.62$ dm^3 atm mol^{-1})

$$N_2(g) + O_2(g) \rightleftharpoons 2\,NO(g)$$

$$N_2O_4(g) \rightleftharpoons 2\,NO_2(g)$$

$$N_2(g) + 3H_2(g) \rightleftharpoons 2\,NH_3(g)$$

(1) 1, 24.62 dm^3 atm mol^{-1}, 606.0 dm^6 atm^2 mol^{-2}

(2) 1, 24.62 dm^3 atm mol^{-1}, 1.65×10^{-3} dm^{-6} atm^{-2} mol^2

(3) 1, 4.1×10^{-2} dm^{-3} atm^{-1} mol, 606 dm^6 atm^2 mol^{-2}

(4) 24.62 dm^3 atm mol^{-1}, 606.0 dm^6 atm^2 mol^{-2}, 1.65×10^{-3} dm^{-6} atm^{-2} mol^2

4. The total number of isotopes of hydrogen and number of radioactive isotopes among them, respectively, are:

(1) 3 and 1 (2) 3 and 2

(3) 2 and 1 (4) 2 and 0

5. Water filled in two glasses A and B have BOD values of 10 and 20, respectively. The correct statement regarding them, is:

(1) B is more polluted than A.

(2) A is suitable for drinking, whereas B is not.

(3) Both A and B are suitable for drinking.

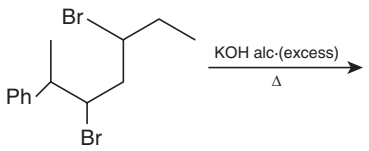
(4) A is more polluted than B.

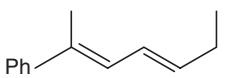
6. Which primitive unit cell has unequal edge lengths ($a \neq b \neq c$) and all axial angles different from 90°?

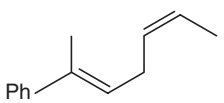
(1) Triclinic (2) Hexagonal

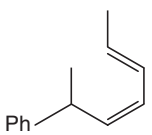
(3) Monoclinic (4) Tetragonal

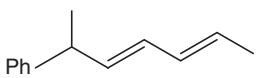
7. The major product of the following reaction is:



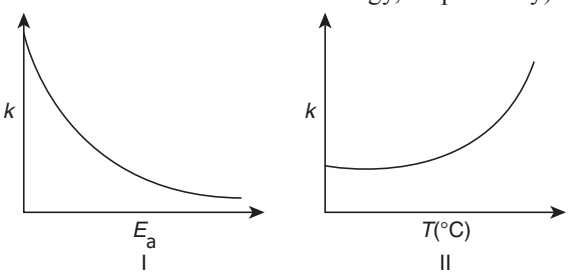
(1) 

(2) 

(3) 

(4) 

8. Consider the given plots for a reaction obeying Arrhenius equation (0°C < T < 300°C) : (k and E_a are rate constant and activation energy, respectively)



Choose the correct option:

(1) I is right but II is wrong

(2) Both I and II are correct

(3) I is wrong but II is right

(4) Both I and II are wrong

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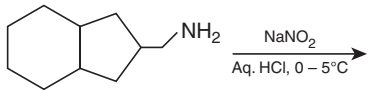
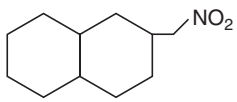
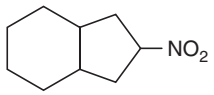
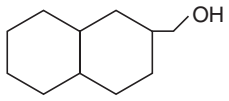
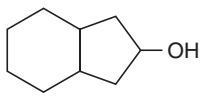
9. The major product formed in the reaction given below will be:



(1) 

(2) 

(3) 

(4) 

10. Wilkinson catalyst is:

(1) $[(Ph_3P)_3IrCl]$

(2) $[(Et_3P)_3RhCl]$

(3) $[(Ph_3P)_3RhCl]$ $(Et = C_2H_5)$

(4) $[(Et_3P)_3IrCl]$

11. If dichloromethane (DCM) and water (H_2O) are used for differential extraction, which one of the following statements is correct?

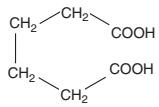
(1) DCM and H_2O would stay as lower and upper layer respectively in the S.F.

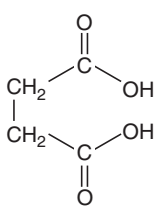
(2) DCM and H_2O will make turbid/colloidal mixture

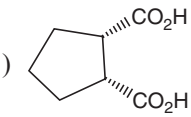
(3) DCM and H_2O would stay as upper and lower layer respectively in the separating funnel (S.F.)

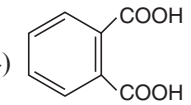
(4) DCM and H_2O will be miscible clearly

12. Which dicarboxylic acid in presence of a dehydrating agent is least reactive to give an anhydride?

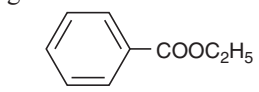
(1) 

(2) 

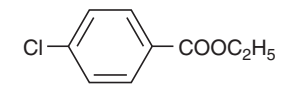
(3) 

(4) 

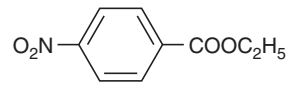
13. The decreasing order of ease of alkaline hydrolysis for the following esters is



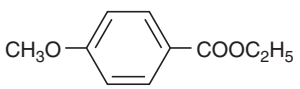
I



II



III

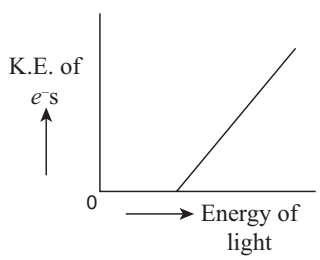


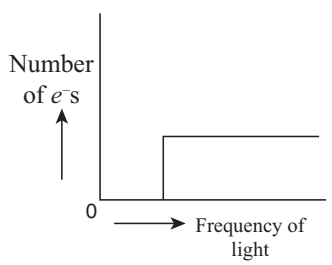
IV

(1) III > II > IV > I (2) III > II > I > IV

(3) IV > II > III > I (4) II > III > I > IV

14. Which of the graphs shown below does not represent the relationship between incident light and the electron ejected from metal surface?

(1) 

(2) 

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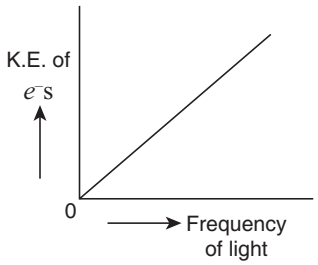
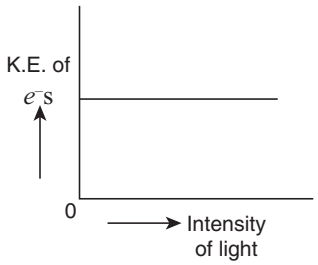
(3)



(4)



15. Which of the following is not an example of heterogeneous catalytic reaction?

(1) Ostwald's process

(2) Combustion of coal

(3) Hydrogenation of vegetable oils

(4) Haber's process

16. The effect of lanthanoid contraction in the lanthanoid series of elements by and large means:

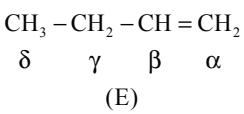
(1) increase in both atomic and ionic radii

(2) decrease in atomic radii and increase in ionic radii

(3) decrease in both atomic and ionic radii

(4) increase in atomic radii and decrease in ionic radii

17. Which hydrogen in compound (E) is easily replaceable during bromination reaction in presence of light?



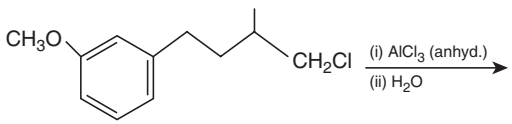
(1) α-hydrogen

(2) γ-hydrogen

(3) δ-hydrogen

(4) β-hydrogen

18. The major product of the following reaction is:



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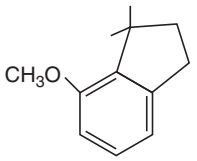

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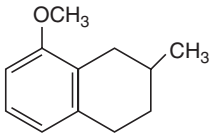

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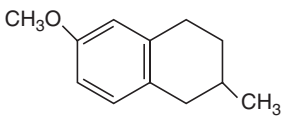

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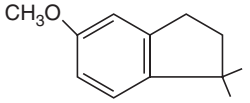
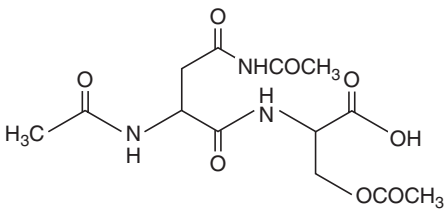


19. The correct structure of product 'P' in the following reaction is:



(1)



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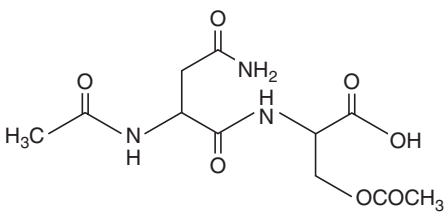

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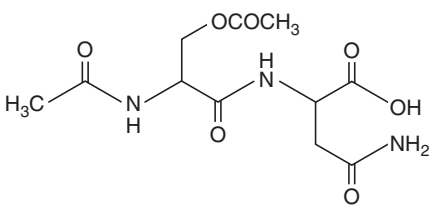

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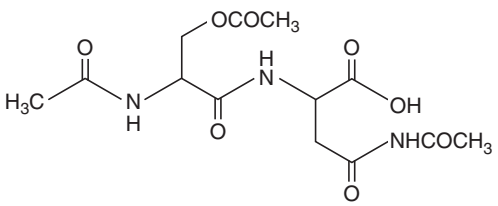

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20. The type of hybridisation and number of lone pair(s) of electrons of Xe in $XeOF_4$, respectively, are:

(1) sp^3d^2 and 1 (2) sp^3d and 2

(3) sp^3d^2 and 2 (4) sp^3d and 1

21. The electronegativity of aluminium is similar to:

(1) carbon (2) beryllium

(3) boron (4) lithium

22. Consider the following reduction processes:

$$Zn^{2+} + 2e^- \rightarrow Zn(s);\ E° = -0.76\ V$$
$$Ca^{2+} + 2e^- \rightarrow Ca(s);\ E° = -2.87\ V$$
$$Mg^{2+} + 2e^- \rightarrow Mg(s);\ E° = -2.36\ V$$
$$Ni^{2+} + 2e^- \rightarrow Ni(s);\ E° = -0.25\ V$$

The reducing power of the metals increases in the order:

(1) Ca < Zn < Mg < Ni

(2) Ni < Zn < Mg < Ca

(3) Zn < Mg < Ni < Ca

(4) Ca < Mg < Zn < Ni

23. The chemical nature of hydrogen peroxide is:

(1) Oxidising agent in acidic medium, but not in basic medium.

(2) Reducing agent in basic medium, but not in acidic medium.

(3) Oxidising and reducing agent in acidic medium, but not in basic medium.

(4) Oxidising and reducing agent in both acidic and basic medium.

24. A mixture of 100 m mol of $Ca(OH)_2$ and 2 g of sodium sulphate was dissolved in water and the volume was made up to 100 mL. The mass of calcium sulphate formed and the concentration of OH^- in resulting solution, respectively, are: (Molar mass of $Ca(OH)_2$, Na_2SO_4 and $CaSO_4$ are 74, 143 and 136 g mol^{-1}, respectively; K_{sp} of $Ca(OH)_2$ is 5.5×10^{-6})

(1) 1.9 g, 0.28 mol L^{-1} (2) 13.6 g, 0.28 mol L^{-1}

(3) 1.9 g, 0.14 mol L^{-1} (4) 13.6 g, 0.14 mol L^{-1}

25. Liquids A and B form an ideal solution in the entire composition range. At 350 K, the vapor pressures of pure A and B are 7×10^3 Pa and 12×10^3 Pa, respectively. The composition of the vapor in equilibrium with a solution containing 40 mol percent of A at this temperature is:

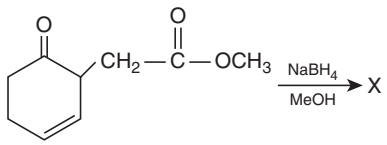
(1) $x_A = 0.37; x_B = 0.63$

(2) $x_A = 0.28; x_B = 0.72$

(3) $x_A = 0.4; x_B = 0.6$

(4) $x_A = 0.76; x_B = 0.24$

26. The major product 'X' formed in the following reaction is:



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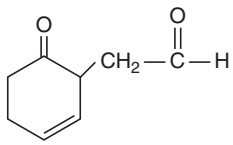

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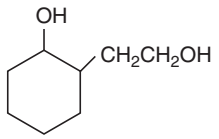

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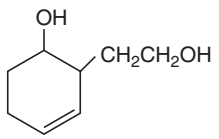

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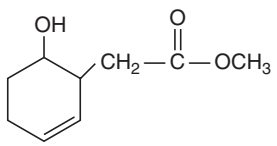
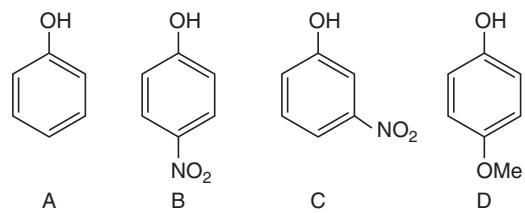


27. The metal used for making X-ray tube window is:

(1) Mg (2) Na

(3) Be (4) Ca

28. The increasing order of the pK_a values of the following compounds is:



(1) C < B < A < D (2) B < C < D < A

(3) D < A < C < B (4) B < C < A < D

29. Hall-Heroult's process is given by:

(1) $Cu^{2+}(aq) + H_2(g) \rightarrow Cu(s) + 2H^+(aq)$

(2) $Cr_2O_3 + 2\ Al \rightarrow Al_2O_3 + 2\ Cr$

(3) $2\ Al_2O_3 + 3\ C \rightarrow 4\ Al + 3\ CO_2$

(4) $ZnO + C \xrightarrow{\text{Coke, 1673 K}} Zn + CO$

30. Two π and half σ bonds are present in:

(1) O_2^+ (2) N_2

(3) O_2 (4) N_2^+

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JEE Main 2019 (January 10, Shift 2)

CHEMISTRY

1. The ground state energy of hydrogen atom is −13.6 eV. The energy of second excited state of He^+ ion in eV is:

(1) −54.4 (2) −3.4

(3) −6.04 (4) −27.2

2. Haemoglobin and gold sol are examples of:

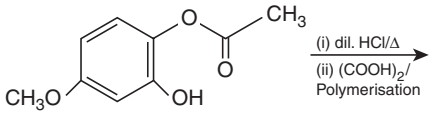
(1) positively and negatively charged sols, respectively

(2) positively charged sols

(3) negatively charged sols

(4) negatively and positively charged sols, respectively

3. The major product of the following reaction is:



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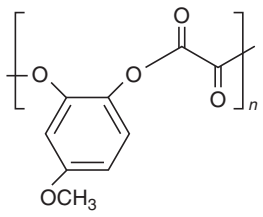

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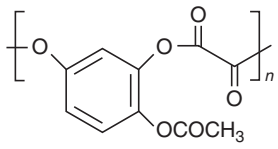

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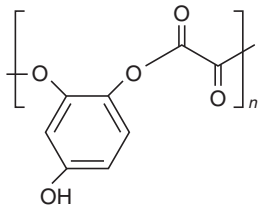

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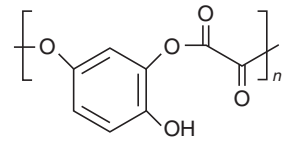

4. The amount of sugar ($C_{12}H_{22}O_{11}$) required to prepare 2 L of its 0.1 M aqueous solution is:

(1) 136.8 g (2) 17.1 g

(3) 68.4 g (4) 34.2 g

5. Among the following reactions of hydrogen with halogens, the one that requires a catalyst is:

(1) $H_2 + I_2 \rightarrow 2\,HI$ (2) $H_2 + Cl_2 \rightarrow 2\,HCl$

(3) $H_2 + Br_2 \rightarrow 2\,HBr$ (4) $H_2 + F_2 \rightarrow 2\,HF$

6. 5.1 g of NH_4SH is introduced in 3.0 L evacuated flask at 327°C. 30% of the solid NH_4SH decomposed to NH_3 and H_2S as gases. The K_p of the reaction at 327°C is (R = 0.082 L atm mol^{-1} K^{-1}, Molar mass of S = 32 g mol^{-1}, molar mass of N = 14 g mol^{-1})

