ORGANIC CHEMISTRY II

Divan Fard
Shasta College

LibreTexts™

Organic Chemistry II

This text is disseminated via the Open Education Resource (OER) LibreTexts Project (https://LibreTexts.org) and like the thousands of other texts available within this powerful platform, it is freely available for reading, printing, and "consuming."

The LibreTexts mission is to bring together students, faculty, and scholars in a collaborative effort to provide an accessible, and comprehensive platform that empowers our community to develop, curate, adapt, and adopt openly licensed resources and technologies; through these efforts we can reduce the financial burden born from traditional educational resource costs, ensuring education is more accessible for students and communities worldwide.

Most, but not all, pages in the library have licenses that may allow individuals to make changes, save, and print this book. Carefully consult the applicable license(s) before pursuing such effects. Instructors can adopt existing LibreTexts texts or Remix them to quickly build course-specific resources to meet the needs of their students. Unlike traditional textbooks, LibreTexts' web based origins allow powerful integration of advanced features and new technologies to support learning.

LibreTexts is the adaptable, user-friendly non-profit open education resource platform that educators trust for creating, customizing, and sharing accessible, interactive textbooks, adaptive homework, and ancillary materials. We collaborate with individuals and organizations to champion open education initiatives, support institutional publishing programs, drive curriculum development projects, and more.

The LibreTexts libraries are Powered by NICE CXone Expert and was supported by the Department of Education Open Textbook Pilot Project, the California Education Learning Lab, the UC Davis Office of the Provost, the UC Davis Library, the California State University Affordable Learning Solutions Program, and Merlot. This material is based upon work supported by the National Science Foundation under Grant No. 1246120, 1525057, and 1413739.

Any opinions, findings, and conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the National Science Foundation nor the US Department of Education.

Have questions or comments? For information about adoptions or adaptions contact info@LibreTexts.org or visit our main website at https://LibreTexts.org.

This text was compiled on 05/15/2026

TABLE OF CONTENTS

Licensing

1: Structure Determination - Mass Spectrometry and Infrared Spectroscopy

- 1.1: Why This Chapter?
- 1.2: Mass Spectrometry of Small Molecules - Magnetic-Sector Instruments
- 1.3: Interpreting Mass Spectra
- 1.4: Mass Spectrometry of Some Common Functional Groups
- 1.5: Mass Spectrometry in Biological - Time-of-flight (TOF) Instruments
- 1.6: Spectroscopy and the Electromagnetic Spectrum
- 1.7: Infrared Spectroscopy
- 1.8: Interpreting Infrared Spectra
- 1.9: Infrared Spectra of Some Common Functional Groups
- 1.10: Chemistry Matters—X-Ray Crystallography
- 1.11: Key Terms
- 1.12: Summary
- 1.13: Additional Problems

2: Structure Determination - Nuclear Magnetic Resonance Spectroscopy

- 2.1: Why This Chapter?
- 2.2: Nuclear Magnetic Resonance Spectroscopy
- 2.3: The Nature of NMR Absorptions
- 2.4: Chemical Shifts
- 2.5: Chemical Shifts in ^{1}H NMR Spectroscopy
- 2.6: Integration of ^{1}H NMR Absorptions- Proton Counting
- 2.7: Spin-Spin Splitting in ^{1}H NMR Spectra
- 2.8: ^{1}H NMR Spectroscopy and Proton Equivalence
- 2.9: More Complex Spin-Spin Splitting Patterns
- 2.10: Uses of ^{1}H NMR Spectroscopy
- 2.11: ^{13}C NMR Spectroscopy - Signal Averaging and FT-NMR
- 2.12: Characteristics of ^{13}C NMR Spectroscopy
- 2.13: DEPT ^{13}C NMR Spectroscopy
- 2.14: Uses of ^{13}C NMR Spectroscopy
- 2.15: Chemistry Matters—Magnetic Resonance Imaging (MRI)
- 2.16: Key Terms
- 2.17: Summary
- 2.18: Additional Problems

3: Conjugated Compounds and Ultraviolet Spectroscopy

- 3.1: Why This Chapter?
- 3.2: Stability of Conjugated Dienes- Molecular Orbital Theory
- 3.3: Electrophilic Additions to Conjugated Dienes- Allylic Carbocations
- 3.4: Kinetic vs. Thermodynamic Control of Reactions
- 3.5: The Diels-Alder Cycloaddition Reaction

- 3.6: Characteristics of the Diels-Alder Reaction
- 3.7: Diene Polymers - Natural and Synthetic Rubbers
- 3.8: Ultraviolet Spectroscopy
- 3.9: Interpreting Ultraviolet Spectra- The Effect of Conjugation
- 3.10: Conjugation, Color, and the Chemistry of Vision
- 3.11: Chemistry Matters—Photolithography
- 3.12: Key Terms
- 3.13: Summary
- 3.14: Summary of Reactions
- 3.15: Additional Problems

4: Benzene and Aromaticity

- 4.1: Why This Chapter?
- 4.2: Naming Aromatic Compounds
- 4.3: Structure and Stability of Benzene
- 4.4: Aromaticity and the Hückel 4n + 2 Rule
- 4.5: Aromatic Ions
- 4.6: Aromatic Heterocycles - Pyridine and Pyrrole
- 4.7: Polycyclic Aromatic Compounds
- 4.8: Spectroscopy of Aromatic Compounds
- 4.9: Chemistry Matters—Aspirin, NSAIDs, and COX-2 Inhibitors
- 4.10: Key Terms
- 4.11: Summary
- 4.12: Additional Problems

5: Chemistry of Benzene - Electrophilic Aromatic Substitution

- 5.1: Why This Chapter?
- 5.2: Electrophilic Aromatic Substitution Reactions - Bromination
- 5.3: Other Aromatic Substitutions
- 5.4: Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction
- 5.5: Substituent Effects in Electrophilic Substitutions
- 5.6: Trisubstituted Benzenes- Additivity of Effects
- 5.7: Nucleophilic Aromatic Substitution
- 5.8: Benzyne
- 5.9: Oxidation of Aromatic Compounds
- 5.10: Reduction of Aromatic Compounds
- 5.11: Synthesis of Polysubstituted Benzenes
- 5.12: Chemistry Matters—Combinatorial Chemistry
- 5.13: Key Terms
- 5.14: Summary
- 5.15: Summary of Reactions
- 5.16: Additional Problems

6: Alcohols and Phenols

- 6.1: Why This Chapter?
- 6.2: Naming Alcohols and Phenols
- 6.3: Properties of Alcohols and Phenols
- 6.4: Preparation of Alcohols- A Review

- 6.5: Alcohols from Carbonyl Compounds - Reduction
- 6.6: Alcohols from Carbonyl Compounds - Grignard Reagents
- 6.7: Reactions of Alcohols
- 6.8: Oxidation of Alcohols
- 6.9: Protection of Alcohols
- 6.10: Phenols and Their Uses
- 6.11: Reactions of Phenols
- 6.12: Spectroscopy of Alcohols and Phenols
- 6.13: Chemistry Matters—Ethanol- Chemical, Drug, and Poison
- 6.14: Key Terms
- 6.15: Summary
- 6.16: Summary of Reactions
- 6.17: Additional Problems

7: Ethers and Epoxides; Thiols and Sulfides

- 7.1: Why This Chapter?
- 7.2: Names and Properties of Ethers
- 7.3: Preparing Ethers
- 7.4: Reactions of Ethers - Acidic Cleavage
- 7.5: Cyclic Ethers - Epoxides
- 7.6: Reactions of Epoxides - Ring-opening
- 7.7: Crown Ethers
- 7.8: Thiols and Sulfides
- 7.9: Spectroscopy of Ethers
- 7.10: Chemistry Matters—Epoxy Resins and Adhesives
- 7.11: Key Terms
- 7.12: Summary
- 7.13: Summary of Reactions
- 7.14: Additional Problems
- 7.15: Preview of Carbonyl Chemistry

8: Aldehydes and Ketones- Nucleophilic Addition Reactions

- 8.1: Why This Chapter?
- 8.2: Naming Aldehydes and Ketones
- 8.3: Preparing Aldehydes and Ketones
- 8.4: Oxidation of Aldehydes and Ketones
- 8.5: Nucleophilic Addition Reactions of Aldehydes and Ketones
- 8.6: Nucleophilic Addition of Water- Hydration
- 8.7: Nucleophilic Addition of HCN - Cyanohydrin Formation
- 8.8: Nucleophilic Addition of Hydride and Grignard Reagents- Alcohol Formation
- 8.9: Nucleophilic Addition of Amines- Imine and Enamine Formation
- 8.10: Nucleophilic Addition of Hydrazine - The Wolff-Kishner Reaction
- 8.11: Nucleophilic Addition of Alcohols - Acetal Formation
- 8.12: Nucleophilic Addition of Phosphorus Ylides- The Wittig Reaction
- 8.13: Biological Reductions
  - 8.13.1: Amines and Heterocycles
    - 8.13.1.1: Why This Chapter?
    - 8.13.1.2: Naming Amines

- 8.13.1.3: Structure and Properties of Amines
- 8.13.1.4: Basicity of Amines
- 8.13.1.5: Basicity of Arylamines
- 8.13.1.6: Biological Amines and the Henderson-Hasselbalch Equation
- 8.13.1.7: Synthesis of Amines
- 8.13.1.8: Reactions of Amines
- 8.13.1.9: Reactions of Arylamines
- 8.13.1.10: Heterocyclic Amines
- 8.13.1.11: Spectroscopy of Amines
- 8.13.1.12: Chemistry Matters - Green Chemistry II- Ionic Liquids
- 8.13.1.13: Key Terms
- 8.13.1.14: Summary
- 8.13.1.15: Summary of Reactions
- 8.13.1.16: Additional Problems
- 8.14: Conjugate Nucleophilic Addition to α,β-Unsaturated Aldehydes and Ketones
- 8.15: Spectroscopy of Aldehydes and Ketones
- 8.16: Chemistry Matters—Enantioselective Synthesis
- 8.17: Key Terms
- 8.18: Summary
- 8.19: Summary of Reactions
- 8.20: Additional Problems
- 8.21: Carbonyl Condensation Reactions

9: Carboxylic Acids and Nitriles

- 9.1: Why This Chapter?
- 9.2: Naming Carboxylic Acids and Nitriles
- 9.3: Structure and Properties of Carboxylic Acids
- 9.4: Biological Acids and the Henderson-Hasselbalch Equation
- 9.5: Substituent Effects on Acidity
- 9.6: Preparing Carboxylic Acids
- 9.7: Reactions of Carboxylic Acids - An Overview
- 9.8: Chemistry of Nitriles
- 9.9: Spectroscopy of Carboxylic Acids and Nitriles
- 9.10: Chemistry Matters—Vitamin C
- 9.11: Key Terms
- 9.12: Summary
- 9.13: Summary of Reactions
- 9.14: Additional Problems

10: Carboxylic Acid Derivatives- Nucleophilic Acyl Substitution Reactions

- 10.1: Why This Chapter?
- 10.2: Naming Carboxylic Acid Derivatives
- 10.3: Nucleophilic Acyl Substitution Reactions
- 10.4: Reactions of Carboxylic Acids
- 10.5: Chemistry of Acid Halides
- 10.6: Chemistry of Acid Anhydrides
- 10.7: Chemistry of Esters
- 10.8: Chemistry of Amides
- 10.9: Chemistry of Thioesters and Acyl Phosphates - Biological Carboxylic Acid Derivatives

- 10.10: Polyamides and Polyesters - Step-Growth Polymers
- 10.11: Spectroscopy of Carboxylic Acid Derivatives
- 10.12: Chemistry Matters—β-Lactam Antibiotics
- 10.13: Key Terms
- 10.14: Summary
- 10.15: Summary of Reactions
- 10.16: Additional Problems
- 10.17: Carbonyl Condensation Reactions

11: Carbonyl Alpha-Substitution Reactions

- 11.1: Why This Chapter?
- 11.2: Keto-Enol Tautomerism
- 11.3: Reactivity of Enols- α-Substitution Reactions
- 11.4: Alpha Halogenation of Aldehydes and Ketones
- 11.5: Alpha Bromination of Carboxylic Acids
- 11.6: Acidity of Alpha Hydrogen Atoms- Enolate Ion Formation
- 11.7: Reactivity of Enolate Ions
- 11.8: Alkylation of Enolate Ions
- 11.9: Chemistry Matters—Barbiturates
- 11.10: Key Terms
- 11.11: Summary
- 11.12: Summary of Reactions
- 11.13: Additional Problems

12: Carbonyl Condensation Reactions

- 12.1: Why This Chapter?
- 12.2: Carbonyl Condensations - The Aldol Reaction
- 12.3: Carbonyl Condensations versus Alpha Substitutions
- 12.4: Dehydration of Aldol Products - Synthesis of Enones
- 12.5: Using Aldol Reactions in Synthesis
- 12.6: Mixed Aldol Reactions
- 12.7: Intramolecular Aldol Reactions
- 12.8: The Claisen Condensation Reaction
- 12.9: Mixed Claisen Condensations
- 12.10: Intramolecular Claisen Condensations - The Dieckmann Cyclization
- 12.11: Conjugate Carbonyl Additions - The Michael Reaction
- 12.12: Carbonyl Condensations with Enamines - The Stork Enamine Reaction
- 12.13: The Robinson Annulation Reaction
- 12.14: Some Biological Carbonyl Condensation Reactions
- 12.15: Chemistry Matters - A Prologue to Metabolism
- 12.16: Key Terms
- 12.17: Summary
- 12.18: Summary of Reactions
- 12.19: Additional Problems

13: Amines and Heterocycles

- 13.1: Why This Chapter?
- 13.2: Naming Amines

- 13.3: Structure and Properties of Amines
- 13.4: Basicity of Amines
- 13.5: Basicity of Arylamines
- 13.6: Biological Amines and the Henderson-Hasselbalch Equation
- 13.7: Synthesis of Amines
- 13.8: Reactions of Amines
- 13.9: Reactions of Arylamines
- 13.10: Heterocyclic Amines
- 13.11: Spectroscopy of Amines
- 13.12: Chemistry Matters - Green Chemistry II- Ionic Liquids
- 13.13: Key Terms
- 13.14: Summary
- 13.15: Summary of Reactions
- 13.16: Additional Problems

14: Orbitals and Organic Chemistry - Pericyclic Reactions

- 14.1: Why This Chapter?
- 14.2: Molecular Orbitals of Conjugated Pi Systems
- 14.3: Electrocyclic Reactions
- 14.4: Stereochemistry of Thermal Electrocyclic Reactions
- 14.5: Photochemical Electrocyclic Reactions
- 14.6: Cycloaddition Reactions
- 14.7: Stereochemistry of Cycloadditions
- 14.8: Sigmatropic Rearrangements
- 14.9: Some Examples of Sigmatropic Rearrangements
- 14.10: A Summary of Rules for Pericyclic Reactions
- 14.11: Chemistry Matters—Vitamin D, the Sunshine Vitamin
- 14.12: Key Terms
- 14.13: Summary
- 14.14: Additional Problems

Index

Glossary

Detailed Licensing

Detailed Licensing

Licensing

*A detailed breakdown of this resource's licensing can be found in **Back Matter/Detailed Licensing**.*

CHAPTER OVERVIEW

1: Structure Determination - Mass Spectrometry and Infrared Spectroscopy

Learning Objectives

After you have completed Chapter 12, you should be able to

1. fulfillall of the detailed objectives listed under each individual section.
2. solve road-map problems that include mass spectral data, infrared data, or both.
3. define, and use in context, the key terms introduced.

The processes of identifying and characterizing organic compounds are of great importance to the working organic chemist. With the use of modern instrumental techniques, these tasks can now be accomplished much more readily than in the past. In this chapter, you will learn about two spectroscopic techniques (mass spectroscopy and infrared spectroscopy) that are used to identify organic compounds.

1.1: Why This Chapter?
1.2: Mass Spectrometry of Small Molecules - Magnetic-Sector Instruments
1.3: Interpreting Mass Spectra
1.4: Mass Spectrometry of Some Common Functional Groups
1.5: Mass Spectrometry in Biological - Time-of-flight (TOF) Instruments
1.6: Spectroscopy and the Electromagnetic Spectrum
1.7: Infrared Spectroscopy
1.8: Interpreting Infrared Spectra
1.9: Infrared Spectra of Some Common Functional Groups
1.10: Chemistry Matters—X-Ray Crystallography
1.11: Key Terms
1.12: Summary
1.13: Additional Problems

This page titled 1: Structure Determination - Mass Spectrometry and Infrared Spectroscopy is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

1.1: Why This Chapter?

Finding the structures of new molecules, whether small ones synthesized in the laboratory or large proteins and nucleic acids found in living organisms, is central to progress in chemistry and biochemistry. We can only scratch the surface of structure determination in this book, but after reading this and the following two chapters, you should have a good idea of the range of structural techniques available and of how and when each is used.

Figure 1.1.1: More than a thousand different chemical compounds have been isolated from coffee. Their structures were determined using various spectroscopic techniques. (credit: “Coffee, Espresso” by John Beans/myfriendscoffee.com, CC BY 4.0)

Every time a reaction is run, the products must be identified, and every time a new compound is found in nature, its structure must be determined. Determining the structure of an organic compound was a difficult and time-consuming process until the mid-20th century, but powerful techniques and specialized instruments are now routinely used to simplify the problem. In this and the next two chapters, we’ll look at four such techniques—mass spectrometry (MS), infrared (IR) spectroscopy, ultraviolet spectroscopy (UV), and nuclear magnetic resonance spectroscopy (NMR)—and we’ll see the kind of information that can be obtained from each.

Mass spectrometry	What is the size and formula?
Infrared spectroscopy	What functional groups are present?
Ultraviolet spectroscopy	Is a conjugated π electron system present?
Nuclear magnetic resonance spectroscopy	What is the carbon–hydrogen framework?

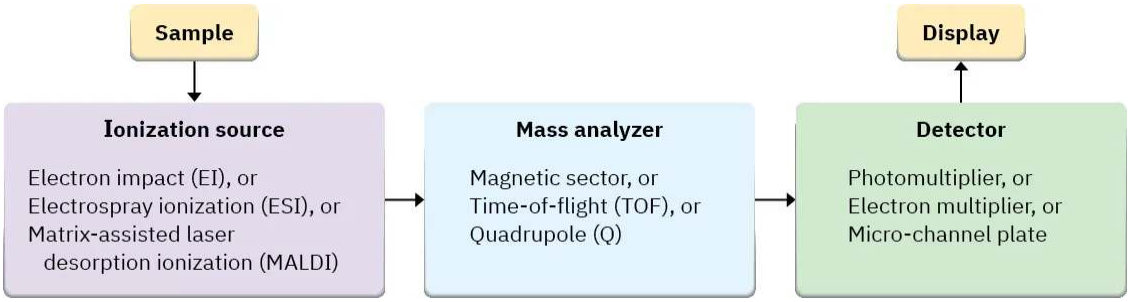
This page titled 1.1: Why This Chapter? is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **12.0: Why This Chapter?** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

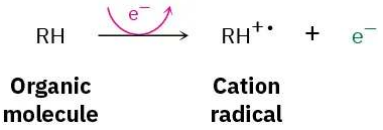
1.2: Mass Spectrometry of Small Molecules - Magnetic-Sector Instruments

At its simplest, mass spectrometry (MS) is a technique for measuring the mass, and therefore the molecular weight (MW), of a molecule. In addition, it's often possible to gain structural information about a molecule by measuring the masses of the fragments produced when molecules are broken apart.

More than 20 different kinds of commercial mass spectrometers are available depending on the intended application, but all have three basic parts: an *ionization source* in which sample molecules are given an electrical charge, a *mass analyzer* in which ions are separated by their mass-to-charge ratio, and a *detector* in which the separated ions are observed and counted.



Among the most common mass spectrometers used for routine purposes in the laboratory is the electron-impact, magnetic-sector instrument shown schematically in Figure 1.2.1. A small amount of sample is vaporized into the ionization source, where it is bombarded by a stream of high-energy electrons. The energy of the electron beam can be varied but is commonly around 70 electron volts (eV), or 6700 kJ/mol. When a high-energy electron strikes an organic molecule, it dislodges a valence electron from the molecule, producing a cation radical—*cation* because the molecule has lost an electron and now has a positive charge; *radical* because the molecule now has an odd number of electrons.



Electron bombardment transfers so much energy that most of the cation radicals fragment after formation. They break apart into smaller pieces, some of which retain the positive charge and some of which are neutral. The fragments then flow through a curved pipe in a strong magnetic field, which deflects them into different paths according to their mass-to-charge ratio (*m*/*z*). Neutral fragments are not deflected by the magnetic field and are lost on the walls of the pipe, but positively charged fragments are sorted by the mass spectrometer onto a detector, which records them as peaks at the various *m*/*z* ratios. Since the number of charges *z* on each ion is usually 1, the value of *m*/*z* for each ion is simply its mass *m*. Masses up to approximately 2500 atomic mass units (amu) can be analyzed by this type of instrument.

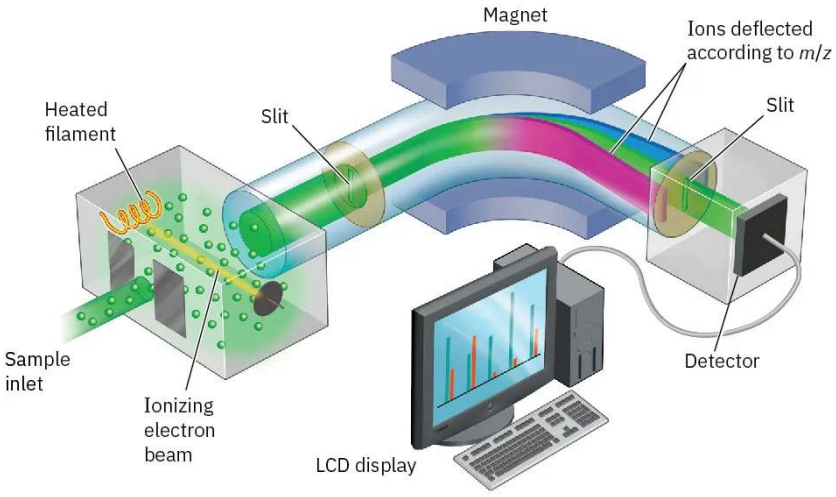


Figure 1.2.1: Representation of an electron-ionization, magnetic-sector mass spectrometer. Molecules are ionized by collision with high-energy electrons, causing some of the molecules to fragment. Passage of the charged fragments through a magnetic field then sorts them according to their mass.

Another common type of mass spectrometer uses what is called a quadrupole mass analyzer, which has a set of four solid rods is arranged parallel to the direction of the ion beam, with an oscillating electrostatic field is generated in the space between the rods. For a given field, only one *m/z* value will make it through the quadrupole region. The others will crash into the rods or the walls of the instrument and never reach the detector Figure 1.2.2.

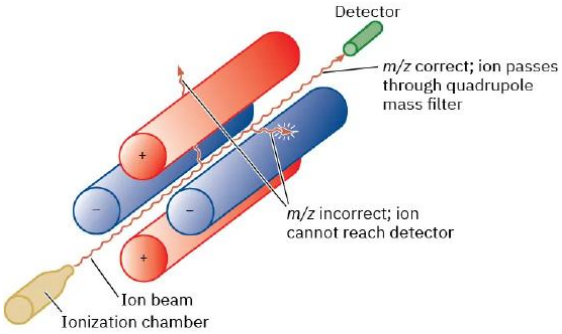


Figure 1.2.2: Representation of a quadrupole mass analyzer. Only ions of a certain *m/z* will reach the detector; other ions will collide with the rods.

The mass spectrum of a compound is typically presented as a bar graph, with masses (*m/z* values) on the *x* axis and intensity, or relative abundance of ions of a given *m/z* striking the detector, on the *y* axis. The tallest peak, assigned an intensity of 100%, is called the base peak, and the peak that corresponds to the unfragmented cation radical is called the parent peak, or the *molecular ion* (M^+, or simply *M*). Figure 1.2.3 shows the mass spectrum of propane.

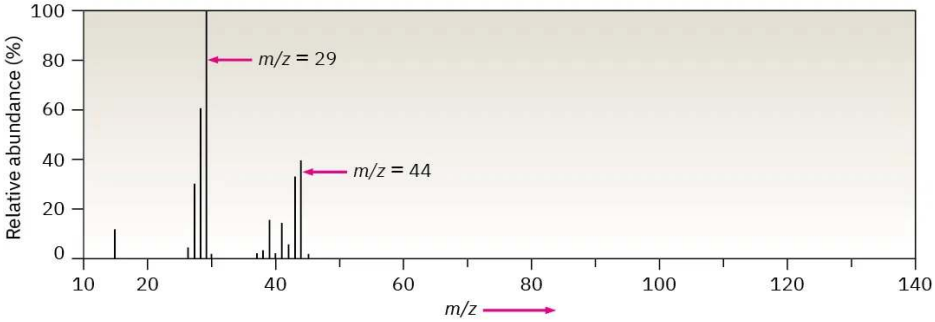


Figure 1.2.3: Mass spectrum of propane (C_3H_8; MW = 44).

Mass spectral fragmentation patterns are usually complex, and the molecular ion is often not the base peak. The mass spectrum of propane in Figure 1.2.3, for instance, shows a molecular ion at m/z = 44 that is only about 30% as high as the base peak at m/z = 29. In addition, many other fragment ions are present.

This page titled 1.2: Mass Spectrometry of Small Molecules - Magnetic-Sector Instruments is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **12.1: Mass Spectrometry of Small Molecules - Magnetic-Sector Instruments** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

1.3: Interpreting Mass Spectra

What kinds of information can we get from a mass spectrum? The most obvious information is the molecular weight of the sample, which in itself can be invaluable. If we were given samples of hexane (MW = 86), 1-hexene (MW = 84), and 1-hexyne (MW = 82), for example, mass spectrometry would easily distinguish them.

Some instruments, called *double-focusing mass spectrometers*, have two magnetic sectors in their mass analyzers, giving these spectrometers have such high resolution that they provide mass measurements accurate to 5 ppm, or about 0.0005 amu, making it possible to distinguish between two formulas with the same nominal mass. For example, both C_5H_{12} and C_4H_8O have MW = 72, but they differ slightly beyond the decimal point: C_5H_{12} has an exact mass of 72.0939 amu, whereas C_4H_8O has an exact mass of 72.0575 amu. A high-resolution instrument can easily distinguish between them. Note, however, that exact mass measurements refer to molecules with specific isotopic compositions. Thus, the sum of the exact atomic masses of the specific isotopes in a molecule is measured—1.007 83 amu for ^{1}H, 12.000 00 amu for ^{12}C, 14.003 07 amu for ^{14}N, 15.994 91 amu for ^{16}O, and so on—rather than the sum of the average atomic masses of elements, as found on a periodic table.

Unfortunately, not every compound shows a molecular ion in its electron-impact mass spectrum. Although M^+ is usually easy to identify if it's abundant, some compounds, such as 2,2-dimethylpropane, fragment so easily that no molecular ion is observed (Figure 1.3.1). In such cases, alternative "soft" ionization methods that don't use electron bombardment can prevent or minimize fragmentation (see Section 12.5).

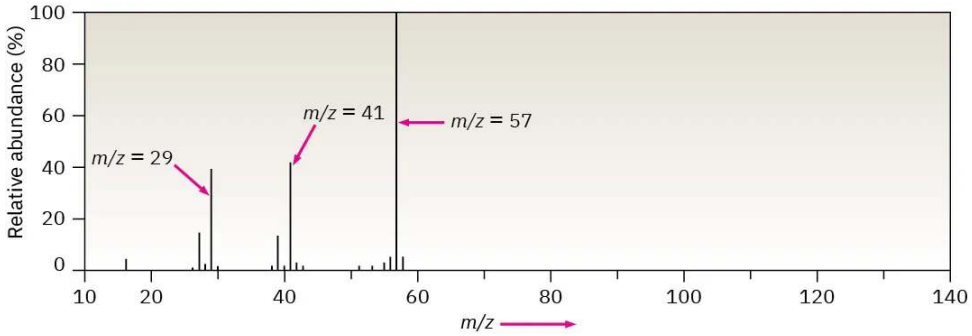


Figure 1.3.1: Mass spectrum of 2,2-dimethylpropane (C_5H_{12}; MW = 72). No molecular ion is observed when electron-impact ionization is used. What do you think is the formula and structure of the M^+ peak at m/z = 57?

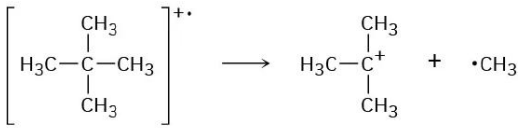
Knowing the molecular weight makes it possible to narrow considerably the choices of molecular formula. For example, if the mass spectrum of an unknown compound shows a molecular ion at m/z = 110, the molecular formula is likely to be C_8H_{14}, $C_7H_{10}O$, $C_6H_6O_2$, or $C_6H_{10}N_2$. There are always a number of molecular formulas possible for all but the lowest molecular weights, and a computer can easily generate a list of the choices.

A further point about mass spectrometry, noticeable in the spectra of both propane (Figure 12.4) and 2,2-dimethylpropane (Figure 1.3.1), is that the peak for the molecular ion is not at the highest *m/z* value. There is also a small peak at M + 1 due to the presence of different isotopes in the molecules. Although ^{12}C is the most abundant carbon isotope, a small amount (1.10% natural abundance) of ^{13}C is also present. Thus, a certain percentage of the molecules analyzed in the mass spectrometer are likely to contain a ^{13}C atom, giving rise to the observed M + 1 peak. In addition, a small amount of ^{2}H (deuterium; 0.015% natural abundance) is present, making a further contribution to the M + 1 peak.

Mass spectrometry would be useful even if molecular weight and formula were the only information that could be obtained, but in fact it provides much more. For one thing, the mass spectrum of a compound serves as a kind of "molecular fingerprint." Every organic compound fragments in a unique way depending on its structure, and the likelihood of two compounds having identical mass spectra is small. Thus, it's sometimes possible to identify an unknown by computer-based matching of its mass spectrum to one of the more than 785,061 searchable spectra recorded in a database called the *Registry of Mass Spectral Data*.

It's also possible to derive structural information about a molecule by interpreting its fragmentation pattern. Fragmentation occurs when the high-energy cation radical flies apart by spontaneous cleavage of a chemical bond. One of the two fragments retains the positive charge and is a carbocation, while the other fragment is a neutral radical.

Not surprisingly, the positive charge often remains with the fragment that is best able to stabilize it. In other words, a relatively stable carbocation is often formed during fragmentation. For example, 2,2-dimethylpropane tends to fragment in such a way that the positive charge remains with the *tert*-butyl group. 2,2-Dimethylpropane therefore has a base peak at *m/z* = 57, corresponding to $C_4H_9^+$ (Figure 1.3.1).



***m/z* = 57**

Because mass-spectral fragmentation patterns are usually complex, it's often difficult to assign structures to fragment ions. Most hydrocarbons fragment in many ways, as demonstrated by the mass spectrum of hexane in Figure 1.3.2. The hexane spectrum shows a moderately abundant molecular ion at *m/z* = 86 and fragment ions at *m/z* = 71, 57, 43, and 29. Since all the carbon–carbon bonds of hexane are electronically similar, all break to a similar extent, giving rise to the observed mixture of ions.

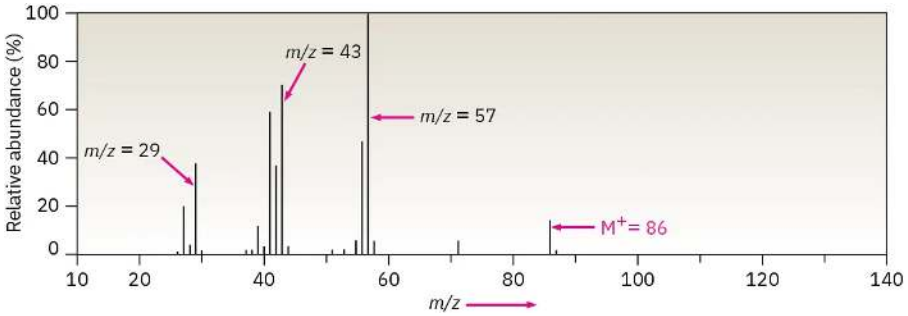


Figure 1.3.2: Mass spectrum of hexane (C_6H_{14}; MW = 86). The base peak is at *m/z* = 57, and numerous other ions are present.

Figure 1.3.3 shows how the hexane fragments might arise. The loss of a methyl radical (CH_3, M = 15) from the hexane cation radical (M^+ = 86) gives rise to a fragment of mass 86 – 15 = 71; the loss of an ethyl radical (C_2H_5, M = 29) accounts for a fragment of mass 86 – 29 = 57; the loss of a propyl radical (C_3H_7, M = 43) accounts for a fragment of mass 86 – 43 = 43; and the loss of a butyl radical accounts for a fragment of mass 29. With practice, it's sometimes possible to analyze the fragmentation pattern of an unknown compound and work backward to a structure that is compatible with the data.

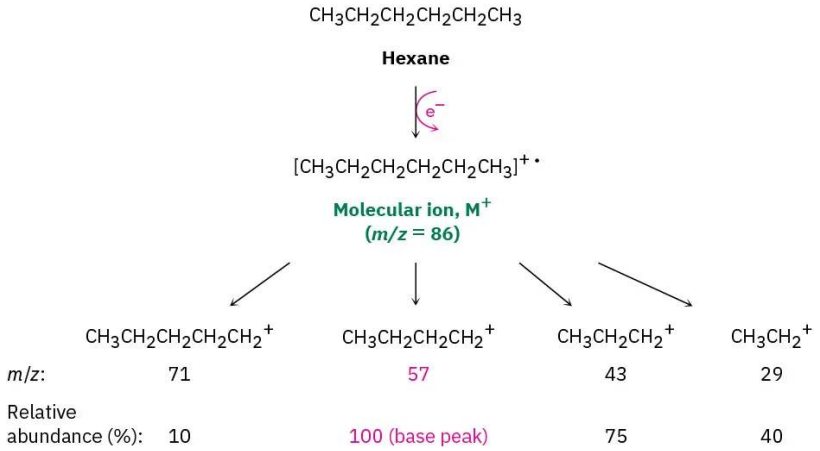


Figure 1.3.3: Fragmentation of hexane in a mass spectrometer.

We'll see in the next section and in later chapters that specific functional groups, such as alcohols, ketones, aldehydes, and amines, show specific kinds of mass spectral fragmentations that can be interpreted to provide structural information.

Worked Example 12.1: Using Mass Spectra to Identify Compounds

Assume that you have two unlabeled samples, one of methylcyclohexane and the other of ethylcyclopentane. How could you use mass spectrometry to tell them apart? The mass spectra of both are shown in Figure 1.3.4.

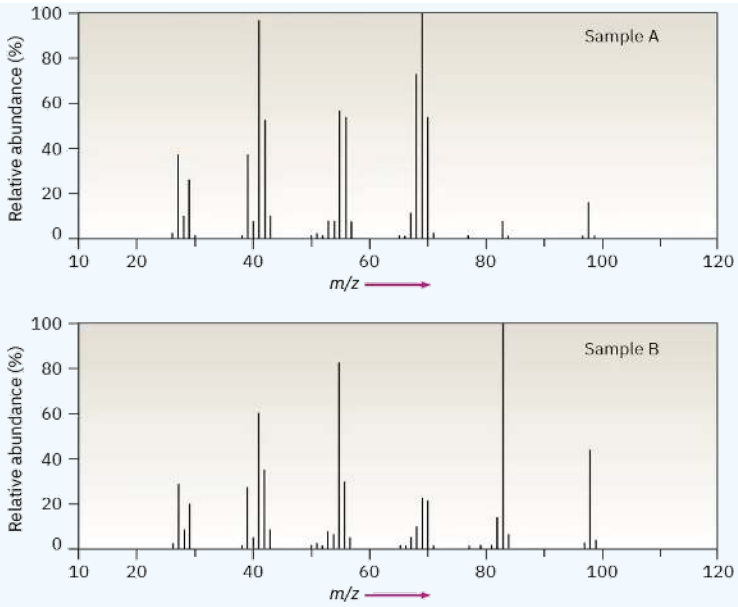


Figure 1.3.4: Mass spectra of unlabeled samples A and B for Worked Example 12.1.

Strategy

Look at the possible structures and decide on how they differ. Then think about how any of these differences in structure might give rise to differences in mass spectra. Methyl cyclohexane, for instance, has a $–CH_3$ group, and ethylcyclopentane has a $–CH_2CH_3$ group, which should affect the fragmentation patterns.

Solution

Both mass spectra show molecular ions at $M^+ = 98$, corresponding to C_7H_{14}, but they differ in their fragmentation patterns. Sample **A** has its base peak at $m/z = 69$, corresponding to the loss of a CH_2CH_3 group (29 mass units), but **B** has a rather small peak at $m/z = 69$. Sample **B** shows a base peak at $m/z = 83$, corresponding to the loss of a CH_3 group (15 mass units), but sample **A** has only a small peak at $m/z = 83$. We can therefore be reasonably certain that **A** is ethylcyclopentane and **B** is methylcyclohexane.

? Exercise 1.3.1

The sex hormone testosterone contains only C, H, and O and has a mass of 288.2089 amu, as determined by high-resolution mass spectrometry. What is the likely molecular formula of testosterone?