(1) 0.242×10^{-4} atm^2 (2) 1×10^{-4} atm^2

(3) 4.9×10^{-3} atm^2 (4) 0.242 atm^2

7. The reaction that is **NOT** involved in the ozone layer depletion mechanism in the stratosphere is:

(1) $CF_2Cl_2(g) \xrightarrow{UV} \dot{C}l(g) + \dot{C}F_2Cl(g)$

(2) $Cl\dot{O}(g) + O(g) \rightarrow \dot{C}l(g) + O_2(g)$

(3) $CH_4 + 2\,O_3 \rightarrow 3\,CH_2 = O + 3\,H_2O$

(4) $HOCl(g) \xrightarrow{h\nu} \dot{O}H(g) + \dot{C}l(g)$

8. In the cell $Pt(s)|H_2(g, 1\,bar)|HCl(aq)|AgCl(s)|Ag(s)|Pt(s)$ the cell potential is 0.92 V when a 10^{-6} molal HCl solution is used. The standard electrode potential of ($AgCl/Ag, Cl^-$) electrode is:

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$$\left\{\text{Given, } \frac{2.303RT}{F} = 0.06 \text{ V at } 298 \text{ K}\right\}$$

(1) 0.94 V (2) 0.76 V

(3) 0.40 V (4) 0.20 V

9. The 71st electron of an element X with an atomic number of 71 enters into the orbital:

(1) $6p$ (2) $4f$

(3) $5d$ (4) $6s$

10. The correct match between item 'I' and item 'II' is

Item 'I' (compound)	**Item 'II'** (reagent)
(A) Lysine	(P) 1-naphthol
(B) Furfural	(Q) ninhydrin
(C) Benzyl alcohol	(R) $KMnO_4$
(D) Styrene	(S) Ceric ammonium nitrate

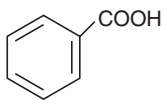
(1) (A) → (Q); (B) → (P); (C) → (S); (D) → (R)

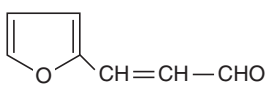
(2) (A) → (Q); (B) → (P); (C) → (R); (D) → (S)

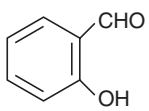
(3) (A) → (R); (B) → (P); (C) → (Q); (D) → (S)

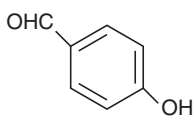
(4) (A) → (Q); (B) → (R); (C) → (S); (D) → (P)

11. An aromatic compound 'A' having molecular formula $C_7H_6O_2$ on treating with aqueous ammonia and heating forms compound 'B'. The compound 'B' on reaction with molecular bromine and potassium hydroxide provides compound 'C' having molecular formula C_6H_7N. The structure of 'A' is:

(1) 

(2) 

(3) 

(4) 

12. The process with negative entropy change is:

(1) Dissociation of $CaSO_4(s)$ to $CaO(s)$ and $SO_3(g)$

(2) Sublimation of dry ice

(3) Dissolution of iodine in water

(4) Synthesis of ammonia from N_2 and H_2

13. An ideal gas undergoes isothermal compression from 5 m^3 to 1 m^3 against a constant external pressure of 4 Nm^{-2}. Heat released in this process is used to increase the temperature of 1 mole of Al. If molar heat capacity of Al is 24 J mol^{-1} K^{-1}, the temperature of Al increases by:

(1) $\frac{3}{2}$K (2) 2 K

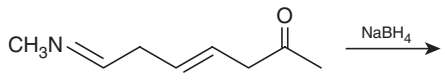
(3) $\frac{2}{3}$K (4) 1 K

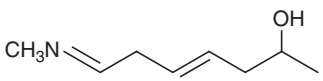
14. Elevation in the boiling point for 1 molal solution of glucose is 2 K. The depression in the freezing point for 2 molal solution of glucose in the same solvent is 2 K. The relation between K_b and K_f is:

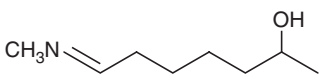
(1) $K_b = 1.5\ K_f$ (2) $K_b = K_f$

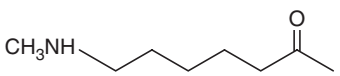
(3) $K_b = 0.5\ K_f$ (4) $K_b = 2\ K_f$

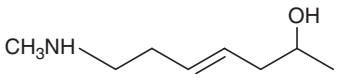
15. The major product of the following reaction is:



(1) 

(2) 

(3) 

(4) 

16. Sodium metal on dissolution in liquid ammonia gives a deep blue solution due to the formation of:

(1) sodium-ammonia complex

(2) sodamide

(3) sodium ion-ammonia complex

(4) ammoniated electrons

17. For an elementary chemical reaction, $A_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2A$, the expression for $\frac{d[A]}{dt}$ is:

(1) $k_1[A_2] - k_{-1}[A]^2$ (2) $2k_1[A_2] - k_{-1}[A]^2$

(3) $k_1[A_2] + k_{-1}[A]^2$ (4) $2k_1[A_2] - 2k_{-1}[A]^2$

18. Which of the following tests cannot be used for identifying amino acids?

(1) Biuret test (2) Barfoed test

(3) Ninhydrin test (4) Xanthoproteic test

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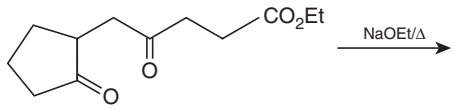
19. The difference in the number of unpaired electrons of a metal ion in its high-spin and low-spin octahedral complexes is two. The metal ion is:

(1) Ni^{2+} (2) Fe^{2+}

(3) Co^{2+} (4) Mn^{2+}

20. The major product obtained in the following reaction is:



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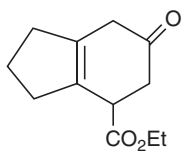

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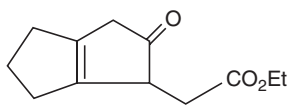

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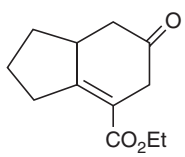

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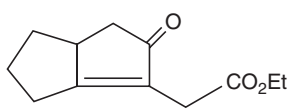
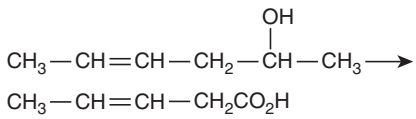


21. The pair that contains two P – H bonds in each of the oxoacids is:

(1) $H_4P_2O_5$ and $H_4P_2O_6$ (2) H_3PO_2 and $H_4P_2O_5$

(3) H_3PO_3 and H_3PO_2 (4) $H_4P_2O_5$ and H_3PO_3

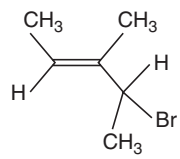
22. Which is the most suitable reagent for the following transformation?



(1) Tollens' reagent (2) I_2/NaOH

(3) CrO_2Cl_2/CS_2 (4) alkaline $KMnO_4$

23. What is the IUPAC name of the following compound?



(1) 3-Bromo-1, 2-dimethylbut-1-ene

(2) 3-Bromo-3-methyl-1, 2-dimethylprop-1-ene

(3) 2-Bromo-3-methylpent-3-ene

(4) 4-Bromo-3-methylpent-2-ene

24. The number of 2-centre-2-electron and 3-centre-2-electron bonds in B_2H_6, respectively, are:

(1) 2 and 1 (2) 4 and 2

(3) 2 and 2 (4) 2 and 4

25. In the reaction of oxalate with permanganate in acidic medium, the number of electrons involved in producing one molecule of CO_2 is:

(1) 1 (2) 10

(3) 2 (4) 5

26. A reaction of cobalt(III) chloride and ethylenediamine in a 1 : 2 mole ratio generates two isomeric products A (violet coloured) and B (green coloured). A can show optical activity, but, B is optically inactive. What type of isomers does A and B represent?

(1) Geometrical isomers (2) Coordination isomers

(3) Linkage isomers (4) Ionisation isomers

27. The electrolytes usually used in the electroplating of gold and silver, respectively, are:

(1) $[Au(CN)_2]^-$ and $[Ag(CN)_2]^-$

(2) $[Au(CN)_2]^-$ and $[AgCl_2]^-$

(3) $[Au(OH)_4]^-$ and $[Ag(OH)_2]^-$

(4) $[Au(NH_3)_2]^+$ and $[Ag(CN)_2]^-$

28. A compound of formula A_2B_3 has the hcp lattice. Which atom forms the hcp lattice and what fraction of tetrahedral voids is occupied by the other atoms:

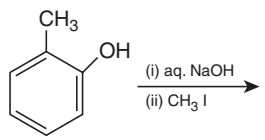
(1) hcp lattice – A, $\frac{2}{3}$ tetrahedral voids – B

(2) hcp lattice – A, $\frac{1}{3}$ tetrahedral voids – B

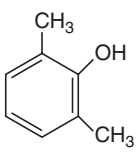
(3) hcp lattice – B, $\frac{2}{3}$ tetrahedral voids – A

(4) hcp lattice – B, $\frac{1}{3}$ tetrahedral voids – A

29. The major product of the following reaction is:



(1)



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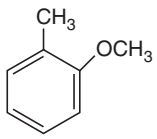
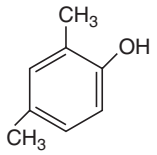
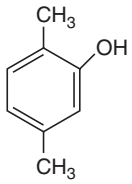
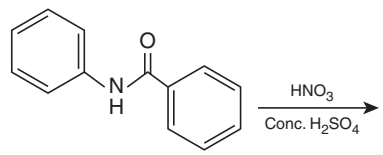
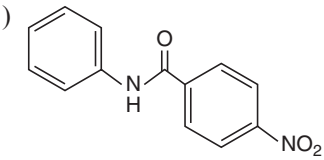
(2) 

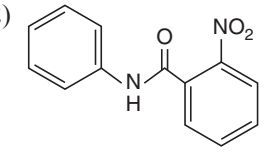
(3) 

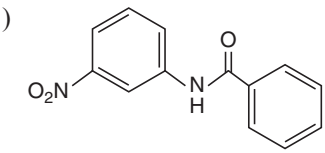
(4) 

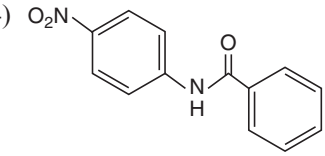
30. What will be the major product in the following mononitration reaction?



(1) 

(2) 

(3) 

(4) 

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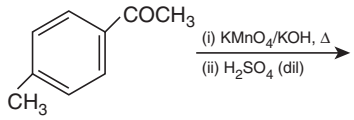
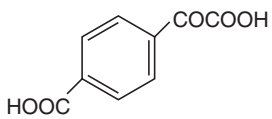
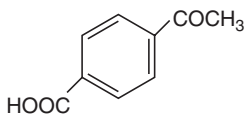
JEE Main 2019 (January 11, Shift 1)

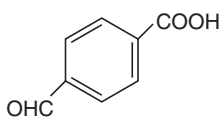
CHEMISTRY

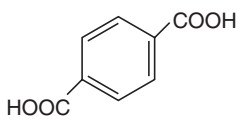
1. The major product of the following reaction is



(1) 

(2) 

(3) 

(4) 

2. The **correct** statements among (a) to (d) regarding H_2 as a fuel are:

(a) It produces less pollutants than petrol.

(b) A cylinder of compressed dihydrogen weighs ~30 times more than a petrol tank producing the same amount of energy.

(c) Dihydrogen is stored in tanks of metal alloys like $NaNi_5$.

(d) On combustion, values of energy released per gram of liquid dihydrogen and LPG are 50 and 142 kJ, respectively.

(1) (a) and (c) only (2) (b) and (d) only

(3) (b), (c) and (d) only (4) (a), (b) and (c) only

3. An organic compound is estimated through Dumus method and was found to evolve 6 moles of CO_2, 4 moles of H_2O and 1 mole of nitrogen gas. The formula of the compound is:

(1) $C_{12}H_8N_2$ (2) $C_{12}H_gN$

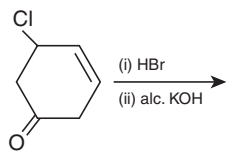
(3) $C_6H_8N_2$ (4) C_6H_8N

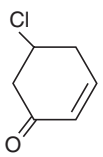
4. An example of solid sol is:

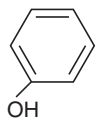
(1) butter (2) paint

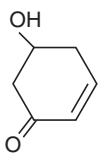
(3) hair cream (4) gem stones

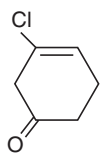
5. The major product of the following reaction is:



(1) 

(2) 

(3) 

(4) 

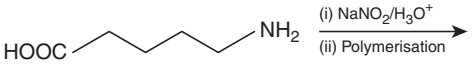
6. Heat treatment of muscular pain involves radiation of wavelength of about 900 nm. Which spectral line of H-atom is suitable for this purpose ?

[$R_H = 1 \times 10^5\ cm^{-1}$, $h = 6.6 \times 10^{-34}$ Js, $c = 3 \times 10^8\ ms^{-1}$]

(1) Balmer, $\infty \rightarrow 2$ (2) Paschen, $5 \rightarrow 3$

(3) Lyman, $\infty \rightarrow 1$ (4) Paschen, $\infty \rightarrow 3$

7. The polymer obtained from the following reactions is:



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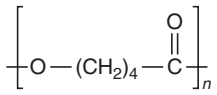
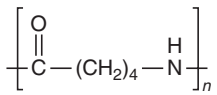
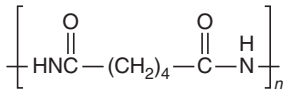
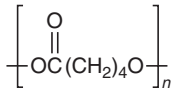
(1) 

(2) 

(3) 

(4) 

8. NaH is an example of:

(1) saline hydride

(2) metallic hydride

(3) molecular hydride

(4) electron-rich hydride

9. Consider the reaction

$$N_2(g) + 3H_2(g) \rightleftharpoons 2NH_3(g)$$

The equilibrium constant of the above reaction is K_p. If pure ammonia is left to dissociate, the partial pressure of ammonia at equilibrium is given by (Assume that $p_{NH_3} << p_{total}$ at equilibrium)

(1) $\frac{3^{3/2} K_p^{1/2} p^2}{4}$ (2) $\frac{3^{3/2} K_p^{1/2} p^2}{16}$

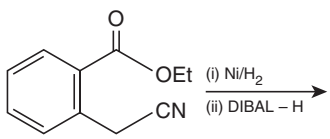
(3) $\frac{K_p^{1/2} p^2}{4}$ (4) $\frac{K_p^{1/2} p^2}{16}$

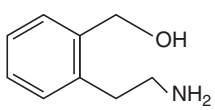
10. The chloride that CANNOT get hydrolysed is:

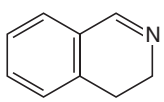
(1) CCl_4 (2) $PbCl_4$

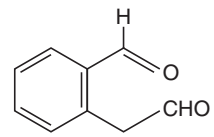
(3) $SnCl_4$ (4) $SiCl_4$

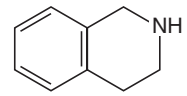
11. The major product of the following reaction is:



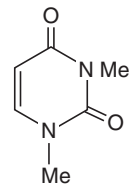
(1) 

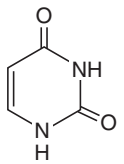
(2) 

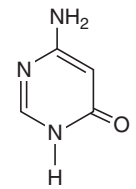
(3) 

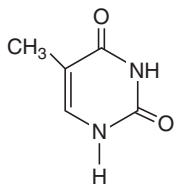
(4) 

12. Among the following compounds, which one is found in RNA?

(1) 

(2) 

(3) 

(4) 

13. Peroxyacetyl nitrate (PAN), an eye irritant is produced by:

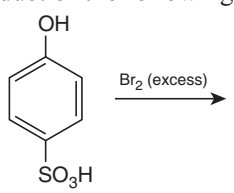
(1) photochemical smog

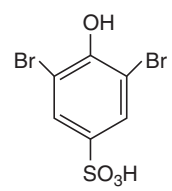
(2) organic waste

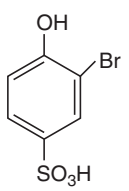
(3) acid rain

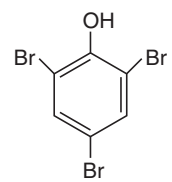
(4) classical smog

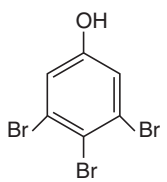
14. The major product of the following reaction is:



(1) 

(2) 

(3) 

(4) 

15. If a reaction follows the Arrhenius equation, the plot ln$k$ vs $1/(RT)$ gives straight line with a gradient $(-y)$ unit. The energy required to activate the reactant is:

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(1) y unit (2) y/R unit

(3) $-y$ unit (4) yR unit

16. The correct match between item (I) and item (II) is:

Item - I	**Item - II**
(A) Norethindrone	(P) Anti-biotic
(B) Ofloxacin	(Q) Anti-fertility
(C) Equanil	(R) Hypertension
	(S) Analgesics

(1) (A) → (R); (B) → (P); (C) → (S)

(2) (A) → (Q); (B) → (P); (C) → (R)

(3) (A) → (Q); (B) → (R); (C) → (S)

(4) (A) → (R); (B) → (P); (C) → (R)

17. For the chemical reaction $X \rightleftharpoons Y$, the standard reaction Gibbs energy depends on temperature T (in K) as

$$\Delta_r G^\circ \text{ (in kJ mol}^{-1}) = 120 - \frac{3}{8}T.$$

The major component of the reaction mixture at T is:

(1) Y if $T = 300$ K (2) Y if $T = 280$ K

(3) X if $T = 315$ K (4) X if $T = 350$ K

18. The element that usually does NOT show variable oxidation states is:

(1) Sc (2) V

(3) Ti (4) Cu

19. Match the ores (List I) with the metals (List II):

(List I)	**(List II)**
Ores	**Metals**
(A) Siderite	(P) Zinc
(B) Kaolinite	(Q) Copper
(C) Malachite	(R) Iron
(D) Calamine	(S) Aluminium

(1) (A) → (R); (B) → (S); (C) → (P); (D) → (Q)

(2) (A) → (P); (B) → (Q); (C) → (R); (D) → (S)

(3) (A) → (Q); (B) → (R); (C) → (S); (D) → (P)

(4) (A) → (R); (B) → (S); (C) → (Q); (D) → (P)

20. The correct match between items I and II is:

Item - I	**Item - II**
(Mixture)	**(Seperation method)**
(A) H_2O: Sugar	(P) Sublimation
(B) H_2O: Aniline	(Q) Recrystallization
(C) H_2O: Toluene	(R) Steam distillation
	(S) Differential extraction

(1) (A) → (R); (B) → (P); (C) → (S)

(2) (A) → (Q); (B) → (R); (C) → (S)

(3) (A) → (S); (B) → (R); (C) → (P)

(4) (A) → (Q); (B) → (R); (C) → (P)

21. The freezing point of a diluted milk sample is found to be −0.2°C, while it should have been −0.5° C for pure milk. How much water has been added to pure milk to make the diluted sample?

(1) 1 cup of water to 2 cups of pure milk

(2) 2 cups of water to 3 cups of pure milk

(3) 3 cups of water to 2cups of pure milk

(4) 1 cup of water to 3 cups of pure milk

22. For the cell $Zn(s)|Zn^{2+}(aq)||M^{x+}(aq)|M(s)$, different half cells and their standard electrode potentials are given below:

M^{x+} (aq)/ M(s)	Au^{3+} (aq)/ Au(s)	Ag^{+} (aq)/ Ag(s)	Fe^{3+} (aq)/ Fe^{2+} (aq)	Fe^{2+} (aq)/ Fe(s)
$E^\circ_{M^{x+}/M}$/(V)	1.40	0.80	0.77	−0.44

If $E^\circ_{Zn^{2+}/Zn} = -0.76$ V, which cathode will give a maximum value of E°_{cell} per electron transferred?

(1) Ag^+/Ag (2) Au^{3+}/Au

(3) Fe^{3+}/Fe^{2+} (4) Fe^{2+}/Fe

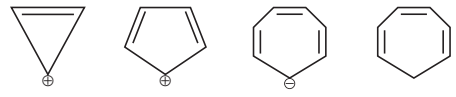
23. A 10 mg effervescent tablet containing sodium bicarbonate and oxalic acid releases 0.25 mL of CO_2 at $T = 298.15$ K and $p = 1$ bar. If molar volume of CO_2 is 25.0 L under such condition, what is the percentage of sodium bicarbonate in each tablet?

[Molar mass of $NaHCO_3$ = 84 g mol^{-1}]

(1) 33.6 (2) 8.4

(3) 16.8 (4) 0.84

24. Which compound (s) out of the following is/are not aromatic?



(A) (B) (C) (D)

(1) (A) and (C) (2) (B), (C) and (D)

(3) (C) and (D) (4) (B)

25. The correct order of the atomic radii of C, Cs, Al, and S is:

(1) C < S < Cs < Al

(2) S < C < Al < Cs

(3) C < S < Al < Cs

(4) S < C < Cs < Al

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26. Match the metals (List I) with the coordination compound(s)/enzyme(s) (List II):

(List I) **Metals**	**(List II)** **Coordination Compound(s)/Enzyme(s)**
(A) Co	(P) Wilkinson catalyst
(B) Zn	(Q) Chlorophyll
(C) Rh	(R) Vitamin B_{12}
(D) Mg	(S) Carbonic anhydrase

(1) (A) → (R); (B) → (S); (C) → (P); (D) → (Q)

(2) (A) → (Q); (B) → (P); (C) → (S); (D) → (R)

(3) (A) → (P); (B) → (Q); (C) → (R); (D) → (S)

(4) (A) → (S); (B) → (R); (C) → (P); (D) → (Q)

27. Two blocks of the same metal having same mass and at temperature T_1 and T_2, respectively, are brought in contact with each other and allowed to attain thermal equilibrium at constant pressure. The change in entropy, ΔS, for this process is:

(1) $2C_p \ln\left[\frac{(T_1+T_2)^{\frac{1}{2}}}{T_1T_2}\right]$ (2) $C_p \ln\left[\frac{(T_1+T_2)^2}{4T_1T_2}\right]$

(3) $2C_p \ln\left[\frac{T_1+T_2}{2T_1T_2}\right]$ (4) $2C_p \ln\left[\frac{T_1+T_2}{4T_1T_2}\right]$

28. The amphoteric hydroxide is:

(1) $Sr(OH)_2$ (2) $Mg(OH)_2$

(3) $Ca(OH)_2$ (4) $Be(OH)_2$

29. A solid having density of 9×10^3 kg m^{-3} forms face centred cubic crystals of edge length $200\sqrt{2}$ pm. What is the molar mass of the solid?

[Avogadro constant $\cong 6 \times 10^{23}$ mol^{-1}, $\pi = 3$]

(1) 0.0432 kg mol^{-1} (2) 0.0305 kg mol^{-1}

(3) 0.0216 kg mol^{-1} (4) 0.4320 kg mol^{-1}

30. The concentration of dissolved oxygen (DO) in cold water can go upto:

(1) 10 ppm (2) 8 ppm

(3) 14 ppm (4) 16 ppm

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JEE Main 2019 (January 11, Shift 2)

CHEMISTRY

1. The reaction, MgO(s) + C(s)→Mg(s) + CO(g), for which $\Delta_r H° = +491.1$ kJ mol^{-1} and $\Delta_r S° = 198.0$ JK^{-1} mol^{-1}, is not feasible at 298 K. Temperature above which reaction will be feasible is:

(1) 2040.5 K (2) 1890.0 K

(3) 2480.3 K (4) 2380.5 K

2. The **correct** match between Item I and Item II is:

Item I	Item II
(A) Allosteric effect	(P) Molecule binding to the active site of enzyme
(B) Competitive inhibitor	(Q) Molecule crucial for communication in the body
(C) Receptor	(R) Molecule binding to a site other than the active site of enzyme
(D) Poison	(S) Molecule binding to the enzyme covalently

(1) (A) →(R); (B) → (P); (C) → (Q); (D) → (S)

(2) (A) → (P); (B) → (R); (C) → (Q); (D) → (S)

(3) (A) → (R); (B) → (P); (C) → (S); (D) → (Q)

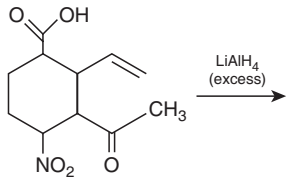
(4) (A) → (P); (B) → (R); (C) → (S); (D) → (Q)

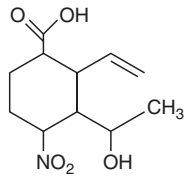
3. The coordination number of Th in $K_4[Th(C_2O_4)_4(OH_2)_2]$ is: $\left(C_2O_4^{2-} = \text{Oxalato}\right)$

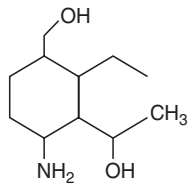
(1) 14 (2) 6

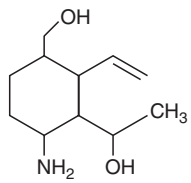
(3) 8 (4) 10

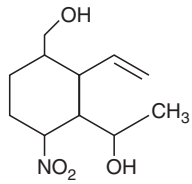
4. The major product obtained in the following reaction is:



(1) 

(2) 

(3) 

(4) 

5. The standard reaction Gibbs energy for a chemical reaction at an absolute temperature T is given by $\Delta_r G° = A - BT$

Where A and B are non-zero constants. Which of the following is **TRUE** about this reaction?

(1) Endothermic if A > 0

(2) Exothermic if A > 0 and B < 0

(3) Endothermic if A < 0 and B > 0

(4) Exothermic if B < 0

6. The radius of the largest sphere which fits properly at the centre of the edge of a body centred cubic unit cell is: (Edge length is represented by '*a*')

(1) 0.027 *a* (2) 0.047 *a*

(3) 0.134 *a* (4) 0.067 *a*

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7. The hydride that is NOT electron deficient is:

(1) SiH_4 (2) B_2H_6

(3) GaH_3 (4) AlH_3

8. Given the equilibrium constant: K_C of the reaction:

$Cu(s) + 2Ag^+(aq) \rightarrow Cu^{2+}(aq) + 2Ag(s)$ is

10×10^{15}, calculate the E°_{cell} of this reaction at 298 K

$\left[2.303\frac{RT}{F} \text{ at } 298\text{ K} = 0.059\text{ V}\right]$

(1) 0.04736 mV (2) 0.4736 mV

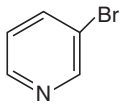
(3) 0.4736 V (4) 0.04736 V

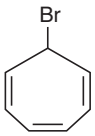
9. The correct option with respect to the Pauling electronegativity values of the elements is:

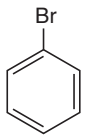
(1) Te > Se (2) Ga < Ge

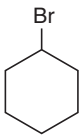
(3) Si < Al (4) P > S

10. Which of the following compounds will produce a precipitate with $AgNO_3$?

(1) 

(2) 

(3) 

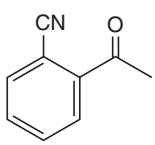
(4) 

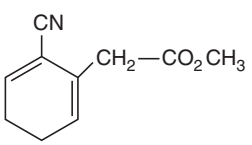
11. The de Broglie wavelength (λ) associated with a photoelectron varies with the frequency (ν) of the incident radiation as, [ν_0 is threshold frequency]:

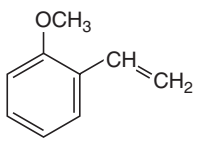
(1) $\lambda \propto \frac{1}{(\nu - \nu_0)}$ (2) $\lambda \propto \frac{1}{(\nu - \nu_0)^{\frac{1}{4}}}$

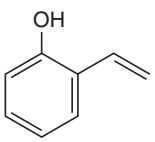
(3) $\lambda \propto \frac{1}{(\nu - \nu_0)^{\frac{3}{2}}}$ (4) $\lambda \propto \frac{1}{(\nu - \nu_0)^{\frac{1}{2}}}$

12. Which of the following compounds reacts with ethylmagnesium bromide and also decolourizes bromine water solution:

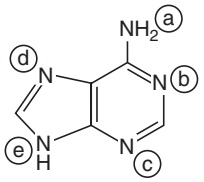
(1) 

(2) 

(3) 

(4) 

13. In the following compound,



the favourable site/s for protonation is/are:

(1) (a) and (e) (2) (b), (c) and (d)

(3) (a) and (d) (4) (a)

14. Taj Mahal is being slowly disfigured and discoloured. This is primarily due to:

(1) global warming (2) acid rain

(3) water pollution (4) soil pollution

15. The relative stability of + 1 oxidation state of Group 13 elements follows the order:

(1) Al < Ga < Tl < In (2) Tl < In < Ga < Al

(3) Ga < Al < In < Tl (4) Al < Ga < In < Tl

16. For the equilibrium, $2H_2O \rightleftharpoons H_3O^+ + OH^-$, the value of ΔG° at 298 K is approximately:

(1) 100 kJ mol^{-1} (2) −80 kJ mol^{-1}

(3) 80 kJ mol^{-1} (4) −100 kJ mol^{-1}

17. The reaction that does NOT define calcination is:

(1) $Fe_2O_3 \cdot XH_2O \xrightarrow{\Delta} Fe_2O_3 + XH_2O$

(2) $2Cu_2S + 3O_2 \xrightarrow{\Delta} 2Cu_2O + 2SO_2$

(3) $ZnCO_3 \xrightarrow{\Delta} ZnO + CO_2$

(4) $CaCO_3 \cdot MgCO_3 \xrightarrow{\Delta} CaO + MgO + 2CO_2$

18. A compound 'X' on treatment with Br_2/NaOH, provided C_3H_9N, which gives positive carbylamine test. Compound 'X' is:

(1) $CH_3COCH_2NHCH_3$ (2) $CH_3CH_2COCH_2NH_2$

(3) $CH_3CH_2CH_2CONH_2$ (4) $CH_3CON(CH_3)_2$

19. Among the colloids cheese (C), milk (M) and smoke (S), the correct combination of the dispersed phase and dispersion medium, respectively is:

(1) C: liquid in solid; M: liquid in solid; S: solid in gas

(2) C: liquid in solid; M: liquid in liquid; S: solid in gas

(3) C: solid in liquid; M: liquid in liquid; S: gas in solid

(4) C: solid in liquid; M: solid in liquid; S: solid in gas

20. The homopolymer formed from 4-hydroxy-butanoic acid is:

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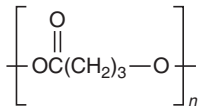
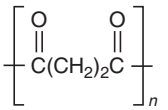
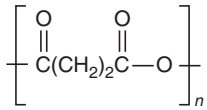
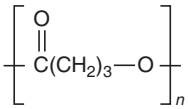
(1) 
(2) 
(3) 
(4) 

21. K_2HgI_4 is 40% ionised in aqueous solution. The value of its van't Hoff factor (i) is:

(1) 1.6 (2) 1.8

(3) 2.0 (4) 2.2

22. 25 mL of the given HCl solution requires 30 mL of 0.1 M sodium carbonate solution. What is the volume of this HCl solution required to titrate 30 mL of 0.2 M aqueous NaOH solution ?