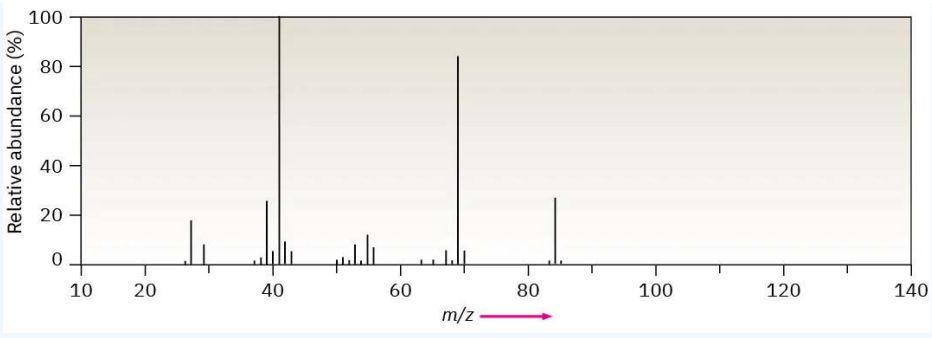
Answer

$C_{19}H_{28}O_2$

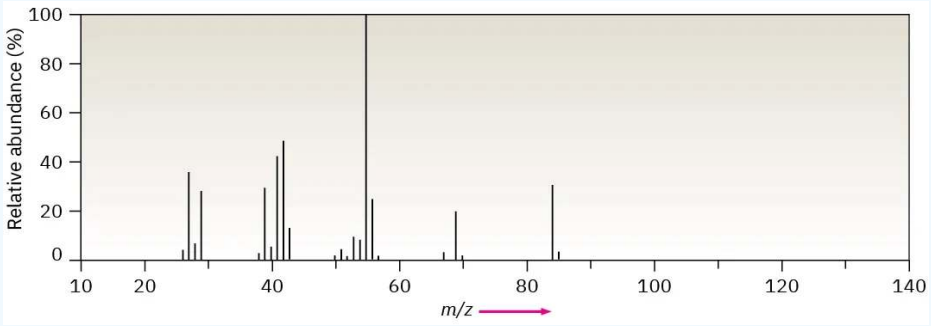
? Exercise 1.3.2

Two mass spectra are shown in Figure 1.3.5. One spectrum is that of 2-methyl-2-pentene; the other is of 2-hexene. Which is which? Explain

a.



b.



Answer

a. 2-Methyl-2-pentene

b. 2-Hexene

Explanation: Note the relative abundances of the group of peaks around 40 amu in **(a)** vs the 55 amu in **(b)**. The larger fragments in **(a)** comes from the preferential breaking of all of the three-carbon chain fragment from both fragments on either side of the double-bond, whereas the 4-carbon chain in 2-hexene splitting at the alkene results in the peaks around 55 amu.

This page titled 1.3: Interpreting Mass Spectra is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **12.2: Interpreting Mass Spectra** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

1.4: Mass Spectrometry of Some Common Functional Groups

As each functional group is discussed in future chapters, mass-spectral fragmentations characteristic of that group will be described. As a preview, though, we'll point out some distinguishing features of several common functional groups.

Alcohols

Alcohols undergo fragmentation in a mass spectrometer by two pathways: *alpha cleavage* and *dehydration*. In the *α*-cleavage pathway, a C–C bond nearest the hydroxyl group is broken, yielding a neutral radical plus a resonance-stabilized, oxygen-containing cation. This type of fragmentation is seen in the spectrum of 2-pentanol in Figure 1.4.1.

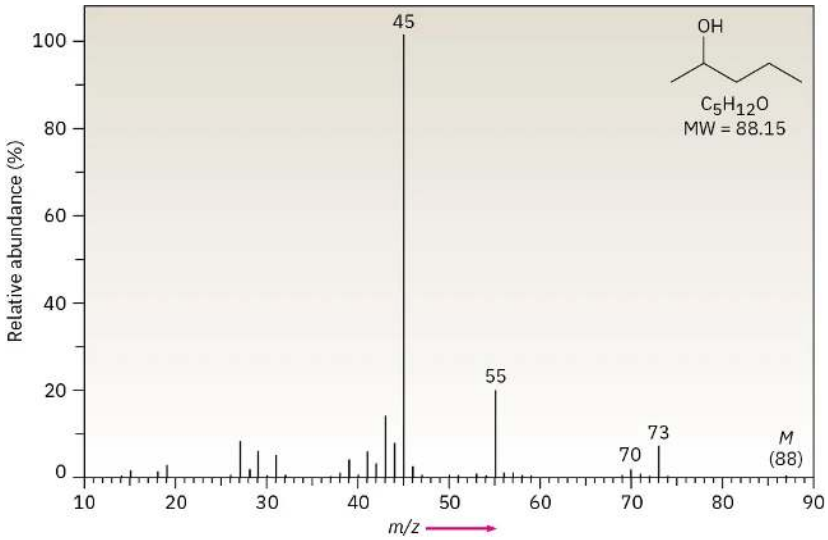
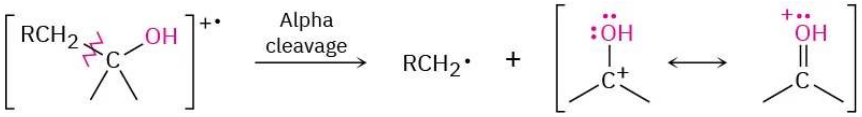
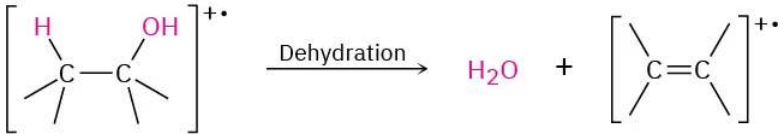


Figure 1.4.1: Mass spectrum of 2-pentanol.



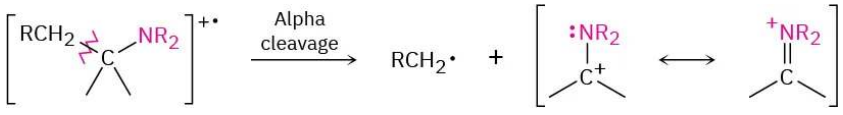
In the dehydration pathway, water is eliminated, yielding an alkene radical cation with a mass 18 amu less than M^+. For simplicity, we have drawn the dehydration below as an E2-type process. Often the hydrogen that is lost is not beta to the hydroxyl. Only a small peak from dehydration is observed in the spectrum of 2-pentanol (Figure 1.4.1).



Amines

The **nitrogen rule** of mass spectrometry says that a compound with an odd number of nitrogen atoms has an odd-numbered molecular weight. The logic behind the rule comes from the fact that nitrogen is trivalent, thus requiring an odd number of hydrogen atoms. The presence of nitrogen in a molecule is often detected simply by observing its mass spectrum. An odd-numbered molecular ion usually means that the unknown compound has one or three nitrogen atoms, and an even-numbered molecular ion usually means that a compound has either zero or two nitrogen atoms.

Aliphatic amines undergo a characteristic *α* cleavage in a mass spectrometer, similar to that observed for alcohols. A C–C bond nearest the nitrogen atom is broken, yielding an alkyl radical and a resonance-stabilized, nitrogen-containing cation.



The mass spectrum of triethylamine has a base peak at m/z = 86, which arises from an alpha cleavage resulting in the loss of a methyl group (Figure 1.4.2).

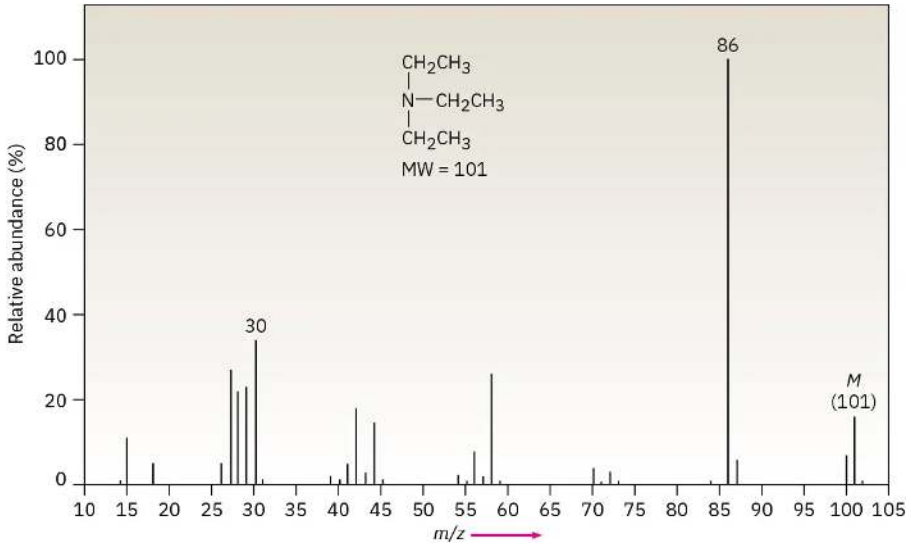


Figure 1.4.2: Mass spectrum of triethylamine.

Halides

The fact that some elements have two common isotopes gives their mass spectra a distinctive appearance. Chlorine, for example, exists as two isotopes, ^{35}Cl and ^{37}Cl, in roughly a 3 : 1 ratio. In a sample of chloroethane, three out of four molecules contain a ^{35}Cl atom and one out of four has a ^{37}Cl atom. In the mass spectrum of chloroethane (Figure 1.4.3 we see the molecular ion (M) at m/z = 64 for ions that contain a ^{35}Cl and another peak at m/z = 66, called the M + 2 peak, for ions containing a ^{37}Cl. The ratio of the relative abundance of M : M + 2 is about 3 : 1, a reflection of the isotopic abundances of chlorine.

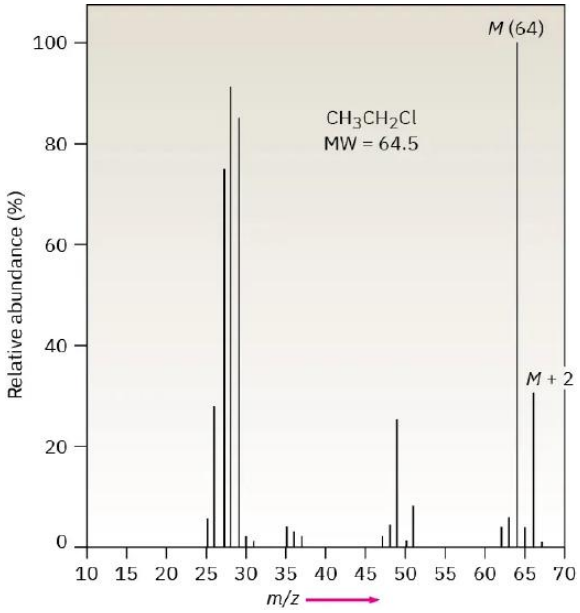


Figure 1.4.3: Mass spectrum of chloroethane.

In the case of bromine, the isotopic distribution is 50.7% ^{79}Br and 49.3% ^{81}Br. In the mass spectrum of 1-bromohexane (Figure 1.4.4) the molecular ion appears at m/z = 164 for ^{79}Br-containing ions and the M + 2 peak is at m/z = 166 for ^{81}Br-containing ions. The ions at m/z = 135 and 137 are informative as well. The two nearly equally large peaks tell us that the ions at those m/z values still contain the bromine atom. The peak at m/z = 85, on the other hand, does not contain bromine because there is not a large peak at m/z = 87.

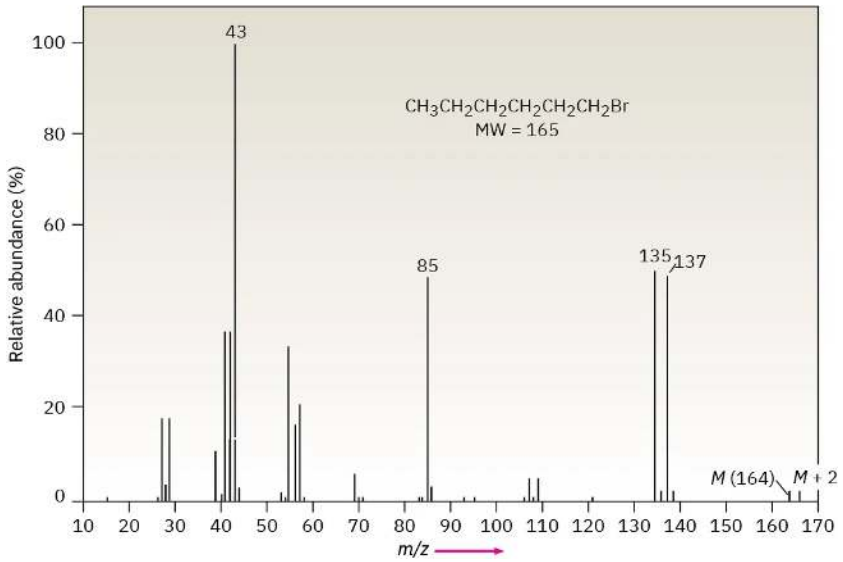
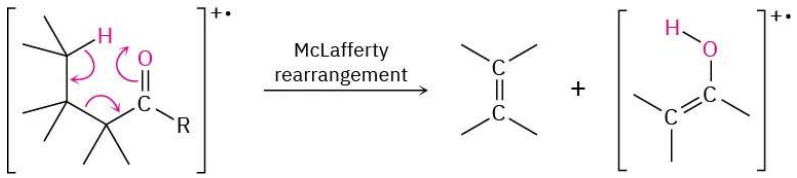


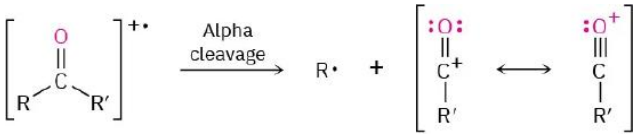
Figure 1.4.4: Mass spectrum of 1-bromohexane.

Carbonyl Compounds

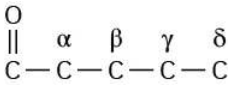
Ketones and aldehydes that have a hydrogen on a carbon three atoms away from the carbonyl group undergo a characteristic mass-spectral cleavage called the **McLafferty rearrangement**. The hydrogen atom is transferred to the carbonyl oxygen, a C–C bond between the alpha and beta carbons is broken, and a neutral alkene fragment is produced. The charge remains with the oxygen-containing fragment.



In addition, ketones and aldehydes frequently undergo *α* cleavage of the bond between the carbonyl carbon and the neighboring carbon to yield a neutral radical and a resonance-stabilized acyl cation. Because the carbon neighboring the carbonyl carbon is called the alpha carbon, the reaction is called an alpha cleavage.



(To be more general about neighboring positions in carbonyl compounds, Greek letters are used in alphabetical order: alpha, beta, gamma, delta, and so on.)



The mass spectrum of butyrophenone illustrates both alpha cleavage and the McLafferty rearrangement (Figure 1.4.5). Alpha cleavage of the propyl substituent results in the loss of C_3H_7 = 43 mass units from the parent ion at *m*/*z* = 148 to give the fragment ion at *m*/*z* = 105. A McLafferty rearrangement of butyrophenone results in the loss of ethylene, C_2H_4 = 28 mass units, from the parent leaving the ion at *m*/*z* = 120.

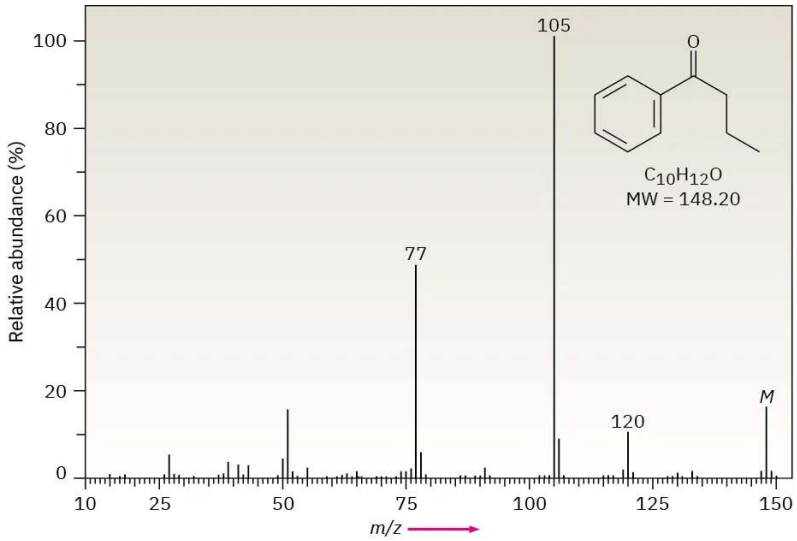


Figure 1.4.5: Mass spectrum of butyrophenone.

Worked Example 12.2: Identifying Fragmentation Patterns in a Mass Spectrum

The mass spectrum of 2-methyl-3-pentanol is shown in Figure 1.4.6. What fragments can you identify?

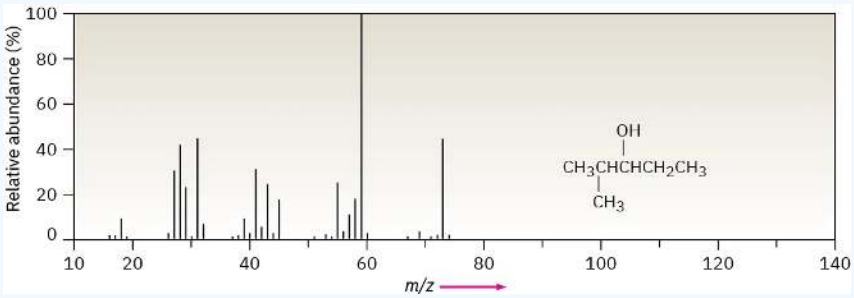


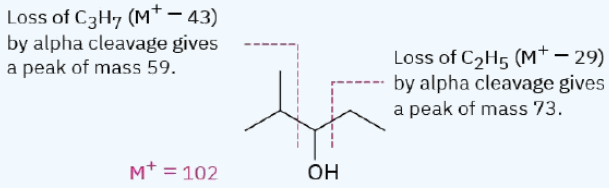
Figure 1.4.6: Mass spectrum of 2-methyl-3-pentanol, for Worked Example 12.2.

Strategy

Calculate the mass of the molecular ion, and identify the functional groups in the molecule. Then write the fragmentation processes you might expect, and compare the masses of the resultant fragments with the peaks present in the spectrum.

Solution

2-Methyl-3-pentanol, an open-chain alcohol, has M^+ = 102 and might be expected to fragment by α cleavage and by dehydration. These processes would lead to fragment ions of m/z = 84, 73, and 59. Of the three expected fragments, dehydration is not observed (no m/z = 84 peak), but both α cleavages take place (m/z = 73, 59).



Exercise 1.4.1

What are the masses of the charged fragments produced in the following cleavage pathways?

a. Alpha cleavage of 2-pentanone ($CH_3COCH_2CH_2CH_3$)
b. Dehydration of cyclohexanol (hydroxycyclohexane)
c. McLafferty rearrangement of 4-methyl-2-pentanone [$CH_3COCH_2CH(CH_3)_2$]

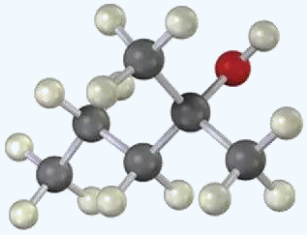
d. Alpha cleavage of triethylamine [$(CH_3CH_2)_3N$]

Answer

(a) 43, 71 **(b)** 82 **(c)** 58 **(d)** 86

? Exercise 1.4.2

List the masses of the parent ion and of several fragments you might expect to find in the mass spectrum of the following molecule:



Answer

102 (M^+), 84 (dehydration), 87 (alpha cleavage), 59 (alpha cleavage)

This page titled 1.4: Mass Spectrometry of Some Common Functional Groups is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **12.3: Mass Spectrometry of Some Common Functional Groups** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

1.5: Mass Spectrometry in Biological - Time-of-flight (TOF) Instruments

MS analyses of sensitive biological samples rarely use magnetic sector ionization. Instead, they typically use either electrospray ionization (*ESI*) or matrix-assisted laser desorption ionization (*MALDI*), typically linked to a time-of-flight (*TOF*) mass analyzer. Both ESI and MALDI are soft ionization methods that produce charged molecules with little fragmentation, even with sensitive biological samples of very high molecular weight.