(1) 25 mL (2) 75 mL

(3) 50 mL (4) 12.5 mL

23. The reaction 2X → B is a zeroth order reaction. If the initial concentration of X is 0.2 M, the half-life is 6 h. When the initial concentration of X is 0.5 M, the time required to reach its final concentration of 0.2 M will be:

(1) 9.0 h (2) 12.0 h

(3) 18.0 h (4) 7.2 h

24. Match the following items in List I with the corresponding items in List II.

List I	**List II**
(A) $Na_2CO_3 \cdot 10\ H_2O$	(P) Portland cement ingredient
(B) $Mg(HCO_3)_2$	(Q) Castner-Kellner process
(C) NaOH	(R) Solvay process
(D) $Ca_3Al_2O_6$	(S) Temporary hardness

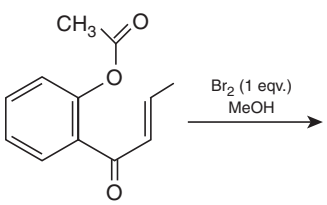
(1) (A) → (Q); (B) → (R); (C) → (P); (D) → (S)

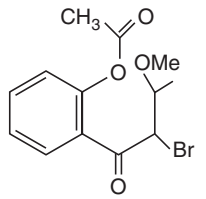
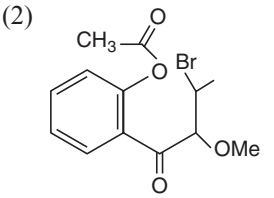
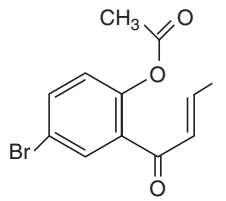
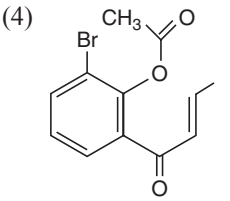
(2) (A) → (R); (B) → (Q); (C) → (S); (D) → (P)

(3) (A) → (S); (B) → (P); (C) → (Q); (D) → (R)

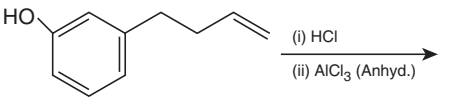
(4) (A) → (R); (B) → (S); (C) → (Q); (D) → (P)

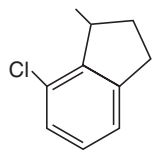
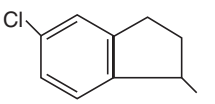
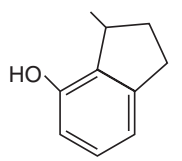
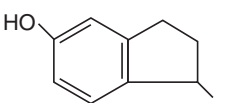
25. The major product obtained in the following conversion is:



(1) 
(2) 
(3) 
(4) 

26. Major product of the following reaction is:



(1) 
(2) 
(3) 
(4) 

27. The higher concentration of which gas in air can cause stiffness of flower buds?

(1) NO_2 (2) CO_2

(3) SO_2 (4) CO

28. The correct match between Item I and Item II is:

Item I	**Item II**
(A) Ester test	(P) Tyr
(B) Carbylamine test	(Q) Asp
(C) Phthalein dye test	(R) Ser
	(S) Lys

(1) (A) → (Q); (B) → (S); (C) → (P)

(2) (A) → (R); (B) → (Q); (C) → (P)

(3) (A) → (R); (B) → (S); (C) → (Q)

(4) (A) → (Q); (B) → (S); (C) → (R)

29. The number of bridging CO ligand(s) and Co-Co bond(s) in $Co_2(CO)_8$, respectively are:

(1) 2 and 1 (2) 2 and 0

(3) 0 and 2 (4) 4 and 0

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30. $\underline{A} \xrightarrow{4KOH,\ O_2} 2\underline{B} + 2H_2O$ (Green)

$3\underline{B} \xrightarrow{4HCl} 2\underline{C} + MnO_2 + 2H_2O$ (Purple)

$2\underline{C} \xrightarrow{H_2O,\ KI} 2\underline{A} + 2\ KOH + \underline{D}$

In the above sequence of reactions, $\underline{A}$ and $\underline{D}$, respectively, are:

(1) KI and $KMnO_4$

(2) MnO_2 and KIO_3

(3) KIO_3 and MnO_2

(4) KI and K_2MnO_4

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JEE Main 2019 (January 12, Shift 1)

CHEMISTRY

1. In the Hall-Heroult process, aluminium is formed at the cathode. The cathode is made out of:

(1) Pure aluminium (2) Carbon

(3) Copper (4) Platinum

2. The correct order for acid strength of compounds $CH \equiv CH$, $CH_3 - C \equiv CH$ and $CH_2 = CH_2$ is as follows:

(1) $CH \equiv CH > CH_2 = CH_2 > CH_3 - C \equiv CH$

(2) $CH_3 - C \equiv CH > CH \equiv CH > CH_2 = CH_2$

(3) $CH_3 - C \equiv CH > CH_2 = CH_2 > HC \equiv CH$

(4) $HC \equiv CH > CH_3 - C \equiv CH > CH_2 = CH_2$

3. In a chemical reaction, $A + 2B \overset{K}{\rightleftharpoons} 2C + D$, the initial concentration of B was 1.5 times of the concentration of A, but the equilibrium concentrations of A and B were found to be equal. The equilibrium constant (K) for the aforesaid chemical reaction is:

(1) 4 (2) 16

(3) $\frac{1}{4}$ (4) 1

4. Given

Gas	H_2	CH_4	CO_2	SO_2
Critical Temperature/K	33	190	304	630

On the basis of data given above, predict which of the following gases shows least adsorption on a definite amount of charcoal?

(1) SO_2 (2) CH_4

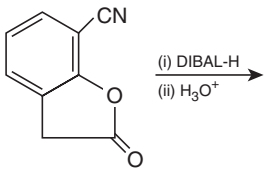
(3) CO_2 (4) H_2

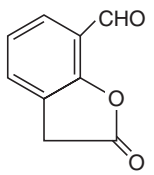
5. $Mn_2(CO)_{10}$ is an organometallic compound due to the presence of:

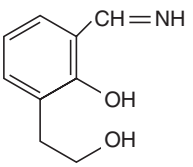
(1) Mn – C bond (2) Mn − Mn bond

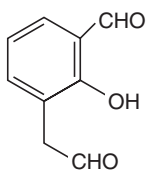
(3) Mn – O bond (4) C – O bond

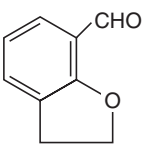
6. The major product of the following reaction is:



(1) 

(2) 

(3) 

(4) 

7. A metal on combustion in excess air forms X. X upon hydrolysis with water yields H_2O_2 and O_2 along with another product. The metal is:

(1) Na (2) Rb

(3) Mg (4) Li

8. The molecule that has minimum/no role in the formation of photochemical smog, is:

(1) N_2 (2) $CH_2 = O$

(3) O_3 (4) NO

9. The pair of metal ions that can give a spin-only magnetic moment of 3.9 BM for the complex $[M(H_2O)_6]Cl_2$, is:

(1) V^{2+} and Co^{2+} (2) V^{2+} and Fe^{2+}

(3) Co^{2+} and Fe^{2+} (4) Cr^{2+} and Mn^{2+}

10. For a diatomic ideal gas in a dosed system, which of the following plots does not correctly describe the relation between various thermodynamic quantities?

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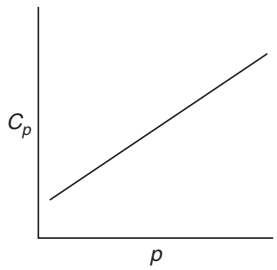
(1)



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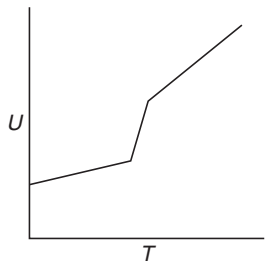

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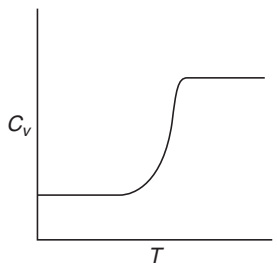

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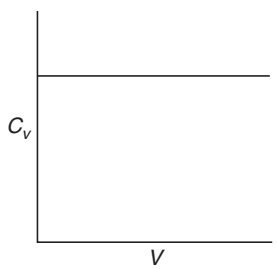


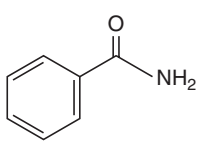
11. Among the following compounds most basic amino acid is

(1) asparagine. (2) lysine.

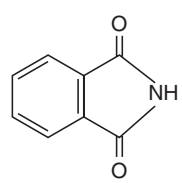
(3) serine. (4) histidine.

12. The increasing order of reactivity of the following compounds towards reaction with alkyl halides directly is:

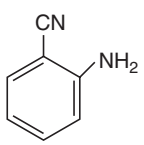
(A)



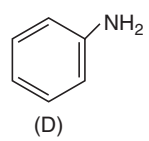
(B)



(C)



(D)



(1) (B) < (A) < (C) < (D)

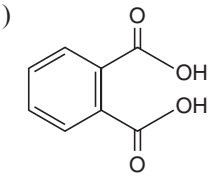
(2) (A) < (B) < (C) < (D)

(3) (B) < (A) < (D) < (C)

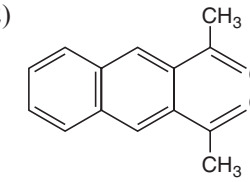
(4) (A) < (C) < (D) < (B)

13. Among the following four aromatic compounds, which one will have the lowest melting point?

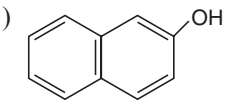
(1)



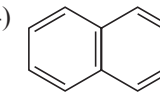
(2)



(3)



(4)



14. 50 mL of 0.5 M oxalic acid is needed to neutralize 25 mL of sodium hydroxide solution. The amount of NaOH in 50 mL of the given sodium hydroxide solution is:

(1) 40 g (2) 10 g

(3) 20 g (4) 80 g

15. The volume of gas A is twice than that of gas B. The compressibility factor of gas A is thrice than that of gas B at same temperature. The pressures of the gases for equal number of moles are:

(1) $3p_A = 2p_B$ (2) $2p_A = 3p_B$

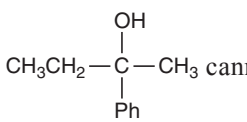
(3) $p_A = 3p_B$ (4) $p_A = 2p_B$

16. The hardness of a water sample (in terms of equivalents of $CaCO_3$) containing 10^{-3}M $CaSO_4$ is:

(Molar mass of $CaSO_4$ = 136 g mol^{-1})

(1) 10 ppm (2) 50 ppm

(3) 90 ppm (4) 100 ppm

17.  cannot be prepared

(1) $CH_3CH_2COCH_3$ + PhMgX

(2) $PhCOCH_2CH_3$ + CH_3MgX

(3) $PhCOCH_3$ + CH_3CH_2MgX

(4) HCHO + $PhCH(CH_3)CH_2MgX$

18. Freezing point of a 4% aqueous solution of X is equal to freezing point of 12% aqueous motion of Y. If molecular weight of X is A then molecular weight of Y is:

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(1) 3A (2) 2A

(3) A (4) 4A

19. The metal *d*-orbitals that are directly facing the ligands in $K_3[Co(CN)_6]$ are:

(1) d_{xy} and $d_{x^2-y^2}$ (2) $d_{x^2-y^2}$ and d_{z^2}

(3) d_{xz}, d_{yz} and d_{z^2} (4) d_{xy}, d_{xz} and d_{yz}

20. Decomposition of X exhibits a rate constant of 0.05 µg/year. How many years are required for the decomposition of 5 µg of X into 2.5 µg?

(1) 50 (2) 25

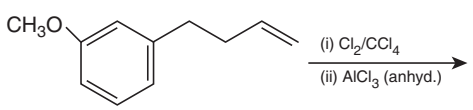
(3) 20 (4) 40

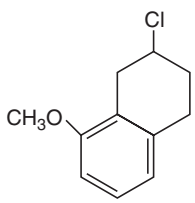
21. The standard electrode potential $E°$ and its temperature coefficient $\left(\frac{dE°}{dT}\right)$ for a cell are 2 V and -5×10^{-4} VK^{-1} at 300 K respectively. The cell reaction is $Zn(s) + Cu^{2+}(aq) \rightarrow Zn^{2+}(aq) + Cu(s)$. The standard reaction enthalpy ($\Delta_r H°$) at 300 K in kJ mol^{-1} is, [Use R = 8 JK^{-1} mol^{-1} and F = 96,000 C mol^{-1}]

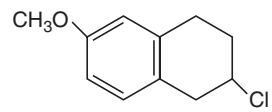
(1) −412.8 (2) −384.0

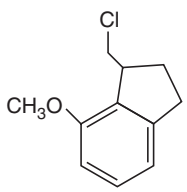
(3) 192.0 (4) 206.4

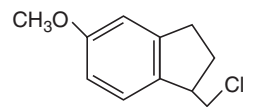
22. The major product of the following reaction is:



(1) 

(2) 

(3) 

(4) 

23. The element with Z = 120 (not yet discovered) will be an/a:

(1) inner-transition metal

(2) alkaline earth metal

(3) alkali metal

(4) transition metal

24. In the following reaction

$$\text{Aldehyde} + \text{Alcohol} \xrightarrow{HCl} \text{Acetal}$$

Aldehyde	Alcohol
HCHO	^{t}BuOH
CH_3CHO	MeOH

The best combination is:

(1) CH_3CHO and ^{t}BuOH

(2) HCHO and MeOH

(3) CH_3CHO and MeOH

(4) HCHO and ^{t}BuOH

25. Two solids dissociate as follows

$$A(s) \rightleftharpoons B(g) + C(g);\ K_{p_1} = x\ atm^2$$

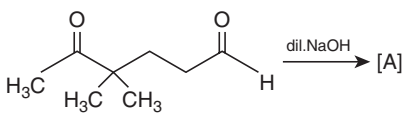
$$D(s) \rightleftharpoons C(g) + E(g);\ K_{p_2} = y\ atm^2$$

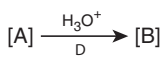
The total pressure when both the solids dissociate simultaneously is:

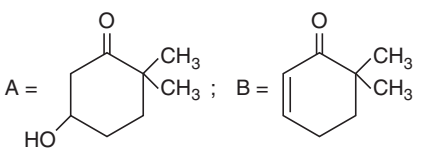
(1) $\sqrt{x+y}$ atm (2) $2(\sqrt{x+y})$ atm

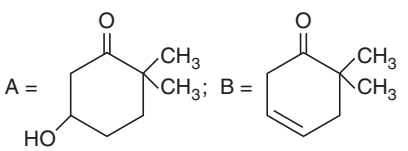
(3) $(x+y)$ atm (4) $x^2 + y^2$ atm

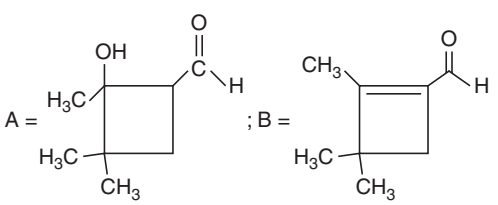
26. In the following reactions, products A and B are:

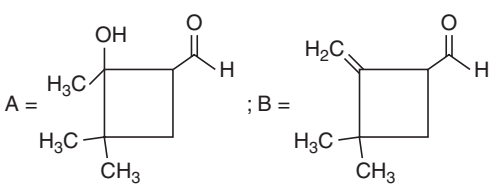




(1) 

(2) 

(3) 

(4) 

27. What is the work function of the metal if the light of wavelength 4000 Å generates photoelectrons of velocity 6×10^5 ms^{-1} from it?

(Mass of electron = 9×10^{-31} kg

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Velocity of light = $3 \times 10^8\ ms^{-1}$

Planck's constant = 6.626×10^{-34} Js

Charge of electron = $1.6 \times 10^{-19}\ JeV^{-1}$)

(1) 0.9 eV (2) 3.1 eV

(3) 2.1 eV (4) 4.0 eV

28. Iodine reacts with concentrated HNO_3 to yield Y along with other products. The oxidation state of iodine in Y, is:

(1) 5 (2) 7

(3) 3 (4) 1

29. Poly-β-hydroxybutyrate-co-β-hydroxyvalerate(PHBV) is a copolymer of _____.

(1) 3-hydroxybutanoic acid and 4-hydroxypentanoic acid

(2) 2-hydroxybutanoic acid and 3-hydroxypentanoic acid

(3) 3-hydroxybutanoic acid and 2-hydroxypentanoic acid

(4) 3-hydroxybutanoic acid and 3-hydroxypentanoic acid

30. Water samples with BOD values of 4 ppm and 18 ppm, respectively, are:

(1) Clean and clean

(2) Highly polluted and clean

(3) Clean and highly polluted

(4) Highly polluted and highly polluted

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JEE Main 2019 (January 12, Shift 2)

CHEMISTRY

1. 8 g of NaOH is dissolved in 18 g of H_2O. Mole fraction of NaOH in solution and molality (in mol kg^{-1}) of the solution respectively are:

(1) 0.2, 22.20 (2) 0.2, 11.11

(3) 0.167, 11.11 (4) 0.167, 22.20

2. The magnetic moment of an octahedral homoleptic Mn(II) complex is 5.9 BM. The suitable ligand for this complex is:

(1) ethylenediamine (2) CN^-

(3) NCS^- (4) CO

3. The element that does NOT show catenation is:

(1) Ge (2) Si

(3) Sn (4) Pb

4. Among the following, the false statement is:

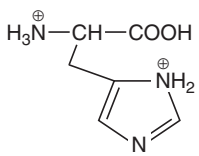
(1) It is possible to cause artificial rain by throwing electrified sand carrying charge opposite to the one on clouds from an aeroplane.