In an ESI source, as a sample solution exits the tube, it is subjected to a high voltage that causes the droplets to become charged. The sample molecules gain one or more protons from charged solvent molecules in the droplet. The volatile solvent quickly evaporates, giving variably protonated sample molecules ($M + H_n^{n+}$). In a MALDI source, the sample is adsorbed onto a suitable matrix compound, such as 2,5-dihydroxybenzoic acid, which is ionized by a short burst of laser light. The matrix compound then transfers the energy to the sample and protonates it, forming $M + H_n^{n+}$ ions.Following ion formation, the variably protonated sample molecules are electrically focused into a small packet with a narrow spatial distribution, and the packet is given a sudden kick of energy by an accelerator electrode. As each molecule in the packet is given the same energy,

$$E = \frac{mv^2}{2}$$

it begins moving with a velocity that depends on the square root of its mass,

$$v = \sqrt{\frac{2E}{m}}.$$

Lighter molecules move faster, and heavier molecules move slower. The analyzer itself—the *drift tube*—is simply an electrically grounded metal tube inside which the different charged molecules become separated as they move at different velocities and take different amounts of time to complete their flight.

The Time of Flight technique is considerably more sensitive than the magnetic sector alternative, and protein samples of up to 100 kilodaltons (100,000 amu) can be separated with a mass accuracy of 3 ppm. Figure 1.5.1 shows a MALDI–TOF spectrum of chicken egg-white lysozyme, MW = 14,306.7578 daltons. Biochemists generally use the unit *dalton*, abbreviated Da, instead of amu, although the two are equivalent (1 dalton = 1 amu).

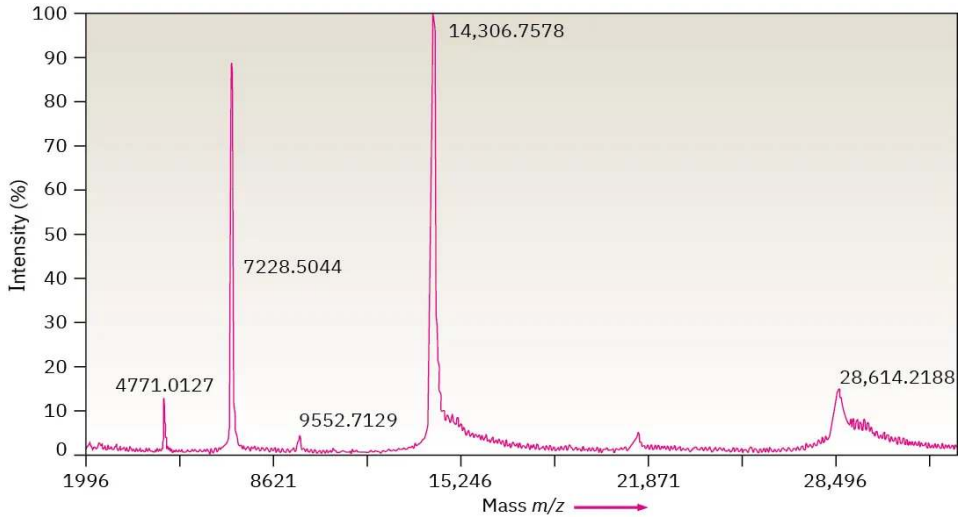


Figure 1.5.1: MALDI–TOF mass spectrum of chicken egg-white lysozyme. The peak at 14,306.7578 daltons (amu) is due to the monoprotonated protein, $M + H^+$, and the peak at 28,614.2188 daltons is due to an impurity formed by dimerization of the protein. Other peaks at lower *m*/*z* values are various protonated species, $M + H_n^{n+}$.

This page titled 1.5: Mass Spectrometry in Biological - Time-of-flight (TOF) Instruments is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **12.4: Mass Spectrometry in Biological - Time-of-flight (TOF) Instruments** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

1.6: Spectroscopy and the Electromagnetic Spectrum

Infrared, ultraviolet, and nuclear magnetic resonance spectroscopies differ from mass spectrometry in that they are nondestructive and involve the interaction of molecules with electromagnetic energy rather than with an ionizing source. Before beginning a study of these techniques, however, let's briefly review the nature of radiant energy and the electromagnetic spectrum.

Visible light, X rays, microwaves, radio waves, and so forth are all different kinds of electromagnetic radiation. Collectively, they make up the electromagnetic spectrum, shown in Figure 1.6.1. The electromagnetic spectrum is arbitrarily divided into regions, with the familiar visible region accounting for only a small portion, from 3.8×10^{-7} m to 7.8×10^{-7} m in wavelength. The visible region is flanked by the infrared and ultraviolet regions.

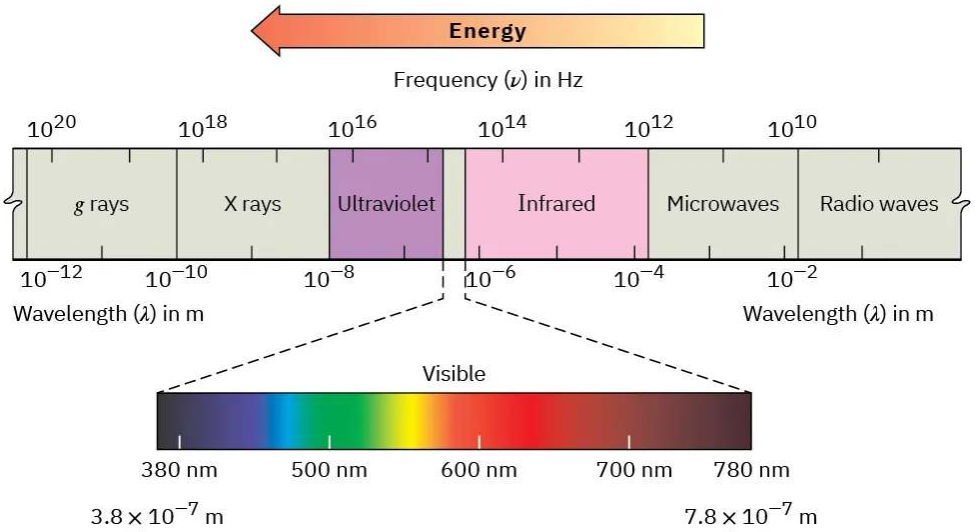


Figure 1.6.1: The electromagnetic spectrum covers a continuous range of wavelengths and frequencies, from radio waves at the low-frequency end to gamma (γ) rays at the high-frequency end. The familiar visible region accounts for only a small portion near the middle of the spectrum.

Electromagnetic radiation is often said to have dual behavior. In some respects, it has the properties of a particle, called a photon, yet in other respects it behaves as an energy wave. Like all waves, electromagnetic radiation is characterized by a *wavelength*, a *frequency*, and an *amplitude* (Figure 1.6.2). The wavelength, λ (Greek lambda), is the distance from one wave maximum to the next. The frequency, ν (Greek nu), is the number of waves that pass by a fixed point per unit time, usually given in reciprocal seconds (s^{-1}), or hertz, Hz (1 Hz = 1 s^{-1}). The amplitude is the height of a wave, measured from midpoint to peak. The intensity of radiant energy, whether a feeble glow or a blinding glare, is proportional to the square of the wave's amplitude.

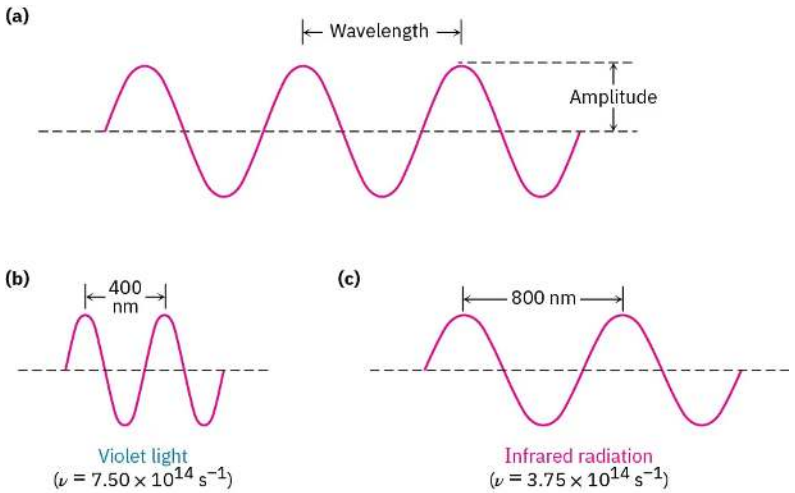


Figure 1.6.2: Electromagnetic waves are characterized by a wavelength, a frequency, and an amplitude. **(a)** Wavelength (λ) is the distance between two successive wave maxima. Amplitude is the height of the wave measured from the center. **(b)–(c)** What we perceive as different kinds of electromagnetic radiation are simply waves with different wavelengths and frequencies.

Multiplying the wavelength of a wave in meters (m) by its frequency in reciprocal seconds (s^{-1}) gives the speed of the wave in meters per second (m/s). The rate of travel of all electromagnetic radiation in a vacuum is a constant value, commonly called the "speed of light" and abbreviated c. Its numerical value is defined as exactly 2.997 924 58 × 10^8 m/s, usually rounded off to 3.00 × 10^8 m/s.

$$\text{Wavelength} \times \text{Frequency} = \text{Speed}$$

$$\lambda(\text{m}) \times \nu\left(\text{s}^{-1}\right) = c(\text{ m/s})$$

$$\lambda = \frac{c}{v} \tag{1.6.1}$$

or

$$\nu = \frac{c}{\lambda} \tag{1.6.2}$$

Just as matter comes only in discrete units called atoms, electromagnetic energy is transmitted only in discrete amounts called **quanta**. The amount of energy ε corresponding to 1 quantum of energy (1 **photon**) of a given frequency ν is expressed by the Planck equation

$$\varepsilon = h\nu = \frac{hc}{\lambda} \tag{1.6.3}$$

where h is Planck's constant (6.62 × 10^{-34} J · s = 1.58 × 10^{-34} cal · s).

The Planck equation says that the energy of a given photon varies directly with its frequency ν but inversely with its wavelength λ. High frequencies and short wavelengths correspond to high-energy radiation such as gamma rays; low frequencies and long wavelengths correspond to low-energy radiation such as radio waves. Multiplying ε by Avogadro's number N_A gives the same equation in more familiar units, where E represents the energy of Avogadro's number (one "mole") of photons of wavelength λ:

$$\begin{aligned} E &= \frac{N_A hc}{\lambda} \\ &= \frac{1.20 \times 10^{-4}\ \text{kJ/mol}}{\lambda(\text{ m})} \\ &= \frac{2.86 \times 10^{-5}\text{kcal/mol}}{\lambda(\text{ m})} \end{aligned}$$

When an organic compound is exposed to a beam of electromagnetic radiation, it absorbs energy of some wavelengths but passes, or transmits, energy of other wavelengths. If we irradiate the sample with energy of many different wavelengths and determine which are absorbed and which are transmitted, we can measure the absorption spectrum of the compound.

An example of an absorption spectrum—that of ethanol exposed to infrared radiation—is shown in Figure 1.6.3. The horizontal axis records the wavelength, and the vertical axis records the intensity of the various energy absorptions in percent transmittance. The baseline corresponding to 0% absorption (or 100% transmittance) runs along the top of the chart, so a downward spike means that energy absorption has occurred at that wavelength.

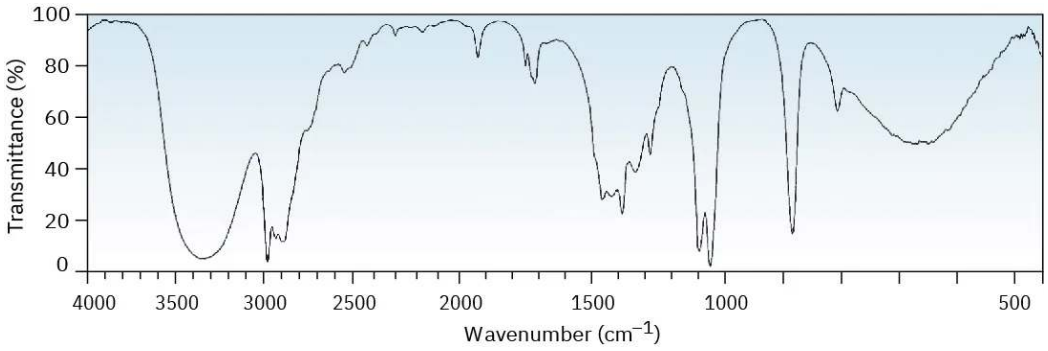


Figure 1.6.3: An infrared absorption spectrum for ethanol, CH_3CH_2OH. A transmittance of 100% means that all the energy is passing through the sample, whereas a lower transmittance means that some energy is being absorbed. Thus, each downward spike corresponds to an energy absorption.

The energy a molecule gains when it absorbs radiation must be distributed over the molecule in some way. With infrared radiation, the absorbed energy causes bonds to stretch and bend more vigorously. With ultraviolet radiation, the energy causes an electron to jump from a lower-energy orbital to a higher-energy one. Different radiation frequencies affect molecules in different ways, but each provides structural information when the results are interpreted.

There are many kinds of spectroscopies, which differ according to the region of the electromagnetic spectrum used. We'll look at three: infrared spectroscopy, ultraviolet spectroscopy, and nuclear magnetic resonance spectroscopy. Let's begin by seeing what happens when an organic sample absorbs infrared energy.

✔ Worked Example 1.6.1: Correlating Energy and Frequency of Radiation

Which is higher in energy, FM radio waves with a frequency of 1.015×10^8 Hz (101.5 MHz) or visible green light with a frequency of 5×10^{14} Hz?

Strategy

Remember the equations $\varepsilon = h\nu$ and $\varepsilon = hc/\lambda$, which say that energy increases as frequency increases and as wavelength decreases.

Solution

Since visible light has a higher frequency than radio waves, it is higher in energy.

? Exercise 1.6.1

Which has higher energy, infrared radiation with $\lambda = 1.0 \times 10^{-6}$ m or an X ray with $\lambda = 3.0 \times 10^{-9}$ m? Radiation with $\nu = 4.0 \times 10^9$ Hz or with $\lambda = 9.0 \times 10^{-6}$ m?

Answer

X-ray energy is higher; $\lambda = 9.0 \times 10^{-6}$ m is higher in energy.

? Exercise 1.6.2

Calculate the energies in KJ/mol of each of the following kinds of radiation:

a. A gamma ray with $\lambda = 5.0 \times 10^{-11}$ m.
b. An X-ray with $\lambda = 3.0 \times 10^{-9}$ m.
c. Ultraviolet light with $\nu = 6.0 \times 10^{15}$ Hz.
d. Visible light with $\nu = 7.0 \times 10^{14}$ Hz.
e. Infrared radiation with $\lambda = 2.0 \times 10^{-5}$ m.
f. Microwave radiation with $\nu = 5.0 \times 10^{11}$ Hz.

Answer

a. 2.4×10^6 kJ/mol
b. 4.0×10^4 kJ/mol
c. 2.4×10^3 kJ/mol
d. 2.8×10^2 kJ/mol
e. 6.0 kJ/mol
f. 4.0×10^{-2} kJ/mol

This page titled 1.6: Spectroscopy and the Electromagnetic Spectrum is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **12.5: Spectroscopy and the Electromagnetic Spectrum** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

1.7: Infrared Spectroscopy

In infrared (IR) spectroscopy, the IR region of the electromagnetic spectrum covers the range from just above the visible (7.8×10^{-7} m) to approximately 10^{-4} m, but only the midportion from 2.5×10^{-6} m to 2.5×10^{-5} m is used by organic chemists (Figure 1.7.1. Wavelengths within the IR region are usually given in micrometers ($1\ \mu m = 10^{-6}$ m), and frequencies are given in wavenumbers rather than in hertz. The wavenumber $\tilde{\nu}$ is the reciprocal of wavelength in centimeters and is therefore expressed in units of cm^{-1}.

$$\text{Wavenumber: } \tilde{\nu}\left(\text{ cm}^{-1}\right) = \frac{1}{\lambda(\text{ cm})}$$

Thus, the useful IR region is from 4000 to 400 cm^{-1}, corresponding to energies of 48.0 kJ/mol to 4.80 kJ/mol (11.5–1.15 kcal/mol).

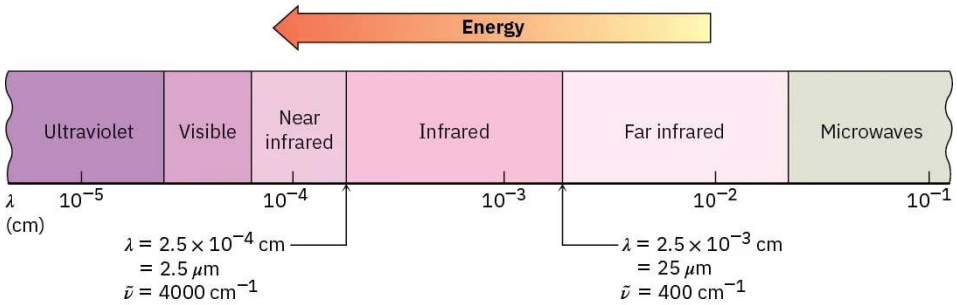
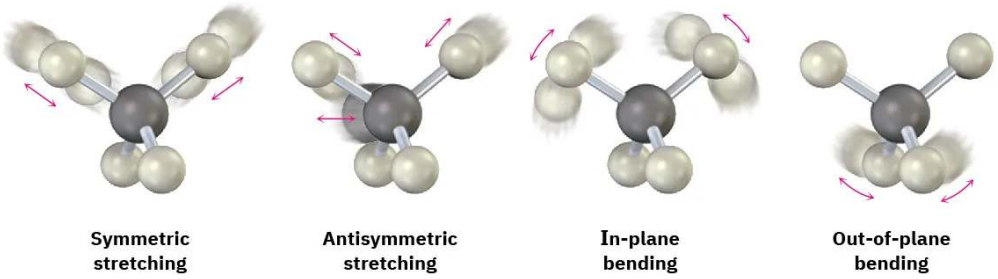


Figure 1.7.1: The infrared and adjacent regions of the electromagnetic spectrum.

Why does an organic molecule absorb some wavelengths of IR radiation but not others? All molecules have a certain amount of energy and are in constant motion. Their bonds stretch and contract, atoms wag back and forth, and other molecular vibrations occur. Some of the kinds of allowed vibrations are shown below:



The amount of energy a molecule contains is not continuously variable but is *quantized*. That is, a molecule can stretch or bend only at specific frequencies corresponding to specific energy levels. Take bond stretching, for example. Although we usually speak of bond lengths as if they were fixed, the numbers given are really averages. In fact, a typical C–H bond with an average bond length of 110 pm is actually vibrating at a specific frequency, alternately stretching and contracting as if there were a spring connecting the two atoms.

When a molecule is irradiated with electromagnetic radiation, energy is absorbed if the frequency of the radiation matches the frequency of the vibration. The result of this energy absorption is an increased amplitude for the vibration; in other words, the "spring" connecting the two atoms stretches and compresses a bit further. Since each frequency absorbed by a molecule corresponds to a specific molecular motion, we can find what kinds of motions a molecule has by measuring its IR spectrum. By interpreting these motions, we can find out what kinds of bonds (functional groups) are present in the molecule.

$$\text{IR spectrum} \rightarrow \text{What molecular motions?} \rightarrow \text{What functional groups?}$$

This page titled 1.7: Infrared Spectroscopy is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **12.6: Infrared Spectroscopy** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

1.8: Interpreting Infrared Spectra

The complete interpretation of an IR spectrum is difficult because most organic molecules have dozens of different bond stretching and bending motions, and thus have dozens of absorptions. On the one hand, this complexity is a problem because it generally limits the laboratory use of IR spectroscopy to pure samples of fairly small molecules—little can be learned from IR spectroscopy about large, complex biomolecules. On the other hand, this complexity is useful because an IR spectrum acts as a unique fingerprint of a compound. In fact, the complex region of the IR spectrum, from 1500 cm^{-1} to around 400 cm^{-1}, is called the *fingerprint region*. If two samples have identical IR spectra, they are almost certainly identical compounds.

Fortunately, we don't need to interpret an IR spectrum fully to get useful structural information. Most functional groups have characteristic IR absorption bands that don't change much from one compound to another. The C=O absorption of a ketone is almost always in the range 1680 to 1750 cm^{-1}; the O–H absorption of an alcohol is almost always in the range 3400 to 3650 cm^{-1}; the C=C absorption of an alkene is almost always in the range 1640 to 1680 cm^{-1}; and so forth. By learning where characteristic functional-group absorptions occur, it's possible to get structural information from IR spectra. Table 1.8.1 lists the characteristic IR bands of some common functional groups.

Table 1.8.1: Characteristic IR Absorptions of Some Functional Groups

Functional Group		Absorption (cm^{-1})	Intensity
Alkane	C–H	2850–2960	Medium
Alkene	=C–H	3020–3100	Medium
	C=C	1640–1680	Medium
Alkyne	≡C–H	3300	Strong
	C≡C	2100–2260	Medium
Alkyl halide	C–Cl	600–800	Strong
	C–Br	500–600	Strong
Alcohol	O–H	3400–3650	Strong, broad
	C–O	1050–1150	Strong
Arene	C–H	3030	Weak
Aromatic ring		1660–2000	Weak
		1450–1600	Medium
Amine	N–H	3300–3500	Medium
	C–N	1030–1230	Medium
Carbonyl compound	C=O	1670–1780	Strong
	Aldehyde	1730	Strong
	Ketone	1715	Strong
	Ester	1735	Strong
	Amide	1690	Strong
	Carboxylic acid	1710	Strong
Carboxylic acid	O–H	2500–3100	Strong, broad
Nitrile	C≡N	2210–2260	Medium
Nitro	NO_2	1540	Strong

Look at the IR spectra of hexane, 1-hexene, and 1-hexyne in Figure 1.8.1 to see an example of how IR spectroscopy can be used. Although all three IR spectra contain many peaks, there are characteristic absorptions of C=C and C≡C functional groups that allow the three compounds to be distinguished. Thus, 1-hexene shows a characteristic C=C absorption at 1660 cm^{-1} and a vinylic =C–H absorption at 3100 cm^{-1}, whereas 1-hexyne has a C≡C absorption at 2100 cm^{-1} and a terminal alkyne ≡C–H absorption at 3300 cm^{-1}.

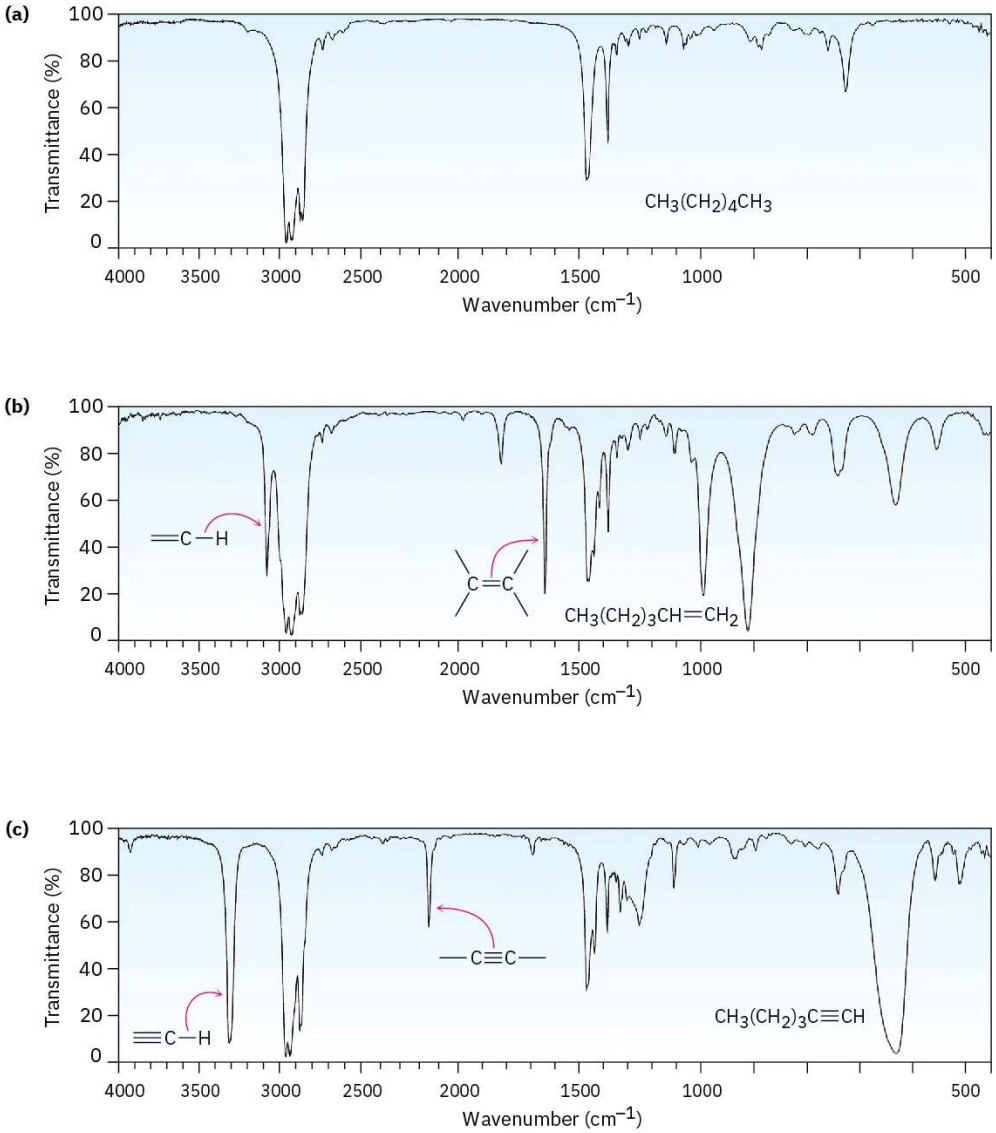


Figure 1.8.1: IR spectra of (a) hexane, (b) 1-hexene, and (c) 1-hexyne. Spectra like these are easily obtained from sub-milligram amounts of material in a few minutes using commercially available instruments.

It helps in remembering the position of specific IR absorptions to divide the IR region from 4000 cm^{-1} to 400 cm^{-1} into four parts, as shown in Figure 1.8.2.

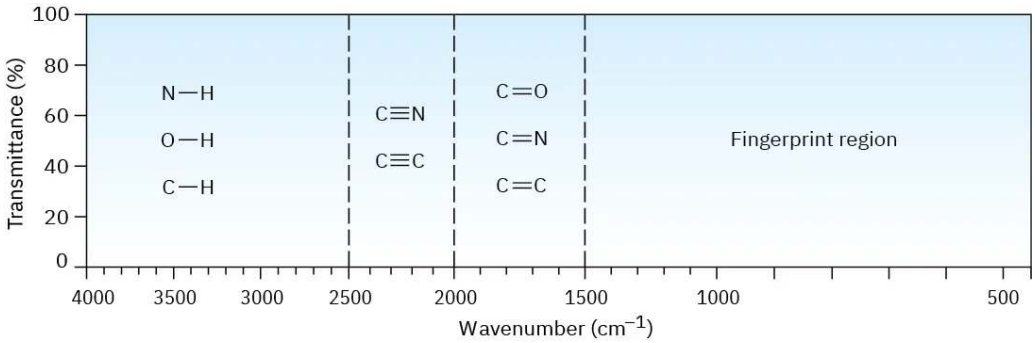


Figure 1.8.2: The four regions of the infrared spectrum: single bonds to hydrogen, triple bonds, double bonds, and fingerprint.

- The region from 4000 to 2500 cm^{-1} corresponds to absorptions caused by N–H, C–H, and O–H single-bond stretching motions. N–H and O–H bonds absorb in the 3300 to 3600 cm^{-1} range; C–H bond stretching occurs near 3000 cm^{-1}.
- The region from 2500 to 2000 cm^{-1} is where triple-bond stretching occurs. Both C≡N and C≡C bonds absorb here.

- The region from 2000 to 1500 cm^{-1} is where double bonds (C=O, C=N, and C=C) absorb. Carbonyl groups generally absorb in the range 1680 to 1750 cm^{-1}, and alkene stretching normally occurs in the narrow range of 1640 to 1680 cm^{-1}.
- The region below 1500 cm^{-1} is the fingerprint portion of the IR spectrum. A large number of absorptions due to a variety of C–C, C–O, C–N, and C–X single-bond vibrations occur here.

Why do different functional groups absorb where they do? As noted previously, a good analogy is that of two weights (atoms) connected by a spring (a bond). Short, strong bonds vibrate at a higher energy and higher frequency than do long, weak bonds, just as a short, strong spring vibrates faster than a long, weak spring. Thus, triple bonds absorb at a higher frequency than double bonds, which in turn absorb at a higher frequency than single bonds. In addition, C–H, O–H, and N–H bonds vibrate at a higher frequency than bonds between heavier C, O, and N atoms.

Worked Example 1.8.1: Distinguishing Isomeric Compounds by IR Spectroscopy

Acetone (CH_3COCH_3) and 2-propen-1-ol ($H_2C{=}CHCH_2OH$) are isomers. How could you distinguish them by IR spectroscopy?

Strategy

Identify the functional groups in each molecule, and refer to Table 1.8.1.

Solution

Acetone has a strong C=O absorption at 1715 cm^{-1}, while 2-propen-1-ol has an –OH absorption at 3500 cm^{-1} and a C=C absorption at 1660 cm^{-1}.

Exercise 1.8.1

What functional groups might the following molecules contain?

a. A compound with a strong absorption at 1710 cm^{-1}
b. A compound with a strong absorption at 1540 cm^{-1}
c. A compound with strong absorptions at 1720 cm^{-1} and 2500 to 3100 cm^{-1}

Answer

a. Ketone or aldehyde
b. Nitro compound
c. Carboxylic acid

Exercise 1.8.2

How might you use IR spectroscopy to distinguish between the following pairs of isomers?

a. CH_3CH_2OH and CH_3OCH_3
b. Cyclohexane and 1-hexene
c. $CH_3CH_2CO_2H$ and $HOCH_2CH_2CHO$

Answer

a. CH_3CH_2OH has an −OH absorption.
b. 1-Hexene has a double-bond absorption.

This page titled 1.8: Interpreting Infrared Spectra is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

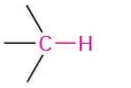
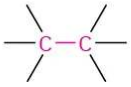
- **12.7: Interpreting Infrared Spectra** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

1.9: Infrared Spectra of Some Common Functional Groups

As each functional group is discussed in future chapters, the spectroscopic properties of that group will be described. For the present, we'll point out some distinguishing features of the hydrocarbon functional groups already studied and briefly preview some other common functional groups. We should also point out, however, that in addition to interpreting absorptions that *are* present in an IR spectrum, it's also possible to get structural information by noticing which absorptions are *not* present. If the spectrum of a compound has no absorptions at 3300 and 2150 cm^{-1}, the compound is not a terminal alkyne; if the spectrum has no absorption near 3400 cm^{-1}, the compound is not an alcohol; and so on.

Alkanes

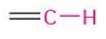
The IR spectrum of an alkane is fairly uninformative because no functional groups are present, and all absorptions are due to C–H and C–C bonds. Alkane C–H bonds show a strong absorption from 2850 to 2960 cm^{-1}, and saturated C–C bonds show a number of bands in the 800 to 1300 cm^{-1} range. Since most organic compounds contain saturated alkane-like portions, most organic compounds have these characteristic IR absorptions. The C–H and C–C bands are clearly visible in the three spectra shown previously.

Alkanes		2850–2960 cm^{-1}
		800–1300 cm^{-1}

Alkenes

Alkenes show several characteristic stretching absorptions. Vinylic =C–H bonds absorb from 3020 to 3100 cm^{-1}, and alkene C=C bonds usually absorb near 1650 cm^{-1}, although in some cases, their peaks can be rather small and difficult to see clearly when the alkene is symmetric, or nearly so. Both absorptions are visible in the 1-hexene spectrum in Figure 12.21b.

Alkenes have characteristic =C–H out-of-plane bending absorptions in the 700 to 1000 cm^{-1} range, thereby allowing the substitution pattern on a double bond to be determined (Figure 1.9.1). For example, monosubstituted alkenes such as 1-hexene show strong characteristic bands at 910 and 990 cm^{-1}, and 1,1-disubstituted alkenes ($R_2C{=}CH_2$) have an intense band at 890 cm^{-1}.

Alkenes		3020–3100 cm^{-1}
		1640–1680 cm^{-1}
	$RCH{=}CH_2$	910 and 990 cm^{-1}
	$R_2C{=}CH_2$	890 cm^{-1}

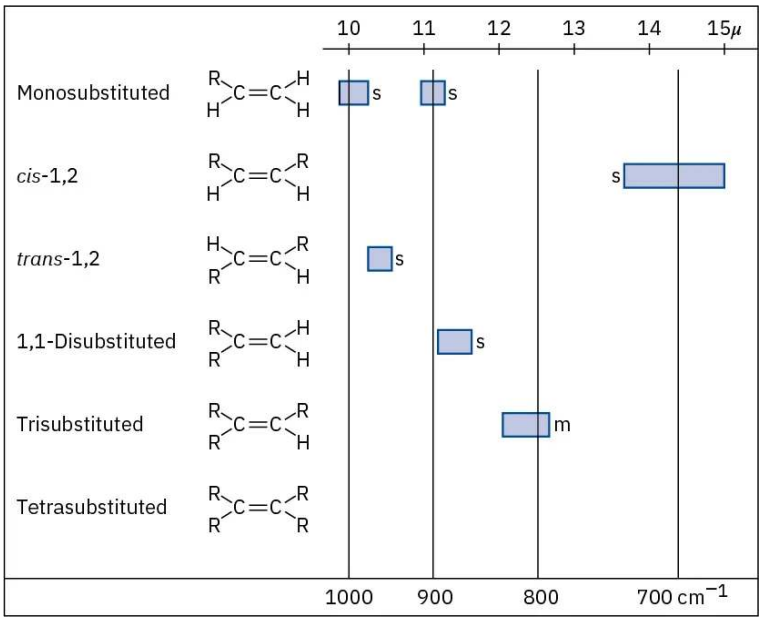


Figure 1.9.1: C–H out-of-plane bending vibrations for substituted alkenes.

Alkynes

Alkynes show a C≡C stretching absorption at 2100 to 2260 cm^{-1}, an absorption that is much more intense for terminal alkynes than for internal alkynes. Terminal alkynes such as 1-hexyne also have a characteristic ≡C–H stretching absorption at 3300 cm^{-1} (Figure 12.21c). This band is diagnostic for terminal alkynes because it is fairly intense and quite sharp.

Alkynes	—C≡C—	2100–2260 cm^{-1}
	≡C—H	3300 cm^{-1}

Aromatic Compounds

Aromatic compounds, such as benzene, have a weak C–H stretching absorption at 3030 cm^{-1}, just to the left of a typical saturated C–H band. In addition, they have a series of weak absorptions in the 1660 to 2000 cm^{-1} range and a series of medium-intensity absorptions in the 1450 to 1600 cm^{-1} region. These latter absorptions are due to complex molecular motions of the entire ring. The C–H out-of-plane bending region for benzene derivatives, between 650 to 1000 cm^{-1}, gives valuable information about the ring's substitution pattern, as it does for the substitution pattern of alkenes (Figure 1.9.2).

Aromatic compounds	C—H	3030 cm^{-1} (weak)
		1660–2000 cm^{-1} (weak) 1450–1600 cm^{-1} (medium)

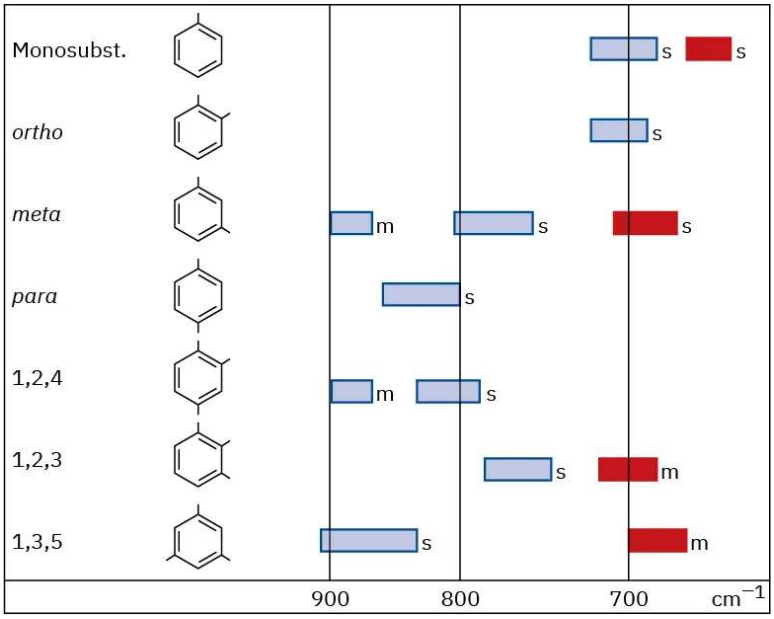


Figure 1.9.2: C–H out-of-plane bending vibrations for substituted benzenes.

The IR spectrum of phenylacetylene, shown in Figure 1.9.7 at the end of this section, gives an example, clearly showing the following absorbances: ≡C–H stretch at 3300 cm^{-1}, C–H stretches from the benzene ring at 3000 to 3100 cm^{-1}, C=C stretches of the benzene ring between 1450 and 1600 cm^{-1}, and out-of-plane bending of the ring's C–H groups, indicating monosubstitution at 750 cm^{-1}.

Alcohols

The O–H functional group of alcohols is easy to spot. Alcohols have a characteristic band in the range 3400 to 3650 cm^{-1} that is usually broad and intense. Hydrogen bonding between O–H groups is responsible for making the absorbance so broad. If an O–H stretch is present, it's hard to miss this band or to confuse it with anything else.

Alcohols —O—H 3400–3650 cm^{-1} (broad, intense)

Cyclohexanol (Figure 1.9.3) is a good example.

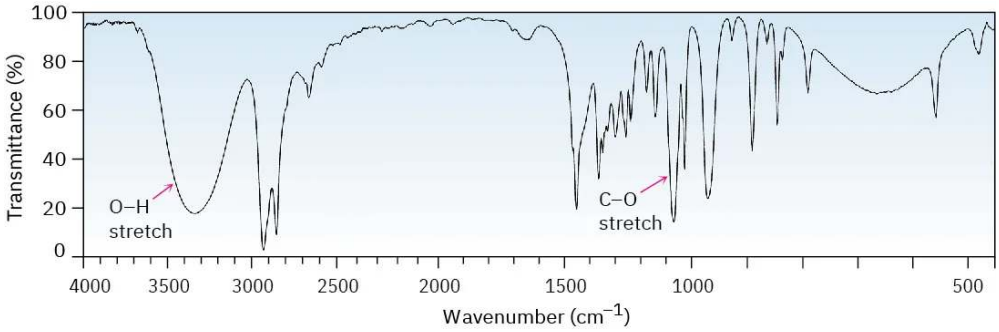


Figure 1.9.3: IR spectrum of cyclohexanol.