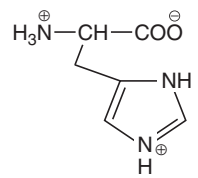
(2) Tyndall effect can be used to distinguish between a colloidal solution and a true solution.

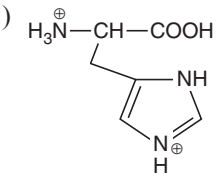
(3) Lyophilic sol can be coagulated by adding an electrolyte.

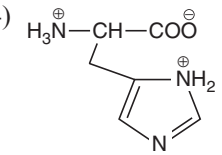
(4) Latex is a colloidal solution of rubber particles which are positively charged

5. The correct structure of histidine in a strongly acidic solution (pH = 2) is:

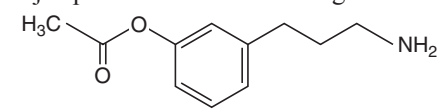
(1) 

(2) 

(3) 

(4) 

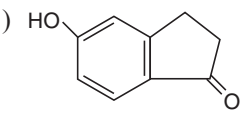
6. The major product of the following reaction is:

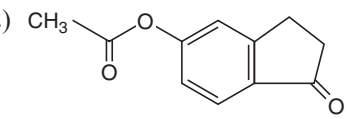


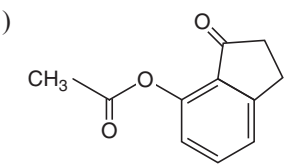
(i) $NaNO_2/H^+$

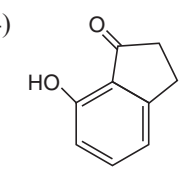
(ii) CrO_3/H^+

(iii) H_2SO_4(conc.), Δ

(1) 

(2) 

(3) 

(4) 

7. Λ_m° for NaCl, HCl and NaA are 126.4, 425.9 and 100.5 S cm^2mol^{-1}, respectively. If the conductivity of 0.001 M HA is 5×10^{-5} S cm^{-1}, degree of dissociation of HA is:

(1) 0.50 (2) 0.25

(3) 0.125 (4) 0.75

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8. Molecules of benzoic acid (C_6H_5COOH) dimerise in benzene. '*w*' g of the acid dissolved in 30 g of benzene shows a depression in freezing point equal to 2 K. If the percentage association of the acid to form dimer in the solution is 80, then w is:

(Given that K_f = 5 K kg mol^{-1}, Molar mass of benzoic acid = 122 g mol^{-1})

(1) 2.4 g (2) 1.0 g

(3) 1.5 g (4) 1.8 g

9. Chlorine on reaction with hot and concentrated sodium hydroxide gives:

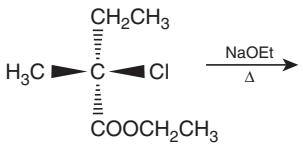
(1) Cl^- and ClO_3^-

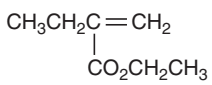
(2) Cl^- and ClO^-

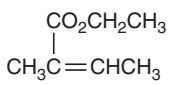
(3) ClO_3^- and ClO_2^-

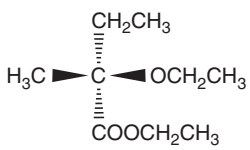
(4) Cl^- and ClO_2^-

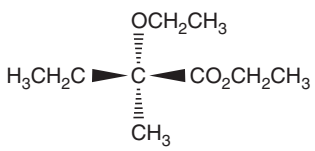
10. The major product of the following reaction is:



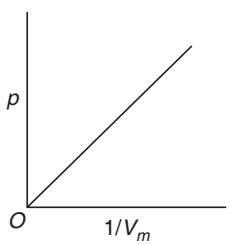
(1) 

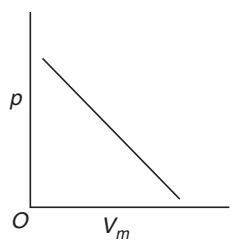
(2) 

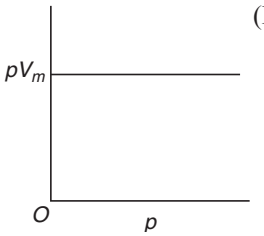
(3) 

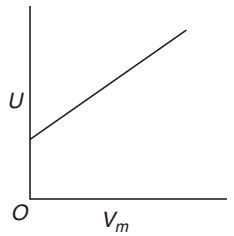
(4) 

11. The combination of plots which does not represent isothermal expansion of an ideal gas is:

(A) 

(B) 

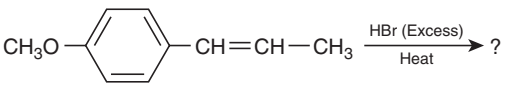
(C) 

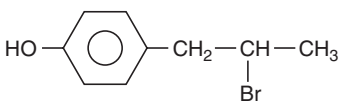
(D) 

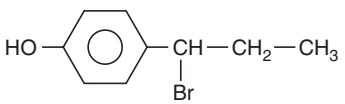
(1) (B) and (D) (2) (A) and (C)

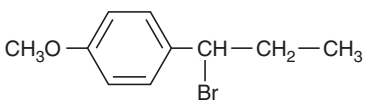
(3) (B) and (C) (4) (A) and (D)

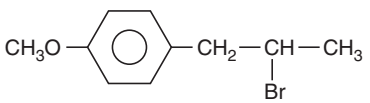
12. The major product in the following conversion is:



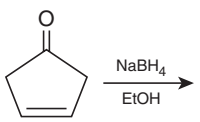
(1) 

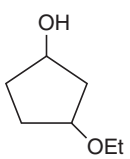
(2) 

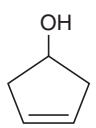
(3) 

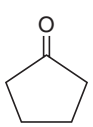
(4) 

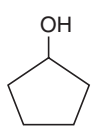
13. The major product of the following reaction is:



(1) 

(2) 

(3) 

(4) 

14. The correct order of atomic radii is:

(1) N > Ce > Eu > Ho (2) Ho > N > Eu > Ce

(3) Ce > Eu > Ho > N (4) Eu > Ce > Ho > N

15. The element that shows greater ability to form $p\pi$ - $p\pi$ multiple bonds, is:

(1) Sn (2) C

(3) Ge (4) Si

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16. The two monomers for the synthesis of nylon 6, 6 are:

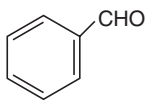
(1) $HOOC(CH_2)_4COOH$, $H_2N(CH_2)_6NH_2$

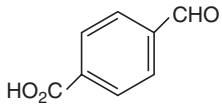
(2) $HOOC(CH_2)_6COOH$, $H_2N(CH_2)_6NH_2$

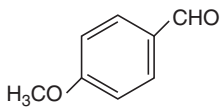
(3) $HOOC(CH_2)_4COOH$, $H_2N(CH_2)_4NH_2$

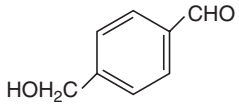
(4) $HOOC(CH_2)_6COOH$, $H_2N(CH_2)_4NH_2$

17. The aldehydes which will not form Grignard product with one equivalent Grignard reagents are:

(A) 

(B) 

(C) 

(D) 

(1) (B), (D) (2) (B), (C)

(3) (B), (C), (D) (4) (C), (D)

18. Given:

(i) C (graphite) + $O_2(g) \rightarrow CO_2(g)$; $\Delta_r H° = x$ kJ mol^{-1}

(ii) C (graphite) + $\frac{1}{2}O_2(g) \rightarrow CO_2(g)$; $\Delta_r H° = y$ kJ mol^{-1}

(iii) $CO(g) + \frac{1}{2}O_2(g) \rightarrow CO_2(g)$; $\Delta_r H° = z$ kJ mol^{-1}

Based on the above thermochemical equations, find out which one of the following algebraic relationships is correct?

(1) $x = y + z$ (2) $z = x + y$

(3) $y = 2z - x$ (4) $x = y - z$

19. The volume strength of 1 M H_2O_2 is: (Molar mass of H_2O_2 = 34 g mol^{-1})

(1) 5.6 (2) 16.8

(3) 11.35 (4) 22.4

20. The correct statement(s) among I to III with respect to potassium ions that are abundant within the cell fluids is/are:

(A) They activate many enzymes.

(B) They participate in the oxidation of glucose to produce ATP.

(C) Along with sodium ions, they are responsible for the transmission of nerve signals.

(1) A and B only

(2) A and C only

(3) A, B and C

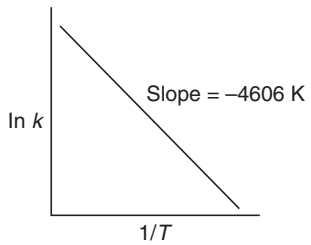
(4) C only

21. The compound that is NOT a common component of photochemical smog is:

(1) O_3 (2) $H_3C-\overset{\overset{O}{\|}}{C}-OONO_2$

(3) $CH_2=CHCHO$ (4) CF_2Cl_2

22. For a reaction, consider the plot of ln k versus $1/T$ given in the figure. If the rate constant of this reaction at 400 K is 10^{-5} s^{-1}, then the rate constant at 500 K is:



(1) 10^{-6} s^{-1} (2) 2×10^{-4} s^{-1}

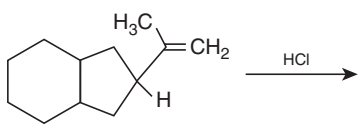
(3) 10^{-4} s^{-1} (4) 4×10^{-4} s^{-1}

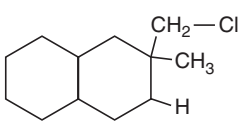
23. An open vessel at 27°C is heated until two fifth of the air (assumed as an ideal gas) in it has escaped from the vessel. Assuming that the volume of the vessel remains constant, the temperature at which the vessel has been heated is:

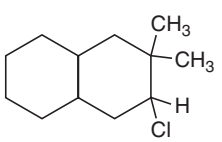
(1) 500 °C (2) 500 K

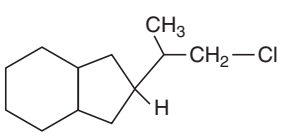
(3) 750 °C (4) 750 K

24. The major product of the following reaction is:



(1) 

(2) 

(3) 

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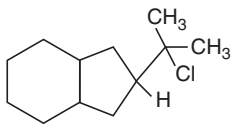
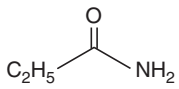
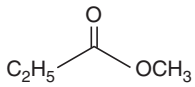
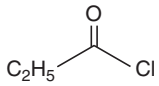
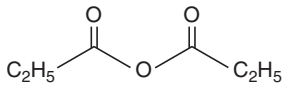
(4) 

25. The increasing order of the reactivity of the following with $LiAlH_4$ is:

(A) 

(B) 

(C) 

(D) 

(1) (B) < (A) < (C) < (D)

(2) (B) < (A) < (D) < (C)

(3) (A) < (B) < (D) < (C)

(4) (A) < (B) < (C) < (D)

26. The pair that does NOT require calcination is:

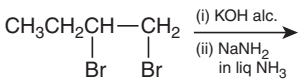
(1) ZnO and MgO

(2) ZnO and $Fe_2O_3 \cdot xH_2O$

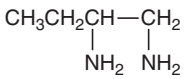
(3) $ZnCO_3$ and CaO

(4) Fe_2O_3 and $CaCO_3 \cdot MgCO_3$

27. The major product of the following reaction is:



(1) $CH_3CH = C = CH_2$

(2) 

(3) $CH_3CH = CHCH_2NH_2$

(4) $CH_3CH_2C \equiv CH$

28. If K_{sp} of Ag_2CO_3 is 8×10^{-12}, the molar solubility of Ag_2CO_3 in 0.1 M $AgNO_3$ is:

(1) 8×10^{-12} M (2) 8×10^{-11} M

(3) 8×10^{-10} M (4) 8×10^{-13} M

29. The upper stratosphere consisting of the ozone layer protects us from the Sun's radiation that falls in the wavelength region of:

(1) 200 − 315 nm (2) 400 − 550 nm

(3) 0.8 − 1.5 nm (4) 600 − 750 nm

30. If the de Broglie wavelength of the electron in n^{th} Bohr orbit in a hydrogenic atom is equal to $1.5\ \pi a_0$ (a_0 is Bohr radius), then the value of n/Z is:

(1) 0.40 (2) 1.50

(3) 1.0 (4) 0.75

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*CHEMISTRY - JEE Main 2019 (January)– Answer Key

JANUARY 9, SHIFT 1

1. (1)	**2.** (4)	**3.** (3)	**4.** (1)	**5.** (4)	**6.** (3)	**7.** (4)	**8.** (1)	**9.** (3)	**10.** (2)
11. (3)	**12.** (2)	**13.** (3)	**14.** (1)	**15.** (1)	**16.** (4)	**17.** (4)	**18.** (2)	**19.** (3)	**20.** (3)
21. (1)	**22.** (4)	**23.** (3)	**24.** (3)	**25.** (1)	**26.** (1)	**27.** (3)	**28.** (2)	**29.** (2)	**30.** (4)

JANUARY 9, SHIFT 2

1. (4)	**2.** (3)	**3.** (3)	**4.** (3)	**5.** (3)	**6.** (4)	**7.** (3)	**8.** (2)	**9.** (2)	**10.** (2)
11. (4)	**12.** (1)	**13.** (3)	**14.** (1)	**15.** (2)	**16.** (3)	**17.** (2)	**18.** (4)	**19.** (3)	**20.** (1)
21. (3)	**22.** (1)	**23.** (3)	**24.** (1)	**25.** (4)	**26.** (2)	**27.** (4)	**28.** (4)	**29.** (3)	**30.** (1)

JANUARY 10, SHIFT 1

1. (4)	**2.** (3)	**3.** (2)	**4.** (1)	**5.** (1)	**6.** (1)	**7.** (1)	**8.** (2)	**9. (N*)**	**10.** (3)
11. (1)	**12.** (1)	**13.** (2)	**14.** (3)	**15.** (2)	**16.** (3)	**17.** (2)	**18.** (4)	**19.** (2)	**20.** (1)
21. (2)	**22.** (2)	**23.** (4)	**24.** (1)	**25.** (2)	**26.** (4)	**27.** (3)	**28.** (4)	**29.** (3)	**30.** (4)

JANUARY 10, SHIFT 2

1. (3)	**2.** (1)	**3.** (1)	**4.** (3)	**5.** (1)	**6.** (4)	**7.** (3)	**8.** (4)	**9.** (3)	**10.** (1)
11. (1)	**12.** (4)	**13.** (3)	**14.** (4)	**15.** (4)	**16.** (4)	**17.** (4)	**18.** (2)	**19.** (3)	**20.** (4)
21. (2)	**22.** (2)	**23.** (4)	**24.** (2)	**25** (1)	**26.** (1)	**27.** (1)	**28.** (4)	**29.** (2)	**30.** (4)

JANUARY 11, SHIFT 1

1. (4)	**2.** (4)	**3.** (3)	**4.** (4)	**5.** (2)	**6.** (4)	**7.** (1)	**8.** (1)	**9.** (2)	**10.** (1)
11. (2)	**12.** (2)	**13.** (1)	**14.** (3)	**15.** (1)	**16.** (2)	**17.** (3)	**18.** (1)	**19.** (4)	**20.** (2)
21. (3)	**22.** (1)	**23.** (2)	**24.** (2)	**25.** (3)	**26.** (1)	**27.** (2)	**28.** (4)	**29.** (2)	**30.** (1)

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JANUARY 11, SHIFT 2

1. (3)	**2.** (1)	**3.** (4)	**4.** (3)	**5.** (1)	**6.** (4)	**7.** (1)	**8.** (3)	**9.** (2)	**10.** (2)
11. (4)	**12.** (4)	**13.** (2)	**14.** (2)	**15.** (4)	**16.** (3)	**17.** (2)	**18.** (3)	**19.** (2)	**20.** (4)
21. (2)	**22.** (1)	**23.** (3)	**24.** (4)	**25** (1)	**26.** (4)	**27.** (3)	**28.** (1)	**29.** (1)	**30.** (2)

JANUARY 12, SHIFT 1

1. (2)	**2.** (4)	**3.** (1)	**4.** (4)	**5.** (1)	**6.** (3)	**7.** (2)	**8.** (1)	**9.** (1)	**10.** (1)
11. (2)	**12.** (1)	**13.** (4)	**14. (N*)**	**15.** (2)	**16.** (4)	**17.** (4)	**18.** (1)	**19.** (2)	**20.** (1)
21. (1)	**22.** (4)	**23.** (2)	**24.** (2)	**25** (2)	**26.** (1)	**27.** (3)	**28.** (1)	**29.** (4)	**30.** (3)

JANUARY 12, SHIFT 2

1. (3)	**2.** (3)	**3.** (4)	**4.** (4)	**5.** (3)	**6.** (1)	**7.** (3)	**8.** (1)	**9.** (1)	**10.** (2)
11. (1)	**12.** (2)	**13.** (2)	**14.** (4)	**15.** (2)	**16.** (1)	**17.** (1)	**18.** (1)	**19.** (3)	**20.** (3)
21. (4)	**22.** (3)	**23.** (2)	**24.** (4)	**25** (3)	**26.** (1)	**27.** (4)	**28.** (3)	**29.** (1)	**30.** (4)

*** For complete solution visit https://www.wileyindia.com/current-year-solved-paper**

Note:

- **(N*) indicates question dropped. Candidate awarded full marks.**

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Glossary

A

Absolute configuration (Section 4.15A): The actual arrangement of groups in a molecule. The absolute configuration of a molecule can be determined by X-ray analysis or by relating the configuration of a molecule, using reactions of known stereochemistry, to another molecule whose absolute configuration is known.