Amines

The N–H functional group of amines is also easy to spot in the IR, with a characteristic absorption in the 3300 to 3500 cm^{-1} range. Although alcohols absorb in the same range, an N–H absorption band is much sharper and less intense than an O–H band.

Amines —N—H 3300–3500 cm^{-1} (sharp, medium intensity)

Primary amines ($R–NH_2$) have two absorbances—one for the symmetric stretching mode and one for the asymmetric mode (Figure 1.9.4). Secondary amines ($R_2N–H$) only have one N–H stretching absorbance in this region.

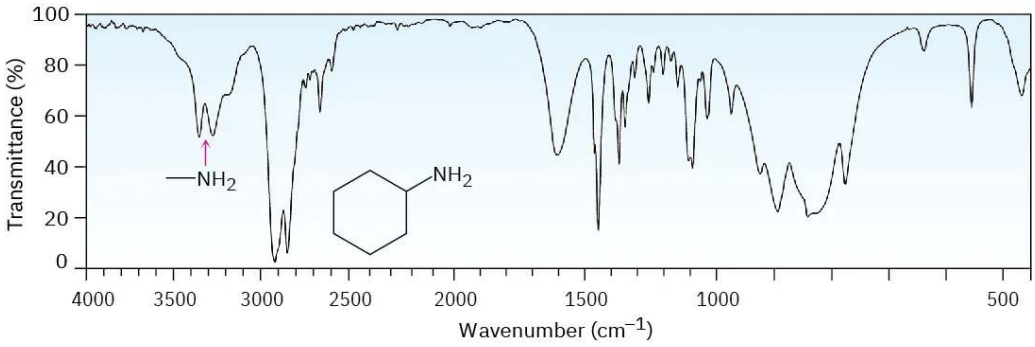


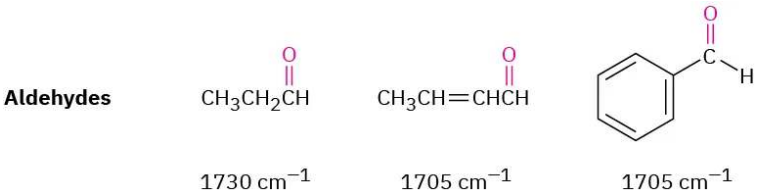
Figure 1.9.4: IR spectrum of cyclohexylamine.

Carbonyl Compounds

Carbonyl functional groups are the easiest to identify of all IR absorptions because of their sharp, intense peak in the range 1670 to 1780 cm^{-1}. Most important, the exact position of absorption within this range can often be used to identify the exact kind of carbonyl functional group—aldehyde, ketone, ester, and so forth.

ALDEHYDES

Saturated aldehydes absorb at 1730 cm^{-1}; aldehydes next to either a double bond or an aromatic ring absorb at 1705 cm^{-1}.



The C–H group attached to the carbonyl is responsible for the characteristic IR absorbance for aldehydes at 2750 and 2850 cm^{-1} (Figure 1.9.5). Although these are not very intense, the absorbance at 2750 cm^{-1} is helpful when trying to distinguish between an aldehyde and a ketone.

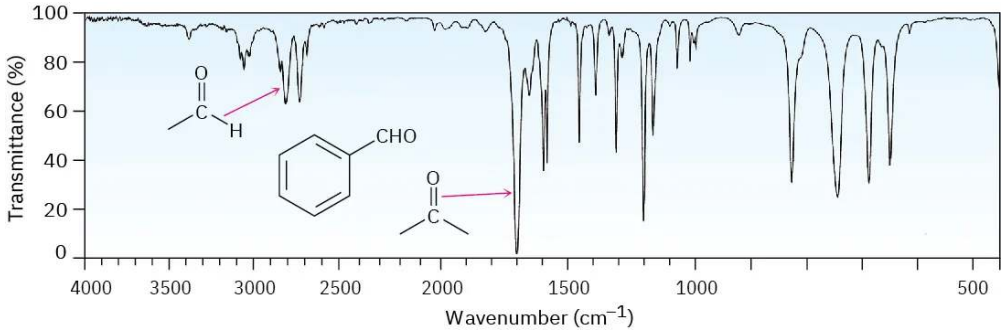
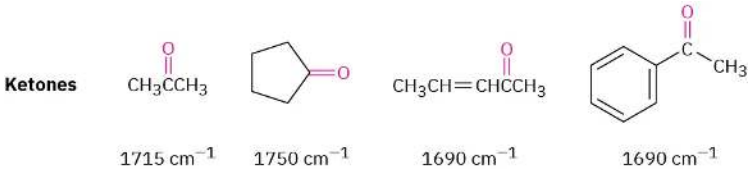


Figure 1.9.5: The IR spectrum of benzaldehyde.

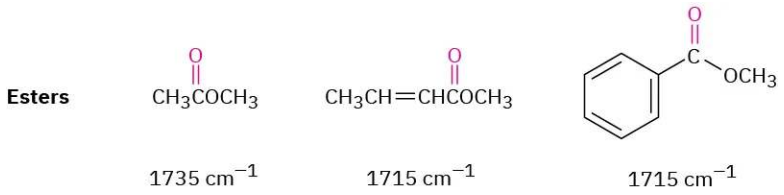
KETONES

Saturated open-chain ketones and six-membered cyclic ketones absorb at 1715 cm^{-1}. Ring strain stiffens the C=O bond, making five-membered cyclic ketones absorb at 1750 cm^{-1} and four-membered cyclic ketones absorb at 1780 cm^{-1}, about 20 to 30 cm^{-1} lower than the corresponding saturated ketone.



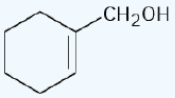
ESTERS

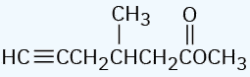
Saturated esters have a C=O absorbance at 1735 cm^{-1} and two strong absorbances in the 1300 to 1000 cm^{-1} range from the C–O portion of the functional group. Like other carbonyl functional groups, esters next to either an aromatic ring or a double bond absorb at 1715 cm^{-1}, about 20 to 30 cm^{-1} lower than a saturated ester.



Worked Example 1.9.1: Predicting IR Absorptions of Compounds

Where might the following compounds have IR absorptions?

a. 

b. 

Strategy

Identify the functional groups in each molecule, and then check Table 12.1 to see where those groups absorb.

Solution

a. *Absorptions:* 3400 to 3650 cm^{-1} (O–H), 3020 to 3100 cm^{-1} (=C–H), 1640 to 1680 cm^{-1} (C=C). This molecule has an alcohol O–H group and an alkene double bond.

b. *Absorptions:* 3300 cm^{-1} (≡C–H), 2100 to 2260 cm^{-1} (C≡C), 1735 cm^{-1} (C=O). This molecule has a terminal alkyne triple bond and a saturated ester carbonyl group.

Worked Example 1.9.2: Identifying Functional Groups from an IR Spectrum

The IR spectrum of an unknown compound is shown in Figure 1.9.6. What functional groups does the compound contain?

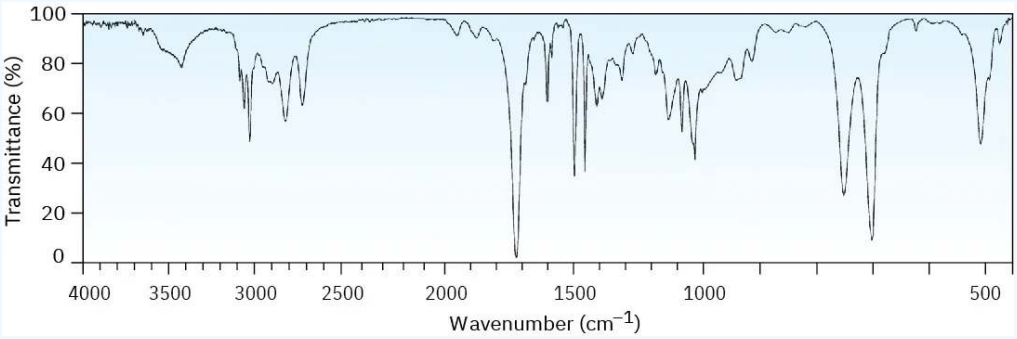


Figure 1.9.6: IR spectrum for Worked Example 1.9.2.

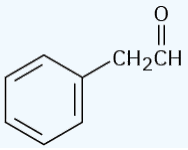
Strategy

All IR spectra have many absorptions, but those useful for identifying specific functional groups are usually found in the region from 1500 cm^{-1} to 3300 cm^{-1}. Pay particular attention to the carbonyl region (1670 to 1780 cm^{-1}), the aromatic region (1660 to 2000 cm^{-1}), the triple-bond region (2000 to 2500 cm^{-1}), and the C–H region (2500 to 3500 cm^{-1}).

Solution

The spectrum shows an intense absorption at 1725 cm^{-1} due to a carbonyl group (perhaps an aldehyde, –CHO), a series of weak absorptions from 1800 to 2000 cm^{-1} characteristic of aromatic compounds, and a C–H absorption near 3030 cm^{-1}, also

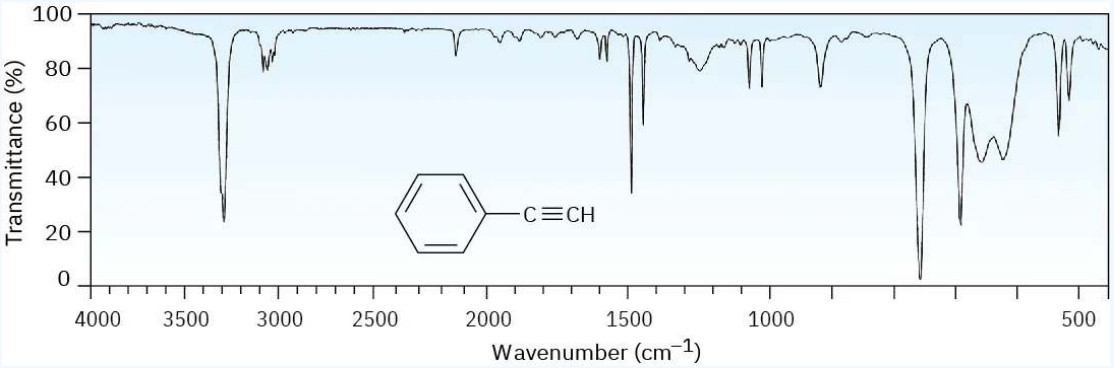
characteristic of aromatic compounds. In fact, the compound is phenylacetaldehyde.



Phenylacetaldehyde

Exercise 1.9.1

The IR spectrum of phenylacetylene is shown below. What absorption bands can you identify?

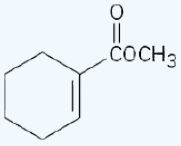


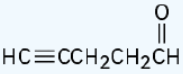
Answer

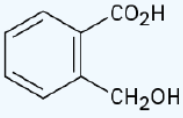
1450–1600 cm^{-1}: aromatic ring; 2100 cm^{-1}: C≡C; 3300 cm^{-1}: C≡C−H

Exercise 1.9.2

Where might the following compounds have IR absorptions?

a. 

b. 

c. 

Answer

a. 1715, 1640, 1250 cm^{-1}

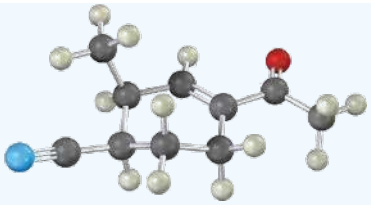
b. 1730, 2100, 3300 cm^{-1}

c. 1720, 2500–3100, 3400–3650 cm^{-1}

Exercise 1.9.3

Where might the following compound have IR absorptions?

https://chem.libretexts.org/@go/page/564134



Answer

1690, 1650, 2230 cm^{-1}

This page titled 1.9: Infrared Spectra of Some Common Functional Groups is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **12.8: Infrared Spectra of Some Common Functional Groups** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

1.10: Chemistry Matters—X-Ray Crystallography

The various spectroscopic techniques described in this and the next two chapters are enormously important in chemistry and have been fine-tuned to such a degree that the structure of almost any molecule can be found. Nevertheless, wouldn't it be nice if you could simply look at a molecule and "see" its structure with your eyes?

Determining the three-dimensional shape of an object around you is easy—you just look at it, let your eyes focus the light rays reflected from the object, and let your brain assemble the data into a recognizable image. If the object is small, you use a microscope and let the microscope lens focus the visible light. Unfortunately, there is a limit to what you can see, even with the best optical microscope. Called the diffraction limit, you can't see anything smaller than the wavelength of light you are using for the observation. Visible light has wavelengths of several hundred nanometers, but atoms in molecules have dimensions on the order of 0.1 nm. Thus, to see a molecule—whether a small one in the laboratory or a large, complex enzyme with a molecular weight in the tens of thousands—you need wavelengths in the 0.1 nm range, which corresponds to X rays.

Let's say that we want to determine the structure and shape of an enzyme or other biological molecule. The technique used is called **X-ray crystallography**. First, the molecule is crystallized (which often turns out to be the most difficult and time-consuming part of the entire process) and a small crystal of 0.4 to 0.5 mm on its longest axis is glued to the end of a glass fiber. The fiber and attached crystal are then mounted in an instrument called an X-ray diffractometer, which consists of a radiation source, a sample positioning and orienting device that can rotate the crystal in any direction, a detector, and a controlling computer.

Once mounted in the diffractometer, the crystal is irradiated with X rays, usually so-called Cu-K_α radiation with a wavelength of 0.154 nm. When the X rays strike the enzyme crystal, they interact with electrons in the molecule and are scattered into a diffraction pattern which, when detected and visualized, appears as a series of intense spots against a null background.

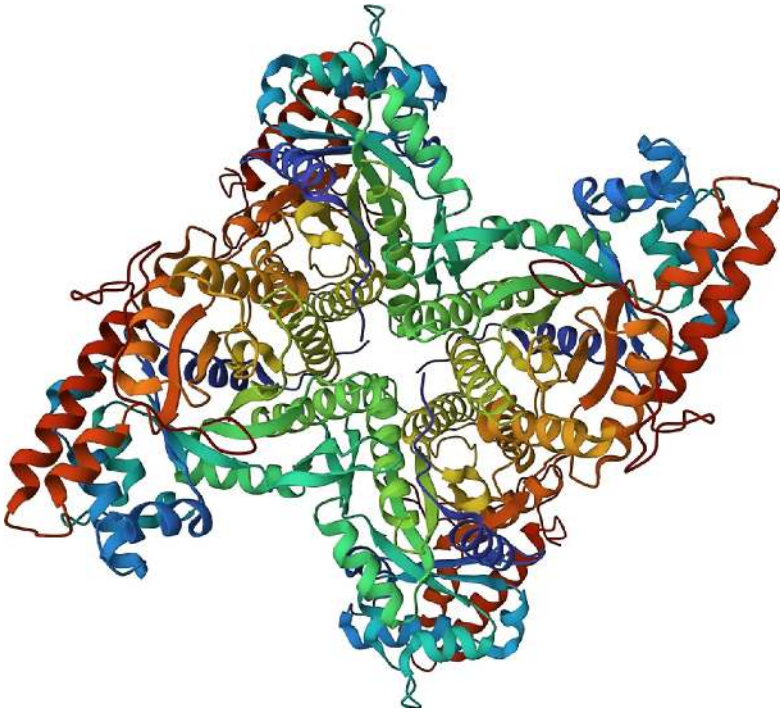


Figure 1.10.1: The structure of human muscle fructose-1,6-bisphosphate aldolase, as determined by X-ray crystallography. (credit: modification of work Protein Data Bank, 1ALD. PDB ID: 1ALD, Gamblin, S.J. Davies, G.J. Grimes, J.M. Jackson, R.M. Littlechild, J.A. Watson, H.C. (1991) J. Mol. Biol. 219: 573-576, CC BY 1.0.)

Manipulation of the diffraction pattern to extract three-dimensional molecular data is a complex process, but the final result is an electron-density map of the molecule. Because electrons are largely localized around atoms, any two centers of electron density located within bonding distance of each other are assumed to represent bonded atoms, leading to a recognizable chemical structure. So important is this structural information for biochemistry that an online database of approximately 145,000 biological substances has been created. Operated by Rutgers University and funded by the U.S. National Science Foundation, the Protein Data Bank

(PDB) is a worldwide repository for processing and distributing three-dimensional structural data for biological macromolecules. We'll see how to access the PDB in the Chapter 26 *Chemistry Matters*.

This page titled 1.10: Chemistry Matters—X-Ray Crystallography is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **12.9: Chemistry Matters—X-Ray Crystallography** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

1.11: Key Terms

- absorption spectrum
- amplitude
- base peak
- cation radical
- electromagnetic spectrum
- frequency, ν
- hertz, Hz,
- infrared (IR) spectroscopy
- MALDI
- mass spectrometry (MS)
- McLafferty Rearrangement
- parent peak
- photon
- quadrupole mass analyzer
- Time of Flight (TOF)
- wavelength, λ
- wavenumber, $\tilde{\upsilon}$

This page titled 1.11: Key Terms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **12.10: Key Terms** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

1.12: Summary

Finding the structure of a new molecule, whether a small one synthesized in the laboratory or a large protein found in living organisms, is central to the progression of chemistry and biochemistry. The structure of an organic molecule is usually determined using spectroscopic methods, including mass spectrometry and infrared spectroscopy. **Mass spectrometry (MS)** tells the molecular weight and formula of a molecule; **infrared (IR) spectroscopy** identifies the functional groups present in the molecule.

In small-molecule mass spectrometry, molecules are first ionized by collision with a high-energy electron beam. The ions then fragment into smaller pieces, which are magnetically sorted according to their mass-to-charge ratio (m/z). The ionized sample molecule is called the *molecular ion*, M^+, and measurement of its mass gives the molecular weight of the sample. Structural clues about unknown samples can be obtained by interpreting the fragmentation pattern of the molecular ion. Mass-spectral fragmentations are usually complex, however, and interpretation is often difficult. In biological mass spectrometry, molecules are protonated using either electrospray ionization (ESI) or matrix-assisted laser desorption ionization (MALDI), and the protonated molecules are separated by time-of-flight (TOF) mass analysis.

Infrared spectroscopy involves the interaction of a molecule with **electromagnetic radiation**. When an organic molecule is irradiated with infrared energy, certain **frequencies** are absorbed by the molecule. The frequencies absorbed correspond to the amounts of energy needed to increase the amplitude of specific molecular vibrations such as bond stretching and bending. Since every functional group has a characteristic combination of bonds, every functional group has a characteristic set of infrared absorptions. For example, the terminal alkyne $\equiv$C–H bond absorbs IR radiation of 3300 cm^{-1}, and the alkene C=C bond absorbs in the range 1640 to 1680 cm^{-1}. By observing which frequencies of infrared radiation are absorbed by a molecule and which are not, it's possible to determine the functional groups a molecule contains.