Acetal (Section 15.7B): A functional group, consisting of a carbon bonded to alkoxy groups [i.e., $RCH(OR')_2$ or $R_2C(OR')_2$], derived by adding 2 molar equivalents of an alcohol to an aldehyde or ketone.

Acetylene (Section 1.9): A common name for ethyne. Also used as a general name for alkynes.

Acetylenic hydrogen atom (Section 7.9): A hydrogen atom attached to a carbon atom that is bonded to another carbon atom by a triple bond.

Achiral molecule (Section 4.6): A molecule that is superposable on its mirror image. Achiral molecules lack handedness and are incapable of existing as a pair of enantiomers.

Acid strength (Section 3.6): The strength of an acid is related to its acidity constant, K_a or to its pK_a. The larger the value of its K_a or the smaller the value of its pK_a, the stronger is the acid.

Acidity constant (Section 3.6A): An equilibrium constant related to the strength of an acid. For the reaction,

$$HA + H_2O \rightleftharpoons H_3O^+ + A^-$$

$$K_a = \frac{[H_3O^+][A^-]}{[HA]}$$

Activating group (Section 14.10): A group that when present on a benzene ring causes the ring to be more reactive in electrophilic substitution than benzene itself.

Activation Energy E_{act}; see **Energy of activation.**

Acyl group (Section 14.7): The general name for groups with the structure RCO— or ArCO—.

Acyl halide (Section 14.7): Also called an *acid halide*. A general name for compounds with the structure RCOX or ArCOX.

Acylation (Section 14.7): The introduction of an acyl group into a molecule.

Acylium ion (Section 14.7): The resonance-stabilized cation:

$$R{-}\overset{+}{C}{=}\ddot{O}: \longleftrightarrow R{-}C{\equiv}\overset{+}{O}$$

Addition polymer (Section 24.2C): A polymer that results from a stepwise addition of monomers to a chain (usually through a chain reaction) with no loss of other atoms or molecules in the process.

Addition reaction (Section 8.1): A reaction that results in an increase in the number of groups attached to a pair of atoms joined by a double or triple bond. An addition reaction is the opposite of an elimination reaction.

Aglycone (Section 20.4): The alcohol obtained by hydrolysis of a glycoside.

Aldaric acid (Section 20.6C): An α,ω-dicarboxylic acid that results from oxidation of the aldehyde group and the terminal 1° alcohol group of an aldose.

Alditol (Section 20.7): The alcohol that results from the reduction of the aldehyde or keto group of an aldose or ketose.

Aldonic acid (Section 20.6B): A monocarboxylic acid that results from oxidation of the aldehyde group of an aldose.

Aliphatic compound (Section 13.1): A nonaromatic compound such as an alkane, cycloalkane, alkene, or alkyne.

Alkylation (Section 14.6): The introduction of an alkyl group into a molecule.

Allyl group (Section 5.5): The $CH_2{=}CHCH_2{-}$group.

Allylic substituent (Section 14.2A): Refers to a substituent on a carbon atom adjacent to a carbon–carbon double bond.

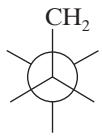
Angle strain (Section 5.10): The increased potential energy of a molecule (usually a cyclic one) caused by deformation of a bond angle away from its lowest energy value.

Annulene (Section 13.7B): Monocyclic hydrocarbons that can be represented by structures having alternating single and double bonds. The ring size of an annulene is represented by a number in brackets, e.g., benzene is [6]annulene and cyclooctatetraene is [8]annulene.

Anomers (Section 20.2C): A term used in carbohydrate chemistry. Anomers are diastereomers that differ only in configuration at the acetal or hemiacetal carbon of a sugar in its cyclic form.

Anti addition (Section 8.11): An addition that places the parts of the adding reagent on opposite faces of the reactant.

Anti conformation (Section 5.9): An anti conformation of butane, for example, has the methyl groups at an angle of 180° to each other:



Anti conformation of butane

Antiaromatic compound (Section 13.7D): A cyclic conjugated system whose p electron energy is greater than that of the corresponding open-chain compound.

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Aprotic solvent (Section 6.13C): A solvent whose molecules do not have a hydrogen atom attached to a strongly electronegative element (such as oxygen). For most purposes, this means that an aprotic solvent is one whose molecules lack an OH group.

Arene (Section 14.12): A general name for an aromatic hydrocarbon.

Aromatic compound (Sections 13.1–13.8): A cyclic conjugated unsaturated molecule or ion that is stabilized by π electron delocalization. Aromatic compounds are characterized by having large resonance energies, by reacting by substitution rather than addition, and by deshielding of protons exterior to the ring in their ^{1}H NMR spectra caused by the presence of an induced ring current.

Aryl group (Section 14.1): The general name for a group obtained (on paper) by the removal of a hydrogen from a ring position of an aromatic hydrocarbon. Abbreviated Ar—.

Aryl halide (Section 6.1): An organic halide in which the halogen atom is attached to an aromatic ring, such as a benzene ring.

Axial bond (Section 5.12): The six bonds of a cyclohexane ring (below) that are perpendicular to the general plane of the ring, and that alternate up and down around the ring.



B

Base strength (Section 3.6): The strength of a base is inversely related to the strength of its conjugate acid; the weaker the conjugate acid, the stronger is the base. In other words, if the conjugate acid has a large p*K*a, the base will be strong.

Benzenoid aromatic compound (Section 13.8A): An aromatic compound whose molecules have one or more benzene rings.

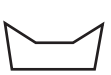
Benzyl group (Section 2.3B): The $C_6H_5CH_2$— group.

Benzylic substituent (Section 14.12A): Refers to a substituent on a carbon atom adjacent to a benzene ring.

Benzyne (Section 19.11B): An unstable, highly reactive intermediate consisting of a benzene ring with an additional bond resulting from sideways overlap of sp^2 orbitals on adjacent atoms of the ring.

Bimolecular reaction (Section 6.5B): A reaction whose rate-determining step involves two initially separate species.

Boat conformation (Section 5.1): A conformation of cyclohexane that resembles a boat and that has eclipsed bonds along its two sides:



It is of higher energy than the chair conformation.

Bond angle (Section 1.7A): The angle between two bonds originating at the same atom.

Bond dissociation energy, see **Homolytic bond dissociation energy**.

Bond length (Section 1.9A): The equilibrium distance between two bonded atoms or groups.

Bond-line formula (Section 1.10C): A formula that shows the carbon skeleton of a molecule with lines. The number of hydrogen atoms necessary to fulfill each carbon's valence is assumed to be present but not written in. Other atoms (e.g., O, Cl, N) are written in.

Bonding molecular orbital (Section 1.7A) (bonding MO): The energy of a bonding molecular orbital is lower than the energy of the isolated atomic orbitals from which it arises. When electrons occupy a bonding molecular orbital they help hold together the atoms that the molecular orbital encompasses.

Bromination (Section 9.7B): A reaction in which one or more bromine atoms are introduced into a molecule.

Bromohydrin (Section 8.13): A bromo alcohol.

Bromonium ion (Section 8.11A): An ion containing a positive bromine atom bonded to two carbon atoms.

Brønsted–Lowry theory of acids and bases (Section 3.2A): An acid is a substance that can donate (or lose) a proton; a base is a substance that can accept (or remove) a proton. The **conjugate acid** of a base is the molecule or ion that forms when a base accepts a proton. The **conjugate base** of an acid is the molecule or ion that forms when an acid loses its proton.

C

Carbanion (Section 3.4): A chemical species in which a carbon atom bears a formal negative charge.

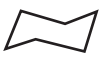
Carbocation (Section 3.4): A chemical species in which a trivalent carbon atom bears a formal positive charge.

Carbohydrate (Section 20.1A): A group of naturally occurring compounds that are usually defined as polyhydroxyaldehydes or polyhydroxyketones, or as substances that undergo hydrolysis to yield such compounds. In actuality, the aldehyde and ketone groups of carbohydrates are often present as hemiacetals and acetals. The name comes from the fact that many carbohydrates possess the empirical formula $C_x(H_2O)_y$.

Carbonyl group (Section 15.1): A functional group consisting of a carbon atom doubly bonded to an oxygen atom. The carbonyl group is found in aldehydes, ketones, esters, anhydrides, amides, acyl halides, and so on. Collectively these compounds are referred to as carbonyl compounds.

Chain reaction (Section 9.4): A reaction that proceeds by a sequential, stepwise mechanism, in which each step generates the reactive intermediate that causes the next step to occur. Chain reactions have *chain initiating steps, chain propagating steps, and chain terminating steps*.

Chair conformation (Section 5.11): The all-staggered conformation of cyclohexane that has no angle strain or torsional strain and is, therefore, the lowest energy conformation:



Chiral molecule (Section 4.1A): A molecule that is not superposable on its mirror image. Chiral molecules have handedness and are capable of existing as a pair of enantiomers.

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Chirality (Section 4.1): The property of having handedness.

Chlorination (Section 9.4): A reaction in which one or more chlorine atoms are introduced into a molecule.

Chlorohydrin (Section 8.13): A chloro alcohol.

Cis–trans isomers (Section 4.2C): Diastereomers that differ in their stereochemistry at adjacent atoms of a double bond or on different atoms of a ring.

Condensation polymer (Section 24.2C): A polymer produced when bifunctional monomers (or potentially bifunctional monomers) react with each other through the intermolecular elimination of water or an alcohol. Polyesters, polyamides, and polyurethanes are all condensation polymers.

Condensation reaction (Section 16.4C): A reaction in which molecules become joined through the intermolecular elimination of water or an alcohol.

Configuration (Section 4.5A): The particular arrangement of atoms (or groups) in space that is characteristic of a given stereoisomer.

Conformation (Section 5.8): A particular temporary orientation of a molecule that results from rotations about its single bonds.

Conformational analysis (Section 5.8): An analysis of the energy changes that a molecule undergoes as its groups undergo rotation (sometimes only partial) about the single bonds that join them.

Conformer (Section 5.8): A particular staggered conformation of a molecule.

Conjugate acid (Section 3.2A): The molecule or ion that forms when a base accepts a proton.

Conjugate addition: (Section 16.4E) A form of nucleophilic addition to an α,β-unsaturated carbonyl compound in which the nucleophile adds to the β-carbon.

Conjugate base (Section 3.2A): The molecule or ion that forms when an acid loses its proton.

Conjugated system (Section 12.1): Molecules or ions that have an extended π system. A conjugated system has a π orbital on an atom adjacent to a multiple bond; the π orbital may be that of another multiple bond or that of a radical, carbocation, or carbanion.

Connectivity (Section 1.3A): The sequence, or order, in which the atoms of a molecule are attached to each other.

Constitutional isomers (Section 1.3A): Compounds that have the same molecular formula but that differ in their connectivity (i.e., molecules that have the same molecular formula but have their atoms connected in different ways).

Coplanar (Section 7.6D): A conformation in which vicinal groups lie in the same plane.

Copolymer (Section 24.2C): A polymer synthesized by polymerizing two monomers.

Covalent bond (Section 1.4B): The type of bond that results when atoms share electrons.

Crown ether (Section 10.14): Cyclic polyethers that have the ability to form complexes with metal ions. Crown ethers are named as *x*-crown-*y* where *x* is the total number of atoms in the ring and *y* is the number of oxygen atoms in the ring.

Cyanohydrin (Section 15.9): A functional group consisting of a carbon atom bonded to a cyano group and to a hydroxyl group, i.e., RHC(OH)(CN) or $R_2C(OH)(CN)$, derived by adding HCN to an aldehyde or ketone.

Cycloaddition (Section 12.5): A reaction, like the Diels–Alder reaction, in which two connected groups add to the end of a π system to generate a new ring.

D

D and L designations (Section 20.2B): A method for designating the configuration of monosaccarides and other similar compounds in which the reference compound is (+)- or (–)-glyceraldehyde. According to this system, (+)-glyceraldehyde is designated D-(+)-glyceraldehyde and (–)-glyceraldehyde is designated L-(–)-glyceraldehyde. Therefore, a monosaccharide whose highest numbered stereogenic center has the same general configuration as D-(+)-glyceraldehyde is designated a D-sugar; one whose highest numbered stereogenic center has the same general configuration as L-(+)-glyceraldehyde is designated an L-sugar.

Deactivating group (Section 14.10): A group that when present on a benzene ring causes the ring to be less reactive in electrophilic substitution than benzene itself.

Debye unit (Section 2.2): The unit in which dipole moments are stated. One debye, D, equals 1×10^{-18} esu cm.

Decarboxylation (Section 17.10): A reaction whereby a carboxylic acid loses CO_2.

Dehydration reaction (Section 7.7): An elimination that involves the loss of a molecule of water from the substrate.

Dehydrohalogenation (Section 6.15G): An elimination reaction that results in the loss of HX from adjacent carbons of the substrate and the formation of a π bond.

Delocalization (Section 6.11B): The dispersal of electrons (or of electrical charge). Delocalization of charge always stabilizes a system.

Dextrorotatory (Section 4.8B): A compound that rotates plane-polarized light clockwise.

Diastereomers (Section 4.2C): Stereoisomers that are not mirror images of each other.

Diastereoselective reaction (See **Stereoselective reaction** and Section 4.10B)

Diastereotopic hydrogens (or ligands) (Section 9.6A): If replacement of each of two hydrogens (or ligands) by the same groups yields compounds that are diastereomers, the two hydrogen atoms (or ligands) are said to be diastereotopic.

Dielectric constant (Section 6.13C): A measure of a solvent's ability to insulate opposite charges from each other. The dielectric constant of a solvent roughly measures its polarity. Solvents with high dielectric constants are better solvents for ions than are solvents with low dielectric constants.

Dienophile (Section 12.5): The diene-seeking component of a Diels–Alder reaction.

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Dipolar ion (Section 21.2C): The charge-separated form of an amino acid that results from the transfer of a proton from a carboxyl group to a basic group.

Dipole moment, μ (Section 2.2): A physical property associated with a polar molecule that can be measured experimentally. It is defined as the product of the charge in electrostatic units (esu) and the distance that separates them in centimeters: $\mu = e \times d$.

Dipole-dipole interaction (Section 2.12B): An interaction between molecules having permanent dipole moments.

Disaccharide (Section 20.1A): A carbohydrate that, on a molecular basis, undergoes hydrolytic cleavage to yield two molecules of a monosaccharide.

E

(E–Z) system (Section 7.2): A system for designating the stereochemistry of alkene diastereomers based on the priorities of groups in the Cahn–Ingold–Prelog convention.