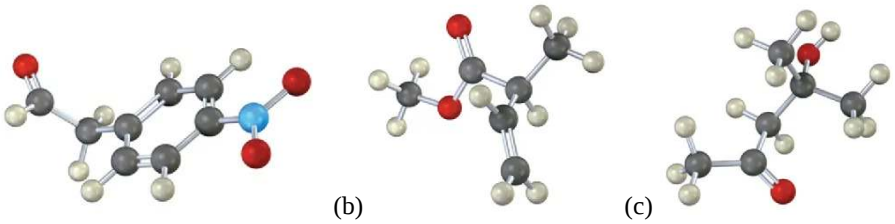
This page titled 1.12: Summary is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **12.11: Summary** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

1.13: Additional Problems

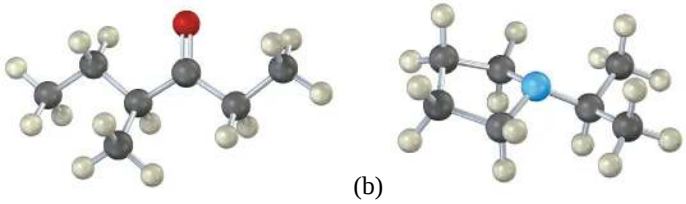
Visualizing Chemistry

PROBLEM 12-12 Where in the IR spectrum would you expect each of the following molecules to absorb?



(a) (b) (c)

PROBLEM 12-13 Show the structures of the fragments you would expect in the mass spectra of the following molecules:



(a) (b)

Mass Spectrometry

PROBLEM 12-14 Propose structures for compounds that fit the following mass-spectral data:

(a) A hydrocarbon with $M^+ = 132$

(b) A hydrocarbon with $M^+ = 166$

(c) A hydrocarbon with $M^+ = 84$

PROBLEM 12-15 Write molecular formulas for compounds that show the following molecular ions in their high-resolution mass spectra, assuming that C, H, N, and O might be present. The exact atomic masses are: 1.007 83 (^{1}H), 12.000 00 (^{12}C), 14.003 07 (^{14}N), 15.994 91 (^{16}O).

(a) $M^+ = 98.0844$ (b) $M^+ = 123.0320$

PROBLEM 12-16 Camphor, a saturated monoketone from the Asian camphor tree, is used among other things as a moth repellent and as a constituent of embalming fluid. If camphor has $M^+ = 152.1201$ by high-resolution mass spectrometry, what is its molecular formula? How many rings does camphor have?

PROBLEM 12-17 The nitrogen rule of mass spectrometry says that a compound containing an odd number of nitrogens has an odd-numbered molecular ion. Conversely, a compound containing an even number of nitrogens has an even-numbered M^+ peak. Explain.

PROBLEM 12-18 In light of the nitrogen rule mentioned in Problem 12-17, what is the molecular formula of pyridine, $M^+ = 79$?

PROBLEM 12-19 Nicotine is a diamino compound isolated from dried tobacco leaves. Nicotine has two rings and $M^+ = 162.1157$ by high-resolution mass spectrometry. Give a molecular formula for nicotine, and calculate the number of double bonds.

PROBLEM 12-20 The hormone cortisone contains C, H, and O, and shows a molecular ion at $M^+ = 360.1937$ by high-resolution mass spectrometry. What is the molecular formula of cortisone? (The degree of unsaturation for cortisone is 8.)

PROBLEM 12-21 Halogenated compounds are particularly easy to identify by their mass spectra because both chlorine and bromine occur naturally as mixtures of two abundant isotopes. Recall that chlorine occurs as ^{35}Cl (75.8%) and ^{37}Cl (24.2%); and bromine occurs as ^{79}Br (50.7%) and ^{81}Br (49.3%). At what masses do the molecular ions occur for the following formulas? What are the relative percentages of each molecular ion?

(a) Bromomethane, CH_3Br (b) 1-Chlorohexane, $C_6H_{13}Cl$

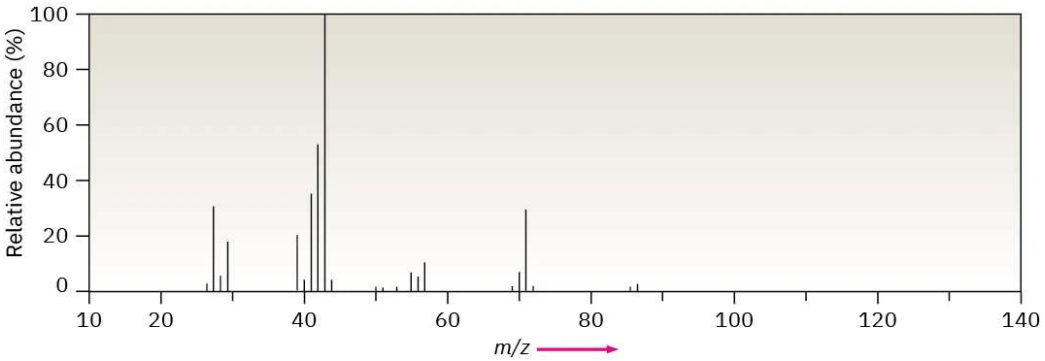
PROBLEM 12-22 By knowing the natural abundances of minor isotopes, it's possible to calculate the relative heights of M^+ and M + 1 peaks. If ^{13}C has a natural abundance of 1.10%, what are the relative heights of the M^+ and M + 1 peaks in the mass spectrum of benzene, C_6H_6?

PROBLEM 12-23 Propose structures for compounds that fit the following data:

(a) A ketone with $M^+ = 86$ and fragments at *m/z* = 71 and *m/z* = 43

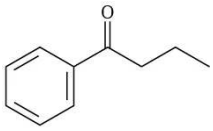
(b) An alcohol with $M^+ = 88$ and fragments at *m/z* = 73, *m/z* = 70, and *m/z* = 59

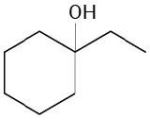
PROBLEM 12-24 2-Methylpentane (C_6H_{14}) has the mass spectrum shown. Which peak represents M^+? Which is the base peak? Propose structures for fragment ions of *m/z* = 71, 57, 43, and 29. Why does the base peak have the mass it does?

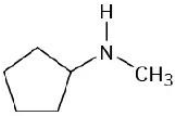


PROBLEM 12-25 Assume that you are in a laboratory carrying out the catalytic hydrogenation of cyclohexene to cyclohexane. How could you use a mass spectrometer to determine when the reaction is finished?

PROBLEM 12-26 What fragments might you expect in the mass spectra of the following compounds?

(a) 

(b) 

(c) 

Infrared Spectroscopy

PROBLEM 12-27 How might you use IR spectroscopy to distinguish among the three isomers 1-butyne, 1,3-butadiene, and 2-butyne?

PROBLEM 12-28 Would you expect two enantiomers such as (*R*)-2-bromobutane and (*S*)-2-bromobutane to have identical or different IR spectra? Explain.

PROBLEM 12-29 Would you expect two diastereomers such as *meso*-2,3-dibromobutane and (2*R*,3*R*)-dibromobutane to have identical or different IR spectra? Explain.

PROBLEM 12-30 Propose structures for compounds that meet the following descriptions:

(a) C_5H_8, with IR absorptions at 3300 and 2150 cm^{-1}

(b) C_4H_8O, with a strong IR absorption at 3400 cm^{-1}

(c) C_4H_8O, with a strong IR absorption at 1715 cm^{-1}

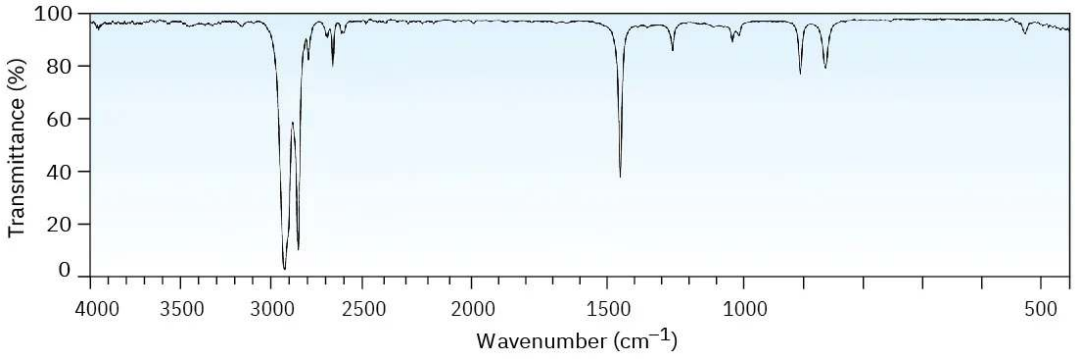
(d) C_8H_{10}, with IR absorptions at 1600 and 1500 cm^{-1}

PROBLEM 12-31 How could you use infrared spectroscopy to distinguish between the following pairs of isomers?

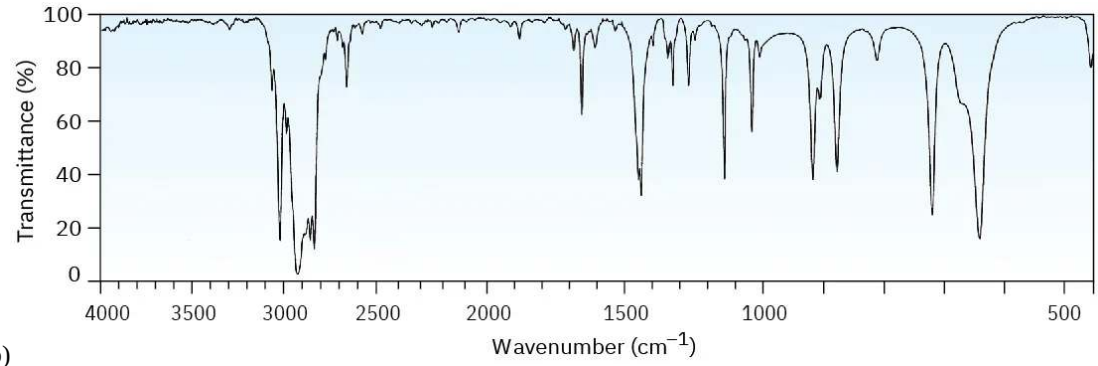
(a) $HC{\equiv}CCH_2NH_2$ and $CH_3CH_2C{\equiv}N$

(b) CH_3COCH_3 and CH_3CH_2CHO

PROBLEM 12-32 Two infrared spectra are shown. One is the spectrum of cyclohexane, and the other is the spectrum of cyclohexene. Identify them, and explain your answer.

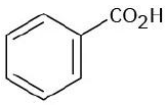


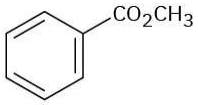
(a)

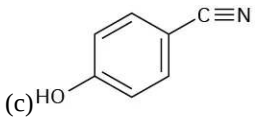


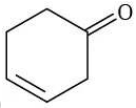
(b)

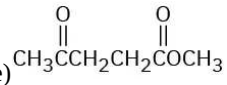
PROBLEM 12-33 At what approximate positions might the following compounds show IR absorptions?

(a) 

(b) 

(c) 

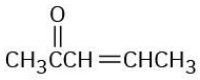
(d) 

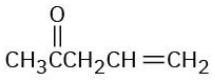
(e) 

PROBLEM 12-34 How would you use infrared spectroscopy to distinguish between the following pairs of constitutional isomers?

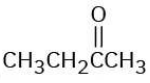
(a) $CH_3C{\equiv}CCH_3$ and $CH_3CH_2C{\equiv}CH$.

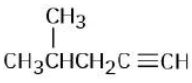
(c) $H_2C{=}CHOCH_3$ and CH_3CH_2CHO

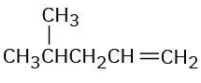
(b) 

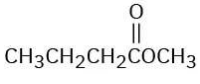
and 

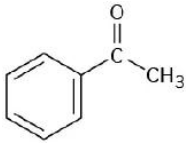
PROBLEM 12-35 At what approximate positions might the following compounds show IR absorptions?

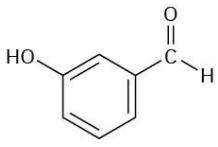
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

PROBLEM 12-36 Assume that you are carrying out the dehydration of 1-methylcyclohexanol to yield 1-methylcyclohexene. How could you use infrared spectroscopy to determine when the reaction is complete?

PROBLEM 12-37 Assume that you are carrying out the base-induced dehydrobromination of 3-bromo-3-methylpentane to yield an alkene. How could you use IR spectroscopy to tell which of the three possible elimination products is formed, if one includes *E/Z* isomers?

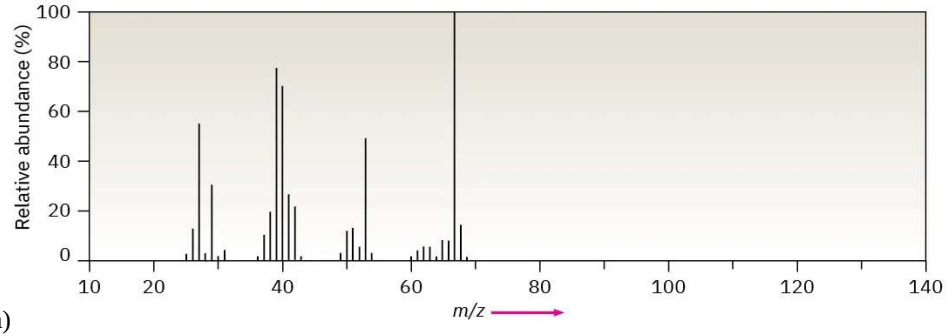
General Problems

PROBLEM 12-38 Which is stronger, the C=O bond in an ester (1735 cm^{-1}) or in a saturated ketone (1715 cm^{-1})? Explain

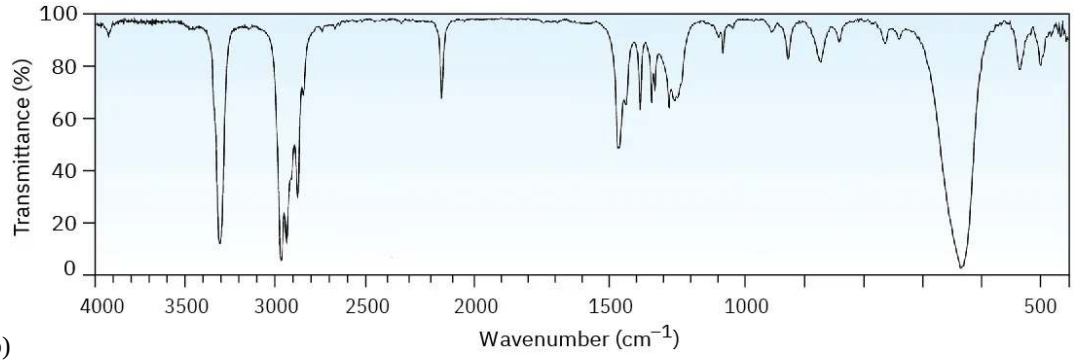
PROBLEM 12-39 Carvone is an unsaturated ketone responsible for the odor of spearmint. If carvone has M^+ = 150 in its mass spectrum and contains three double bonds and one ring, what is its molecular formula?

PROBLEM 12-40 Carvone (Problem 39) has an intense IR absorption at 1690 cm^{-1}. What kind of ketone does carvone contain?

PROBLEM 12-41 The mass spectrum **(a)** and the infrared spectrum **(b)** of an unknown hydrocarbon are shown. Propose as many structures as you can.

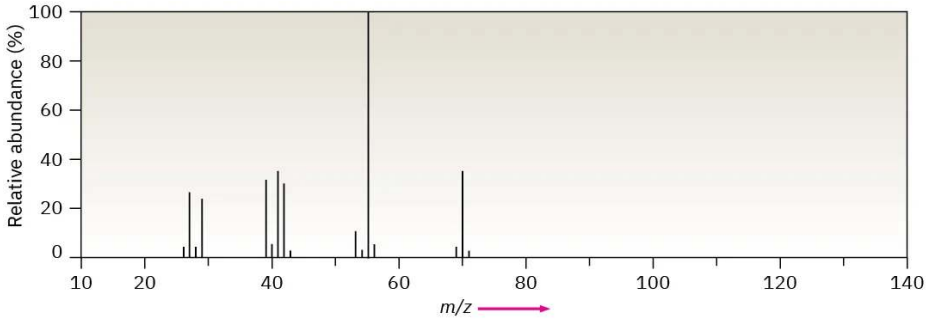


(a)



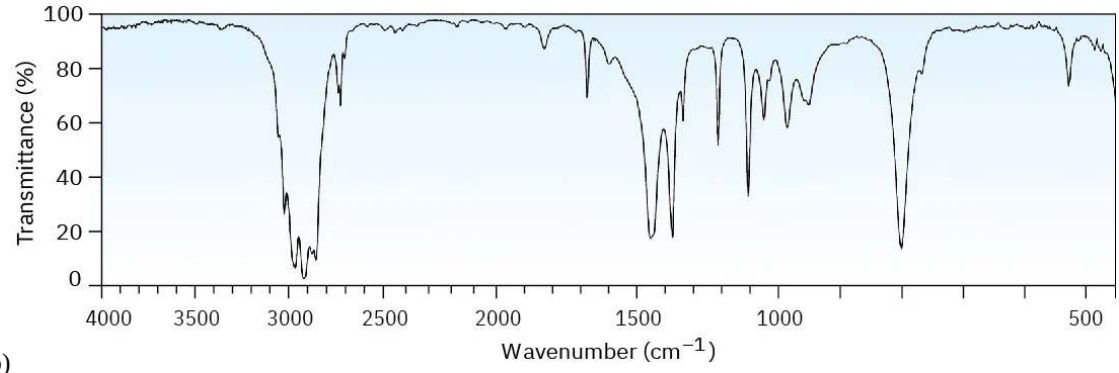
(b)

PROBLEM 12-42 The mass spectrum **(a)** and the infrared spectrum **(b)** of another unknown hydrocarbon are shown. Propose as many structures as you can.



(a)

https://chem.libretexts.org/@go/page/564138



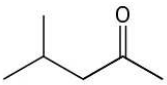
(b)

PROBLEM 12-43 Propose structures for compounds that meet the following descriptions:

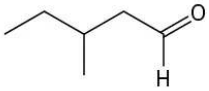
(a) An optically active compound $C_5H_{10}O$ with an IR absorption at 1730 cm^{-1}

(b) A non-optically active compound C_5H_9N with an IR absorption at 2215 cm^{-1}

PROBLEM 12-44 4-Methyl-2-pentanone and 3-methylpentanal are isomers. Explain how you could tell them apart, both by mass spectrometry and by infrared spectroscopy.

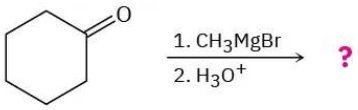


4-Methyl-2-pentanone



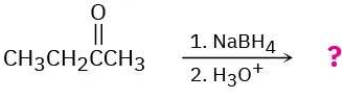
3-Methylpentanal

PROBLEM 12-45 Grignard reagents (alkylmagnesium halides) undergo a general and very useful reaction with ketones. Methylmagnesium bromide, for example, reacts with cyclohexanone to yield a product with the formula $C_7H_{14}O$. What is the structure of this product if it has an IR absorption at 3400 cm^{-1}?