E1 reaction (Section 6.17): A unimolecular elimination in which, in a slow, rate-determining step, a leaving group departs from the substrate to form a carbocation. The carbocation then in a fast step loses a proton with the resulting formation of a π bond.

E2 reaction (Section 6.16): A bimolecular 1,2 elimination in which, in a single step, a base removes a proton and a leaving group departs from the substrate, resulting in the formation of a π bond.

Eclipsed conformation (Section 5.8A): A temporary orientation of groups around two atoms joined by a single bond such that the groups directly oppose each other.



An eclipsed conformation

Electronegativity (Section 1.4A): A measure of the ability of an atom to attract electrons it is sharing with another and thereby polarize the bond.

Electrophile (Section 3.4A): A Lewis acid, an electron-pair acceptor, an electron seeking reagent.

Elimination (Section 6.15): A reaction that results in the loss of two groups from the substrate and the formation of a π bond. The most common elimination is a 1,2 elimination or β elimination, in which the two groups are lost from adjacent atoms.

Enantiomeric excess or enantiomeric purity (Section 4.9B): A percentage calculated for a mixture of enantiomers by dividing the moles of one enantiomer minus the moles of the other enantiomer by the moles of both enantiomers and multiplying by 100. The enantiomeric excess equals the percentage optical purity.

Enantiomers (Section 4.2C): Stereisomers that are mirror images of each other.

Enantioselective reaction (See **Stereoselective reaction** and Section 4.10B)

Endergonic reaction (Section 6.7): A reaction that proceeds with a positive free energy change.

Endothermic reaction (Section 3.9A): A reaction that absorbs heat. For an endothermic reaction $\Delta H°$ is positive.

Energy (Section 3.9): Energy is the capacity to do work.

Energy of activation, E_{act} (Section 6.7): A measure of the difference in potential energy between the reactants and the transition state of a reaction. It is related to, but not the same as, the free energy of activation, $\Delta G^{‡}$.

Enolate anion (Section 16.1): The delocalized anion formed when an enol loses its hydroxylic proton or when the carbonyl tautomer that is in equilibrium with the enol loses an α proton.

Enthalpy change (Section 3.9A): Also called the heat of reaction. The *standard enthalpy change*, $\Delta H°$, is the change in enthalpy after a system in its standard state has undergone a transformation to another system, also in its standard state. For a reaction, $\Delta H°$ is a measure of the difference in the total bond energy of the reactants and products. It is one way of expressing the change in potential energy of molecules as they undergo reaction. The enthalpy change is related to the **free-energy change**, $\Delta G°$, and to the **entropy change**, $\Delta S°$, through the expression:

$$\Delta H° = \Delta G° + T\Delta S°$$

Entropy change (Section 3.10): The standard entropy change, $\Delta S°$, is the change in entropy between two systems in their standard states. Entropy changes have to do with changes in the relative order of a system. The more random a system is, the greater is its entropy. When a system becomes more disorderly its entropy change is positive.

Epoxide (Section 10.11). An oxirane. A three-membered ring containing one oxygen and two carbon atoms.

Equatorial bond (Section 5.12): The six bonds of a cyclohexane ring that lie generally around the "equator" of the molecule:



Equilibrium constant (Section 3.6A): A constant that expresses the position of an equilibrium. The equilibrium constant is calculated by multiplying the molar concentrations of the products together and then dividing this number by the number obtained by multiplying together the molar concentrations of the reactants.

Equilibrium control (Section 3.7): see **Thermodynamic control**.

Exergonic reaction (Section 6.7): A reaction that proceeds with a negative free-energy change.

Exothermic reaction (Section 3.9A): A reaction that evolves heat. For an exothermic reaction, $\Delta H°$ is negative.

F

Fischer projection formula (Section 4.13): A two-dimensional formula for representing the configuration of a chiral molecule. By convention, Fischer projection formulas are written with the main carbon chain extending from top to bottom with all groups eclipsed. Vertical lines represent bonds that project behind the plane of the page (or that lie in it). Horizontal lines represent bonds that project out of the plane of the page.

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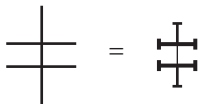


Fischer projection | Wedge-dashed wedge formula

Formal charge (Section 1.5A): The difference between the number of electrons assigned to an atom in a molecule and the number of electrons it has in its outer shell in its elemental state. Formal charge can be calculated using the formula: $F = Z - S/2 - U$, where F is the formal charge, Z is the group number of the atom (i.e., the number of electrons the atom has in its outer shell in its elemental state), S equals the number of electrons the atom is sharing with other atoms, and U is the number of unshared electrons the atom possesses.

Free energy of activation, $\Delta G^{\ddagger}$, (Section 6.7): The difference in free energy between the transition state and the reactants.

Free-energy change (Section 3.9): The *standard free-energy change*, $\Delta G°$, is the change in free energy between two systems in their standard states. At constant temperature, $\Delta G° = \Delta H° - T\Delta S° = -RT \ln K_{eq}$, where $\Delta H°$ is the standard enthalpy change, $\Delta S°$ is the standard entropy change, and K_{eq} is the equilibrium constant. A negative value of $\Delta G°$ for a reaction means that the formation of products is favored when the reaction reaches equilibrium.

Free energy diagram (Section 6.7): A plot of free energy changes that take place during a reaction versus the reaction coordinate. It displays free energy changes as a function of changes in bond orders and distances as reactants proceed through the transition state to become products.

Functional class nomenclature (Section 5.3E): A system for naming compounds that uses two or more words to describe the compound. The final word corresponds to the functional group present; the preceding words, usually listed in alphabetical order, describe the remainder of the molecule. Examples are: methyl alcohol, ethyl methyl ether, and ethyl bromide.

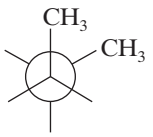
Functional group (Section 2.3): The particular group of atoms in a molecule that primarily determines how the molecule reacts.

Functional group interconversion (Section 6.14): A process that converts one functional group into another.

Furanose (Section 20.2C): A sugar in which the cyclic acetal or hemiacetal ring is five membered.

G

Gauche conformation (Section 5.9): A gauche conformation of butane, for example, has the methyl groups at an angle of 60° to each other:



A gauche conformation of butane

Geminal (gem) substituents (Section 7.10A): Substituents that are on the same atom.

Glycol (Sections 5.3F): A diol.

Glycoside (Section 20.4): A cyclic mixed acetal of a sugar with an alcohol.

Grignard reagent (Section 11.6B): An organomagnesium halide, usually written RMgX.

Ground state (Section 1.9): The lowest electronic energy state of an atom or molecule.

H

Halogenation (Section 9.3): A reaction in which one or more halogen atoms are introduced into a molecule.

Halohydrin (Section 8.13): A halo alcohol.

Halonium ion (Section 8.11A): An ion containing a positive halogen atom bonded to two carbon atoms.

Hammond–Leffler postulate (Section 6.13A): A postulate stating that the structure and geometry of the transition state of a given step will show a greater resemblance to the reactants or products of that step depending on which is closer to the transition state in energy. This means that the transition state of an endothermic step will resemble the products of that step more than the reactants, whereas the transition state of an exothermic step will resemble the reactants of that step more than the products.

Heat of hydrogenation (Section 7.3A): The standard enthalpy change that accompanies the hydrogenation of 1 mol of a compound to form a particular product.

Hemiacetal (Section 15.7A): A functional group, consisting of a carbon atom bonded to an alkoxy group and to a hydroxyl group, [i.e., RCH(OH)(OR′) or $R_2C(OH)(OR')$]. Hemiacetals are synthesized by adding one molar equivalent of an alcohol to an aldehyde or a ketone.

Hemiketal (Section 15.7A): Also called a hemiacetal. A functional group, consisting of a carbon atom bonded to an alkoxy group and to a hydroxyl group, [i.e., $R_2C(OH)(OR')$]. Hemiketals are synthesized by adding one molar equivalent of an alcohol to a ketone.

Heterocyclic compound (Section 13.9): A compound whose molecules have a ring containing an element other than carbon.

Heterolysis (Section 3.1A): The cleavage of a covalent bond so that one fragment departs with both of the electrons of the covalent bond that joined them. Heterolysis of a bond normally produces positive and negative ions.

Hofmann rule (Section 7.6C). When an elimination yields the alkene with the less substituted double bond, it is said to follow the Hofmann rule.

HOMO (Section 3.5C): The highest occupied molecular orbital.

Homologous series (Section 5.7): A series of compounds in which each member differs from the next member by a constant unit.

Homolysis (Section 3.1A): The cleavage of a covalent bond so that each fragment departs with one of the electrons of the covalent bond that joined them.

Homolytic bond dissociation energy, $\Delta H°$ (Section 9.2): The enthalpy change that accompanies the homolytic cleavage of a covalent bond.

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Hückel's rule (Section 13.7): A rule stating that planar monocyclic rings with $(4n + 2)$ delocalized π electrons (i.e., with 2, 6, 10, 14, . . . , delocalized π electrons) will be aromatic.

Hybridization of atomic orbitals (Section 1.7): A mathematical (and theoretical) mixing of two or more atomic orbitals to give the same number of new orbitals, called *hybrid orbitals*, each of which has some of the character of the original atomic orbitals.

Hydration (Section 8.4): The addition of water to a molecule, such as the addition of water to an alkene to form an alcohol.

Hydroboration (Section 8.6): The addition of a boron hydride (either BH_3 or an alkylborane) to a multiple bond.

Hydrogen bond (Section 2.12B): A strong dipole–dipole interaction (4–38 kJ mol^{-1}) that occurs between hydrogen atoms bonded to small strongly electronegative atoms (O, N, or F) and the nonbonding electron pairs on other such electronegative atoms.

Hydrogenation (Sections 7.12): A reaction in which hydrogen adds to a double or triple bond. Hydrogenation is often accomplished through the use of a metal catalyst such as platinum, palladium, rhodium, or ruthenium.

Hydrophilic group (Section 2.12D): A polar group that seeks an aqueous environment.

Hydrophobic group (also called a **lipophilic group**) (Section 2.20): A nonpolar group that avoids an aqueous surrounding and seeks a nonpolar environment.

Hydroxylation (Section 8.14): The addition of hydroxyl groups to each carbon or atom of a double bond.

I

Index of hydrogen deficiency (Section 13.1): The index of hydrogen deficiency (or IHD) equals the number of pairs of hydrogen atoms that must be subtracted from the molecular formula of the corresponding alkane to give the molecular formula of the compound under consideration.

Inductive effect (Section 3.8B): An intrinsic electron-attracting or -releasing effect that results from a nearby dipole in the molecule and that is transmitted through space and through the bonds of a molecule.

Intermediate (Section 3.1): A transient species that exists between reactants and products in a state corresponding to a local energy minimum on a potential energy diagram.

Ion (Section 1.4): A chemical species that bears an electrical charge.

Ion–dipole interaction (Section 2.12B): The interaction of an ion with a permanent dipole. Such interactions (resulting in solvation) occur between ions and the molecules of polar solvents.

Ionic bond (Section 1.4A): A bond formed by the transfer of electrons from one atom to another resulting in the creation of oppositely charged ions.

Ionic reaction (Section 3.1A): A reaction involving ions as reactants, intermediates, or products. Ionic reactions occur through the heterolysis of covalent bonds.

Isoelectric point (Section 21.2C): The pH at which the number of positive and negative charges on an amino acid or protein are equal.

Isomers (Sections 1.3A and 5.1): Different molecules that have the same molecular formula.

K

Kekulé structure (Section 2.1D): A structure in which lines are used to represent bonds. The Kekulé structure for benzene is a hexagon of carbon atoms with alternating single and double bonds around the ring, and with one hydrogen atom attached to each carbon.

Ketal (Section 15.7): Properly called an acetal. A functional group, consisting of a carbon bonded to alkoxyl groups, [i.e., $R_2C(OR')_2$], derived by adding two molar equivalents of an alcohol to a ketone.

Kinetic control (Section 12.4A): A principle stating that when the ratio of products of a reaction is determined by relative rates of reaction, the most abundant product will be the one that is formed fastest.

Kinetic energy (Section 3.9): Energy that results from the motion of an object. Kinetic energy $(KE) = \frac{1}{2} mv^2$, where m is the mass of the object, and v is its velocity.

Kinetics (Section 6.5): A term that refers to rates of reactions.

L

Lactam (Section 17.8I): A cyclic amide.

Lactone (Section 17.7C): A cyclic ester.

Leaving group (Section 6.4): The substituent with an unshared electron pair that departs from the substrate in a nucleophilic substitution reaction.

Leveling effect of a solvent (Section 3.14): An effect that restricts the use of certain solvents with strong acids and bases. In principle, no acid stronger than the conjugate acid of a particular solvent can exist to an appreciable extent in that solvent, and no base stronger than the conjugate base of the solvent can exist to an appreciable extent in that solvent.

Levorotatory (Section 4.8B): A compound that rotates plane-polarized light in a counterclockwise direction.

Lewis structure (or electron-dot structure) (Section 1.4B): A representation of a molecule showing electron pairs as a pair of dots or as a dash.

Lewis theory of acids and bases (Section 3.3): An acid is an electron pair acceptor, and a base is an electron pair donor.

LUMO (Section 6.6): The lowest unoccupied molecular orbital.

M

Macromolecule (Section 9.10): A very large molecule.

Markovnikov's rule (Section 8.2): A rule for predicting the regiochemistry of electrophilic additions to alkenes and alkynes that can be stated in various ways. As originally stated

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(in 1870) by Vladimir Markovnikov, the rule provides that "if an unsymmetrical alkene combines with a hydrogen halide, the halide ion adds to the carbon with the fewer hydrogen atoms." More commonly the rule has been stated in reverse: that in the addition of HX to an alkene or alkyne the hydrogen atom adds to the carbon atom that already has the greater number of hydrogen atoms. A modern expression of Markovnikov's rule is: *In the ionic addition of an unsymmetrical reagent to a multiple bond, the positive portion of the reagent (the electrophile) attaches itself to a carbon atom of the reagent in the way that leads to the formation of the more stable intermediate carbocation.*

Mechanism, see **Reaction mechanism.**

Meso compound (Section 4.12A): An optically inactive compound whose molecules are achiral even though they contain tetrahedral atoms with four different attached groups.

Mesylate (Section 10.8): A methanesulfonate ester.

Molecular orbital (MO): (Section 4.7B) Orbitals that encompass more than one atom of a molecule. When atomic orbitals combine to form molecular orbitals, the number of molecular orbitals that results always equals the number of atomic orbitals that combine.

Molecularity (Section 6.5B): The number of species involved in a single step of a reaction (usually the rate determining step).

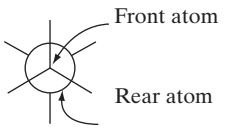
Monomer (Section 24.1): The simple starting compound from which a polymer is made. For example, the polymer polyethylene is made from the monomer, ethylene.

Monosaccharide (Section 20.1A): The simplest type of carbohydrate, one that does not undergo hydrolytic cleavage to a simpler carbohydrate.

Mutarotation (Section 20.3): The spontaneous change that takes place in the optical rotation of α and β anomers of a sugar when they are dissolved in water. The optical rotations of the sugars change until they reach the same value.

N

Newman projection formula (Section 5.8A): A means of representing the spatial relationships of groups attached to two atoms of a molecule. In writing a Newman projection formula we imagine ourselves viewing the molecule from one end directly along the bond axis joining the two atoms. Bonds that are attached to the front atom are shown as radiating from the center of a circle; those attached to the rear atom are shown as radiating from the edge of the circle:



Nonbenzenoid aromatic compound (Section 13.8B): An aromatic compound, such as azulene, that does not contain benzene rings.

Nucleophile (Section 3.4A): A Lewis base, an electron pair donor that seeks a positive center in a molecule.

Nucleophilic substitution reaction (Section 6.2): A reaction initiated by a nucleophile (a species with an unshared electron pair) in which the nucleophile reacts with a substrate to replace a substituent (called the leaving group), that departs with an unshared electron pair.

Nucleophilicity (Section 6.13B): The relative reactivity of a nucleophile in an S_N2 reaction as measured by relative rates of reaction.

O

Olefin (Section 7.1): An old name for an alkene.

Optical purity (Section 4.9B): A percentage calculated for a mixture of enantiomers by dividing the observed specific rotation for the mixture by the specific rotation of the pure enantiomer and multiplying by 100. The optical purity equals the enantiomeric purity or enantiomeric excess.

Optically active compound (Section 4.8): A compound that rotates the plane of polarization of plane polarized light.

Organometallic compound (Section 11.5): A compound that contains a carbon–metal bond.

Oxidation (Section 11.2): A reaction that increases the oxidation state of atoms in a molecule or ion. For an organic substrate, oxidation usually involves increasing its oxygen content or decreasing its hydrogen content. Oxidation also accompanies any reaction in which a less electronegative substituent is replaced by a more electronegative one.

Oxonium ion (Section 3.13): A chemical species with an oxygen atom that bears a formal positive charge.

Oxymercuration (Section 8.5): The addition of —OH and —HgO_2CR to a multiple bond.

Ozonolysis (Section 8.15B): The cleavage of a multiple bond that makes use of the reagent O_3, called ozone. The reaction leads to the formation of a cyclic compound called an *ozonide*, which is then reduced to carbonyl compounds by treatment with zinc and acetic acid.

P

Periplanar (See **coplanar**, Section 7.6C).

Peroxide (Section 9.1A): A compound with an oxygen–oxygen single bond.

Peroxy acid (Section 10.12A): An acid with the general formula RCO_3H, containing an oxygen – oxygen single bond.

Phase-transfer catalyst (Section 10.15): A reagent that transports an ion from an aqueous phase into a nonpolar phase where reaction takes place more rapidly. Tetraalkylammonium ions and crown ethers are phase-transfer catalysts.

Pi (π) bond (Section 1.7): A bond formed when electrons occupy a bonding π molecular orbital (i.e., the lower energy molecular orbital that results from overlap of parallel *p* orbitals on adjacent atoms).

Pi (π) molecular orbital (Section 1.7): A molecular orbital formed when parallel *p* orbitals on adjacent atoms overlap. Pi molecular

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orbitals may be *bonding* (*p* lobes of the same phase sign overlap) or *antibonding* (*p* orbitals of opposite phase sign overlap).

pK_a (Section 3.6): The pK_a is the negative logarithm of the acidity constant, Ka. pK_a = –log K_a.

Plane of symmetry (Section 4.6A): An imaginary plane that bisects a molecule in a way such that the two halves of the molecule are mirror images of each other. Any molecule with a plane of symmetry will be achiral.

Plane-polarized light (Section 4.8A): Ordinary light in which the oscillations of the electrical field occur only in one plane.

Polar covalent bond (Section 2.2): A covalent bond in which the electrons are not equally shared because of differing electronegativities of the bonded atoms.

Polar molecule (Section 2.2): A molecule with a dipole moment.

Polarimeter (Section 4.8B): A device used for measuring optical activity.

Polarizability (Section 6.13C): The susceptibility of the electron cloud of an uncharged molecule to distortion by the influence of an electric charge.

Polymer (Section 24.1): A large molecule made up of many repeating subunits. For example, the polymer polyethylene is made up of the repeating subunit —$(CH_2CH_2)_n$.

Polysaccharide (Section 20.1A): A carbohydrate that, on a molecular basis, undergoes hydrolytic cleavage to yield many molecules of a monosaccharide.

Potential energy (Section 3.9): Potential energy is stored energy; it exists when attractive or repulsive forces exist between objects.

Primary structure (Section 21.5): The covalent structure of a polypeptide or protein. This structure is determined, in large part, by determining the sequence of amino acids in the protein.

Protecting group (Section 10.10D): A group that is introduced into a molecule to protect a sensitive group from reaction while a reaction is carried out at some other location in the molecule. Later, the protecting group is removed.

Protein (Section 21.1): A large biological polymer of α-amino acids joined by amide linkages.

Protic solvent (Section 3.12): A solvent whose molecules have a hydrogen atom attached to a strongly electronegative element such as oxygen or nitrogen. Molecules of a protic solvent can therefore form hydrogen bonds to unshared electron pairs of oxygen or nitrogen atoms of solute molecules or ions, thereby stabilizing them. Water, methanol, ethanol, formic acid, and acetic acid are typical protic solvents.

Pyranose (Section 20.2C): A sugar in which the cyclic acetal or hemiacetal ring is six membered.

R

R (Section 2.3A): A symbol used to designate an alkyl group. Oftentimes it is taken to symbolize any organic group.

(*R*–*S*) System (Section 4.7): A method for designating the configuration of tetrahedral stereogenic centers.

Racemic form (racemate or racemic mixture) (Section 4.9A): An equimolar mixture of enantiomers. A racemic form is optically inactive.

Racemization (Section 6.12A): A reaction that transforms an optically active compound into a racemic form is said to proceed with racemization. Racemization takes place whenever a reaction causes chiral molecules to be converted to an achiral intermediate.

Radical (or **free radical**) (Section 3.1A): An uncharged chemical species that contains an unpaired electron.

Radical reaction (Section 9.1): A reaction involving radicals. Homolysis of covalent bonds occurs in radical reactions.

Rate-determining step (Section 6.9): If a reaction takes place in a series of steps, and if the first step is intrinsically slower than all of the others, then the rate of the overall reaction will be the same as (will be determined by) the rate of this slow step.

Reaction coordinate (Section 6.7): The abscissa in a potential energy diagram that represents the progress of the reaction. It represents the changes in bond orders and bond distances that must take place as reactants are converted to products.

Reaction mechanism (Section 3.1): A step-by-step description of the events that are postulated to take place at the molecular level as reactants are converted to products. A mechanism will include a description of all intermediates and transition states. Any mechanism proposed for a reaction must be consistent with all experimental data obtained for the reaction.

Rearrangement (Section 3.1): A reaction that results in a product with a different carbon skeleton from the reactant. The type of rearrangement called a 1,2 shift involves the migration of an organic group (with its electrons) from one atom to the atom next to it.

Reducing sugar (Section 20.6A): Sugars that reduce Tollens' or Benedict's reagents. All sugars that contain hemiacetal or hemiketal groups (and therefore are in equilibrium with aldehydes or α-hydroxyketones) are reducing sugars. Sugars in which only acetal or ketal groups are present are nonreducing sugars.

Reduction (Section 11.2): A reaction that lowers the oxidation state of atoms in a molecule or ion. Reduction of an organic compound usually involves increasing its hydrogen content or decreasing its oxygen content. Reduction also accompanies any reaction that results in replacement of a more electronegative substituent by a less electronegative one.

Regioselective reaction (Section 8.2C): A reaction that yields only one (or a predominance of one) constitutional isomer as the product when two or more constitutional isomers are possible products.

Relative configuration (Section 4.15A): The relationship between the configurations of two chiral molecules. Molecules are said to have the same relative configuration when similar or identical groups in each occupy the same position in space.

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The configurations of molecules can be related to each other through reactions of known stereochemistry, for example, through reactions that cause no bonds to a stereogenic center to be broken.

Resolution (Section 4.16): The process by which the enantiomers of a racemic form are separated.

Resonance effect (Section 3.11A): An effect by which a substituent exerts either an electron-releasing or -withdrawing effect through the pi system of the molecule.

Resonance energy (Section 13.5): An energy of stabilization that represents the difference in energy between the actual compound and that calculated for a single resonance structure. The resonance energy arises from delocalization of electrons in a conjugated system.

Resonance structures (or **resonance contributors**) (Section 1.5): Lewis structures that differ from one another only in the position of their electrons. A single resonance structure will not adequately represent a molecule. The molecule is better represented as a *hybrid* of all of the resonance structures.

Ring flip (Section 5.12): The change in a cyclohexane ring (resulting from partial bond rotations) that converts one ring conformation to another. A chair–chair ring flip converts any equatorial substitutent to an axial substituent and vice versa.

Ring strain (Section 5.10): The increased potential energy of the cyclic form of a molecule (usually measured by heats of combustion) when compared to its acyclic form.

S

Saponification (Section 17.7B): Base-promoted hydrolysis of an ester.

Saturated compound (Section 2.1): A compound that does not contain any multiple bonds.

Secondary carbon (Section 2.4): A carbon atom that has two other carbon atoms attached to it.

Secondary structure (Section 21.6A): The local conformation of a polypeptide backbone. These local conformations are specified in terms of regular folding patterns such as pleated sheets, α-helixes, and turns.

Sigma (σ) bond (Section 1.7B): A single bond. A bond formed when electrons occupy the bonding σ orbital formed by the end-on overlap of atomic orbitals (or hybrid orbitals) on adjacent atoms. In a sigma bond the electron density has circular symmetry when viewed along the bond axis.

S_N1 reaction (Section 6.9): Literally, substitution nucleophilic unimolecular. A multistep nucleophilic substitution in which the leaving group departs in a unimolecular step before the attack of the nucleophile. The rate equation is first order in substrate but zero order in the attacking nucleophile.

S_N2 reaction (Section 6.5): Literally, substitution nucleophilic bimolecular. A bimolecular nucleophilic substitution reaction that takes place in a single step in which a nucleophile attacks a carbon bearing a leaving group from the backside, causing an inversion of configuration at this carbon and displacement of the leaving group.

Solvent effect (Section 6.13C): An effect on relative rates of reaction caused by the solvent. For example, the use of a polar solvent will increase the rate of reaction of an alkyl halide in an S_N1 reaction.

Solvolysis (Section 6.12B): Literally, cleavage by the solvent. A nucleophilic substitution reaction in which the nucleophile is a molecule of the solvent.

***sp* orbital** (Section 1.9): A hybrid orbital that is derived by mathematically combining one s atomic orbital and one *p* atomic orbital. Two *sp* hybrid orbitals are obtained by this process, and they are oriented in opposite directions with an angle of 180° between them.

***sp^2* orbital** (Section 1.8): A hybrid orbital that is derived by mathematically combining one *s* atomic orbital and two *p* atomic orbitals. Three sp^2 hybrid orbitals are obtained by this process, and they are directed toward the corners of an equilateral triangle with angles of 120° between them.

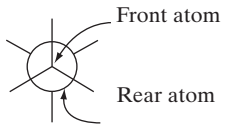
***sp^3* orbital** (Section 1.7): A hybrid orbital that is derived by mathematically combining one *s* atomic orbital and three *p* atomic orbitals. Four sp^3 hybrid orbitals are obtained by this process, and they are directed toward the corners of a regular tetrahedron with angles of 109.5° between them.

Specific rotation (Section 4.8C): A physical constant calculated from the observed rotation of a compound using the following equation:

$$[\alpha]_D = \frac{\alpha}{c \times l}$$

where α is the observed rotation using the D line of a sodium lamp, c is the concentration of the solution in grams per milliliter or the density of a neat liquid in g mL^{-1}, and l is the length of the tube in decimeters.

Staggered conformation (Section 5.8A): A temporary orientation of groups around two atoms joined by a single bond such that the bonds of the back atom exactly bisect the angles formed by the bonds of the front atom in a Newman projection formula:



A staggered conformation

Stereogenic center (Section 4.4): An atom bearing groups of such nature that an interchange of any two groups will produce a stereoisomer.

Stereochemistry (Section 4.1): Chemical studies that take into account the spatial aspects of molecules.

Stereoisomers (Section 1.8B): Compounds with the same molecular formula that differ *only* in the arrangement of their atoms in space. Stereoisomers have the same connectivity and, therefore, are not constitutional isomers. Stereoisomers are classified further as being either enantiomers or diastereomers.

Stereoselective reaction (Section 4.10B): In reactions where stereogenic centers are altered or created, a stereoselective reaction produces a preponderance of one stereoisomer. Furthermore, a

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stereoselective reaction can be either enantioselective, in which case the reaction produces a preponderance of one enantiomer, or diastereoselective, in which case the reaction produces a preponderance of one diastereomer.

Stereospecific reaction (Section 8.12): A reaction in which a particular stereoisomeric form of the reactant reacts in such a way that it leads to a specific stereoisomeric form of the product.

Steric effect (Section 6.13A): An effect on relative reaction rates caused by the space-filling properties of those parts of a molecule attached at or near the reacting site.

Steric hindrance (Section 6.13A): An effect on relative reaction rates caused when the spatial arrangement of atoms or groups at or near the reacting site hinders or retards a reaction.

Structural formula (Section 1.3A): A formula that shows how the atoms of a molecule are attached to each other.

Substituent effect (Section 3.11C): An effect on the rate of reaction (or on the equilibrium constant) caused by the replacement of a hydrogen atom by another atom or group. Substituent effects include those effects caused by the size of the atom or group, called steric effects, and those effects caused by the ability of the group to release or withdraw electrons, called electronic effects. Electronic effects are further classified as being inductive effects or resonance effects.

Substitution reaction (Section 6.2): A reaction in which one group replaces another in a molecule.

Substitutive nomenclature (Section 5.3F): A system for naming compounds in which each atom or group, called a substituent, is cited as a prefix or suffix to a parent compound. In the IUPAC system only one group may be cited as a suffix. Locants (usually numbers) are used to tell where the group occurs.

Substrate (Section 6.2): The molecule or ion that undergoes reaction.

Sugar (Section 20.1A): A carbohydrate.

Superposable (Section 4.1): Two objects are superposable if, when one object is placed on top of the other, all parts of each coincide. To be superposable is different than to be superimposable. Any two objects can be superimposed simply by putting one object on top of the other, whether or not all parts coincide. The condition of superposability must be met for two things to be identical.

Syn addition (Section 7.14A): An addition that places both parts of the adding reagent on the same face of the reactant.

Synthon (Section 8.19B): The fragments that result (on paper) from the disconnection of a bond. The actual reagent that will, in a synthetic step, provide the synthon is called the *synthetic equivalent*.

T

Tautomers (Section 16.2): Constitutional isomers that are easily interconverted. Keto and enol tautomers, for example, are rapidly interconverted in the presence of acids and bases.

Tertiary carbon (Section 2.4): A carbon atom that has three other carbon atoms attached to it.

Tertiary structure (Section 21.1): The three-dimensional shape of a protein that arises from folding of its polypeptide chains superimposed on its α helixes and pleated sheets.

Thermodynamic control (Section 12.4A): A principle stating that the ratio of products of a reaction that reaches equilibrium is determined by the relative stabilities of the products (as measured by their standard free energies, $\Delta G°$). The most abundant product will be the one that is the most stable.

Torsional barrier (Section 5.8B): The barrier to rotation of groups joined by a single bond caused by repulsions between the aligned electron pairs in the eclipsed form.

Torsional strain (Section 5.9): The strain associated with an eclipsed conformation of a molecule; it is caused by repulsions between the aligned electron pairs of the eclipsed bonds.

Tosylate (Section 10.8): A *p*-toluenesulfonate ester.

Transition state (Section 6.7): A state on a potential energy diagram corresponding to an energy maximum (i.e., characterized by having higher potential energy than immediately adjacent states). The term transition state is also used to refer to the species that occurs at this state of maximum potential energy; another term used for this species is *the activated complex*.

U

Unimolecular reaction (Section 6.8B): A reaction whose rate-determining step involves only one species.

Unsaturated compound (Section 2.1): A compound that contains multiple bonds.

V

van der Waals force (or London force) (Section 2.12A): Weak forces that act between nonpolar molecules or between parts of the same molecule. Bringing two groups (or molecules) together first results in an attractive force between them because a temporary unsymmetrical distribution of electrons in one group induces an opposite polarity in the other. When groups are brought closer than their *van der Waals radii*, the force between them becomes repulsive because their electron clouds begin to interpenetrate each other.

Vicinal (*vic*) substituents (Section 7.10): Substituents that are on adjacent atoms.

Vinyl group (Section 5.5): The $CH_2{=}CH{-}$ group.

Vinylic halide (Section 6.1): An organic halide in which the halogen atom is attached to a carbon atom of a double bond.

Vinylic substituent (Section 7.14B): Refers to a substituent on a carbon atom that participates in a carbon–carbon double bond.

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W

Wave function (or **ψ function**) (Section 1.7A): A mathematical expression derived from *quantum mechanics* corresponding to an energy state for an electron, i.e., for an orbital. The square of the ψ function, ψ^2, gives the probability of finding the electron in a particular place in space.

Y

Ylide (Section 15.10): An electrically neutral molecule that has a negative carbon with an unshared electron pair adjacent to a positive heteroatom.

Z

Zaitsev's rule (Section 7.6B): A rule stating that an elimination will give as the major product the most stable alkene (i.e., the alkene with the most highly substituted double bond).

Zwitterion (Section 21.2C) (see **Dipolar ion**): Another name for a dipolar ion.

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