Cyclohexanone

PROBLEM 12-46 Ketones undergo a reduction when treated with sodium borohydride, $NaBH_4$. What is the structure of the compound produced by the reaction of 2-butanone with $NaBH_4$ if it has an IR absorption at 3400 cm^{-1} and M^+ = 74 in the mass spectrum?

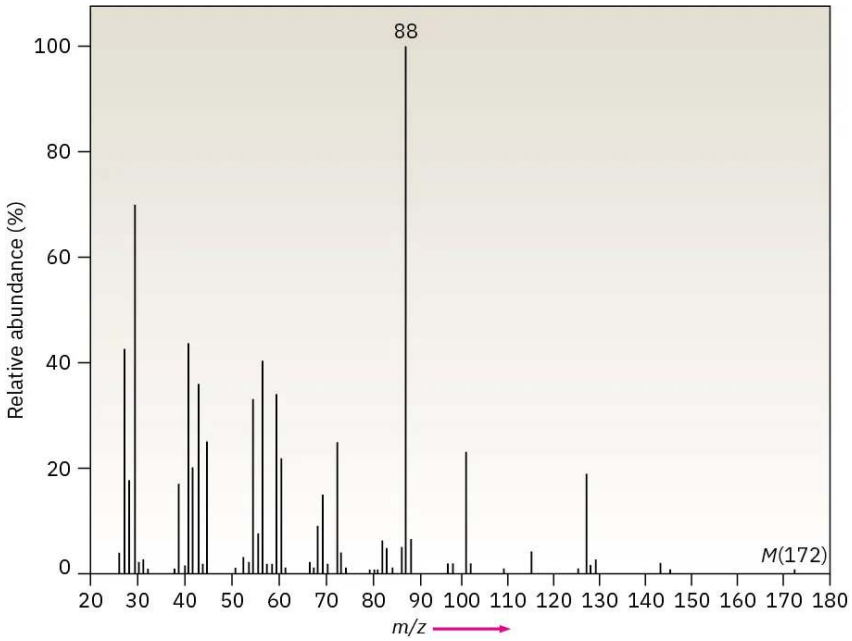


2-Butanone

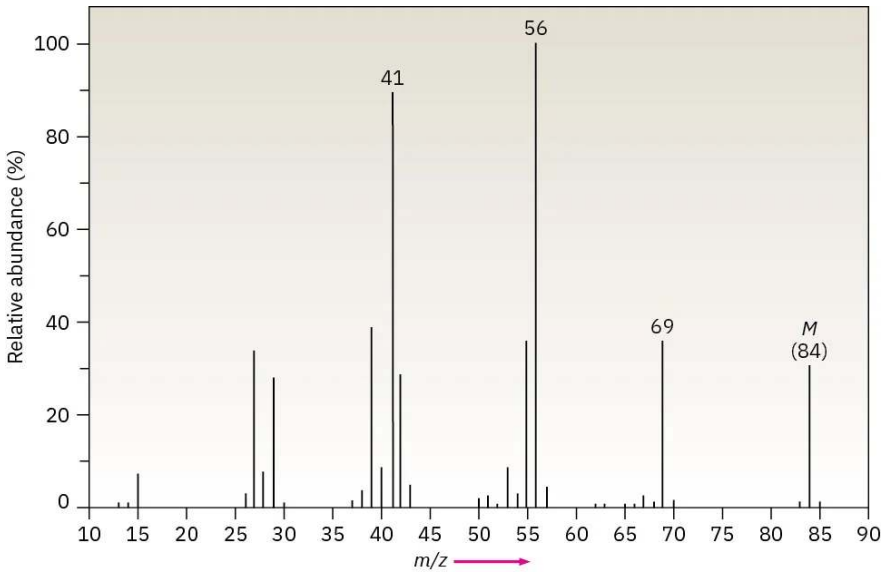
PROBLEM 12-47 Nitriles, R–C≡N, undergo a hydrolysis reaction when heated with aqueous acid. What is the structure of the compound produced by hydrolysis of propanenitrile, $CH_3CH_2C{\equiv}N$, if it has IR absorptions from 2500–3100 cm^{-1} and at 1710 cm^{-1}, and has M^+ = 74?

PROBLEM 12-48 The infrared spectrum of the compound with the following mass spectrum lacks any significant absorption above 3000 cm^{-1}. There is a prominent peak near 1740 cm^{-1} and another strong peak near 1200 cm^{-1}. Propose a structure.

https://chem.libretexts.org/@go/page/564138

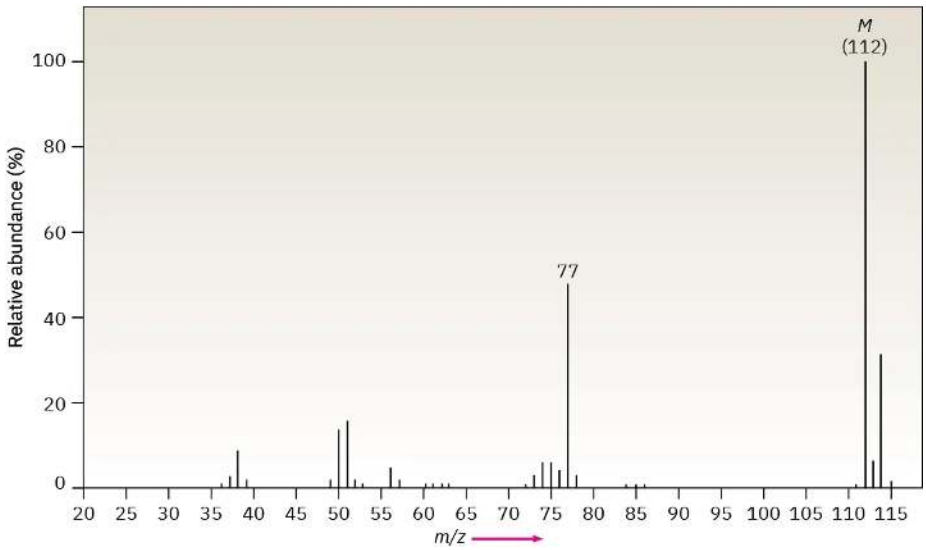


PROBLEM 12-49 The infrared spectrum of the compound with the following mass spectrum has a medium-intensity peak at about 1650 cm^{-1}. There is also a C–H out-of-plane bending peak near 880 cm^{-1}. Propose a structure.



PROBLEM 12-50 The infrared spectrum of the compound with the following mass spectrum has strong absorbances at 1584, 1478, and 1446 cm^{-1}. Propose a structure.

https://chem.libretexts.org/@go/page/564138



This page titled 1.13: Additional Problems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **12.12: Additional Problems** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

CHAPTER OVERVIEW

2: Structure Determination - Nuclear Magnetic Resonance Spectroscopy

Learning Objectives

- fulfillall of the detailed objectives listed under each individual section.
- solve road-map problems which may require the interpretation of ^{1}H NMR spectra in addition to other spectral data.
- define, and use in context, the key terms introduced.

In Chapter 12, you learned how an organic chemist could use two spectroscopic techniques, mass spectroscopy and infrared spectroscopy, to assist in determining the structure of an unknown compound. This chapter introduces a third technique, nuclear magnetic resonance (NMR). The two most common forms of NMR spectroscopy, ^{1}H NMR and ^{13}C NMR, will be discussed, the former in much more detail than the latter. Nuclear magnetic resonance spectroscopy is a very powerful tool, particularly when used in combination with other spectroscopic techniques.

2.1: Why This Chapter?
2.2: Nuclear Magnetic Resonance Spectroscopy
2.3: The Nature of NMR Absorptions
2.4: Chemical Shifts
2.5: Chemical Shifts in ^{1}H NMR Spectroscopy
2.6: Integration of ^{1}H NMR Absorptions- Proton Counting
2.7: Spin-Spin Splitting in ^{1}H NMR Spectra
2.8: ^{1}H NMR Spectroscopy and Proton Equivalence
2.9: More Complex Spin-Spin Splitting Patterns
2.10: Uses of ^{1}H NMR Spectroscopy
2.11: ^{13}C NMR Spectroscopy - Signal Averaging and FT-NMR
2.12: Characteristics of ^{13}C NMR Spectroscopy
2.13: DEPT ^{13}C NMR Spectroscopy
2.14: Uses of ^{13}C NMR Spectroscopy
2.15: Chemistry Matters—Magnetic Resonance Imaging (MRI)
2.16: Key Terms
2.17: Summary
2.18: Additional Problems

This page titled 2: Structure Determination - Nuclear Magnetic Resonance Spectroscopy is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

2.1: Why This Chapter?

Nuclear magnetic resonance (NMR) spectroscopy has far-reaching applications in many scientific fields, particularly in chemical structure determination. Although we'll just give an overview of the subject in this chapter, focusing on NMR applications with small molecules, more advanced NMR techniques are also used in biological chemistry to study protein structure and folding.

Figure 2.1.1: NMR spectroscopy is an invaluable aid in carrying out the design and synthesis of new drugs. (credit: modification of work by Unknown/Pxhere, CC0 1.0)

Nuclear magnetic resonance (NMR) spectroscopy is the most valuable spectroscopic technique available to organic chemists. It's the method of structure determination that organic chemists usually turn to first.

We saw in the chapter on Structure Determination: Mass Spectrometry and Infrared Spectroscopy that mass spectrometry gives a molecule's formula and infrared spectroscopy identifies a molecule's functional groups. Nuclear magnetic resonance spectroscopy complements these other techniques by mapping a molecule's carbon–hydrogen framework. Taken together, MS, IR, and NMR make it possible to determine the structures of even very complex molecules.

Mass spectrometry	Molecular size and formula
Infrared spectroscopy	Functional groups present
NMR spectroscopy	Map of carbon–hydrogen framework

This page titled 2.1: Why This Chapter? is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **13.0: Why This Chapter?** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

2.2: Nuclear Magnetic Resonance Spectroscopy

Many kinds of nuclei behave as if they were spinning about an axis, somewhat as the earth spins daily. Because they're positively charged, these spinning nuclei act like tiny magnets and can interact with an external magnetic field, denoted $\boldsymbol{B}_0$. Not all nuclei act this way, but fortunately for organic chemists, both the proton (^{1}H) and the ^{13}C nucleus do have spins. The more common ^{12}C isotope, however, does not have nuclear spin. (In speaking about NMR, the words *proton* and *hydrogen* are often used interchangeably, since a hydrogen nucleus is just a proton.) Let's see what the consequences of nuclear spin are and how we can use the results.

In the absence of an external magnetic field, the spins of magnetic nuclei are oriented randomly. When a sample containing these nuclei is placed between the poles of a strong magnet, however, the nuclei adopt specific orientations, much as a compass needle orients in the earth's magnetic field. A spinning ^{1}H or ^{13}C nucleus can orient so that its own tiny magnetic field is aligned either with (parallel to) or against (antiparallel to) the external field. The two orientations don't have the same energy, however, and aren't equally likely. The parallel orientation is slightly lower in energy by an amount that depends on the strength of the external field, making this spin state very slightly favored over the antiparallel orientation (Figure 2.2.1).

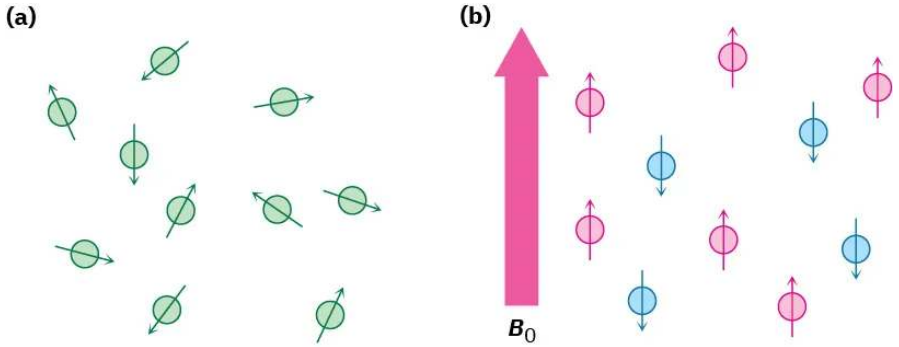


Figure 2.2.1: (a) Nuclear spins are oriented randomly in the absence of an external magnetic field but (b) have a specific orientation in the presence of an external field, B_0. Some of the spins (red) are aligned parallel to the external field while others (blue) are antiparallel. The parallel spin state is slightly lower in energy and therefore favored.

If the oriented nuclei are irradiated with electromagnetic radiation of the proper frequency, energy absorption occurs and the lower-energy spin state "flips" to the higher-energy state. When this spin-flip occurs, the magnetic nuclei are said to be in resonance with the applied radiation—hence the name *nuclear magnetic resonance*.

The exact frequency necessary for resonance depends both on the strength of the external magnetic field, the identity of the nucleus, and the electronic environment of the nucleus. If a very strong magnetic field is applied, the energy difference between the two spin states is larger and higher-frequency (higher-energy) radiation is required for a spin-flip. If a weaker magnetic field is applied, less energy is required to effect the transition between nuclear spin states (Figure 2.2.2).

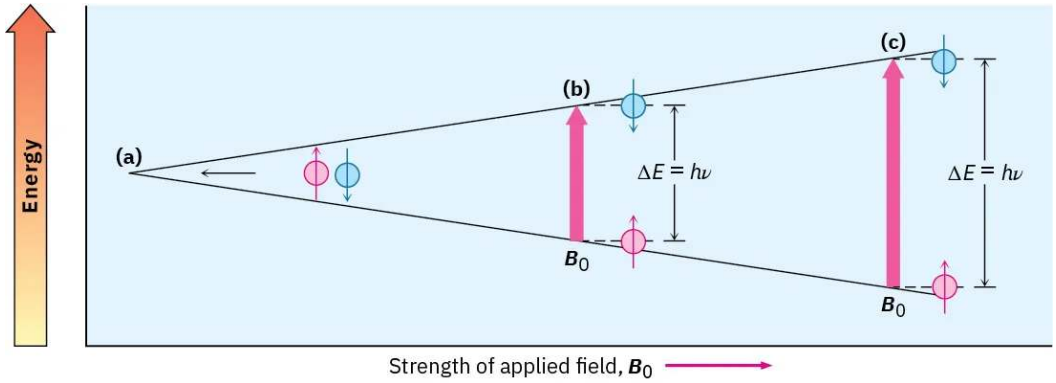


Figure 2.2.2: The energy difference ΔE between nuclear spin states depends on the strength of the applied magnetic field. Absorption of energy with frequency ν converts a nucleus from a lower spin state to a higher spin state. **(a)** Spin states have equal energies in the absence of an applied magnetic field but **(b)** have unequal energies in the presence of a magnetic field. At ν = 200 MHz, $\Delta E = 8.0 \times 10^{-5}$ kJ/mol (1.9×10^{-5} kcal/mol). **(c)** The energy difference between spin states is greater at larger applied fields. At ν = 500 MHz, $\Delta E = 2.0 \times 10^{-4}$ kJ/mol.

In practice, superconducting magnets that produce enormously powerful fields up to 23.5 tesla (T) are sometimes used, but field strengths in the range of 4.7 to 7.0 T are more common. At a magnetic field strength of 4.7 T, so-called radiofrequency (rf) energy in the 200 MHz range (1 MHz = 10^6 Hz) brings a ^{1}H nucleus into resonance, and rf energy of 50 MHz brings a ^{13}C nucleus into resonance. At the highest field strength currently available in commercial instruments (23.5 T), 1000 MHz energy is required for ^{1}H spectroscopy. These energies needed for NMR are much smaller than those required for IR spectroscopy; 200 MHz rf energy corresponds to only 8.0×10^{-5} kJ/mol versus the 4.8 to 48 kJ/mol needed for IR spectroscopy.

^{1}H and ^{13}C nuclei are not unique in their ability to exhibit the NMR phenomenon. All nuclei with an odd number of protons (^{1}H, ^{2}H, ^{14}N, ^{19}F, ^{31}P, for example) and all nuclei with an odd number of neutrons (^{13}C, for example) show magnetic properties. Only nuclei with even numbers of both protons and neutrons (^{12}C, ^{16}O, ^{32}S) do not give rise to magnetic phenomena (Table 2.2.1).

Table 2.2.1: The NMR Behavior of Some Common Nuclei

Magnetic nuclei	Nonmagnetic nuclei
^{1}H	^{12}C
^{13}C	^{16}O
^{2}H	^{32}S
^{14}N	
^{19}F	
^{31}P	

Exercise 2.2.1

The amount of energy required to spin-flip a nucleus depends both on the strength of the external magnetic field and on the nucleus. At a field strength of 4.7 T, rf energy of 200 MHz is required to bring a ^{1}H nucleus into resonance, but energy of only 187 MHz will bring a ^{19}F nucleus into resonance. Calculate the amount of energy required to spin-flip a ^{19}F nucleus. Is this amount greater or less than that required to spin-flip a ^{1}H nucleus?

Answer

- 7.5×10^{-5} kJ/mol for ^{19}F
- 8.0×10^{-5} kJ/mol for ^{1}H

Exercise 2.2.2

Calculate the amount of energy required to spin-flip a proton in a spectrometer operating at 300 MHz. Does increasing the spectrometer frequency from 200 to 300 MHz increase or decrease the amount of energy necessary for resonance?

Answer

1.2×10^{-4} kJ/mol

This page titled 2.2: Nuclear Magnetic Resonance Spectroscopy is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **13.1: Nuclear Magnetic Resonance Spectroscopy** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

2.3: The Nature of NMR Absorptions

From the description thus far, you might expect all ^{1}H nuclei in a molecule to absorb energy at the same frequency and all ^{13}C nuclei to absorb at the same frequency. If so, we would observe only a single NMR absorption signal in the ^{1}H or ^{13}C spectrum of a molecule, a situation that would be of little use. In fact, the absorption frequency is not the same for all ^{1}H or all ^{13}C nuclei.All nuclei in molecules are surrounded by electrons. When an external magnetic field is applied to a molecule, the electrons moving around nuclei set up tiny local magnetic fields of their own. These local magnetic fields act in opposition to the applied field so that the effective field actually felt by the nucleus is a bit weaker than the applied field.

$$B_{\text{effective}} = B_{\text{applied}} - B_{\text{local}}$$

In describing this effect of local fields, we say that nuclei experience **shielding** from the full effect of the applied field by the surrounding electrons. Because each chemically distinct nucleus in a molecule is in a slightly different electronic environment, each nucleus is shielded to a slightly different extent and the effective magnetic field felt by each is slightly different. These tiny differences in the effective magnetic fields experienced by different nuclei can be detected, and we thus see a distinct NMR signal for each chemically distinct ^{13}C or ^{1}H nucleus in a molecule. As a result, an NMR spectrum effectively maps the carbon–hydrogen framework of an organic molecule. With practice, it's possible to read this map and derive structural information.

Figure 2.3.1 shows both the ^{1}H and the ^{13}C NMR spectra of methyl acetate, $CH_3CO_2CH_3$. The horizontal axis shows the effective field strength felt by the nuclei, and the vertical axis indicates the intensity of absorption of rf energy. Each peak in the NMR spectrum corresponds to a chemically distinct ^{1}H or ^{13}C nucleus in the molecule. Note that NMR spectra are formatted with the zero absorption line at the bottom, whereas IR spectra are formatted with the zero absorption line at the top; Section 12.6. Note also that ^{1}H and ^{13}C spectra can't be observed simultaneously on the same spectrometer because different amounts of energy are required to spin-flip the different kinds of nuclei. The two spectra must be recorded separately.

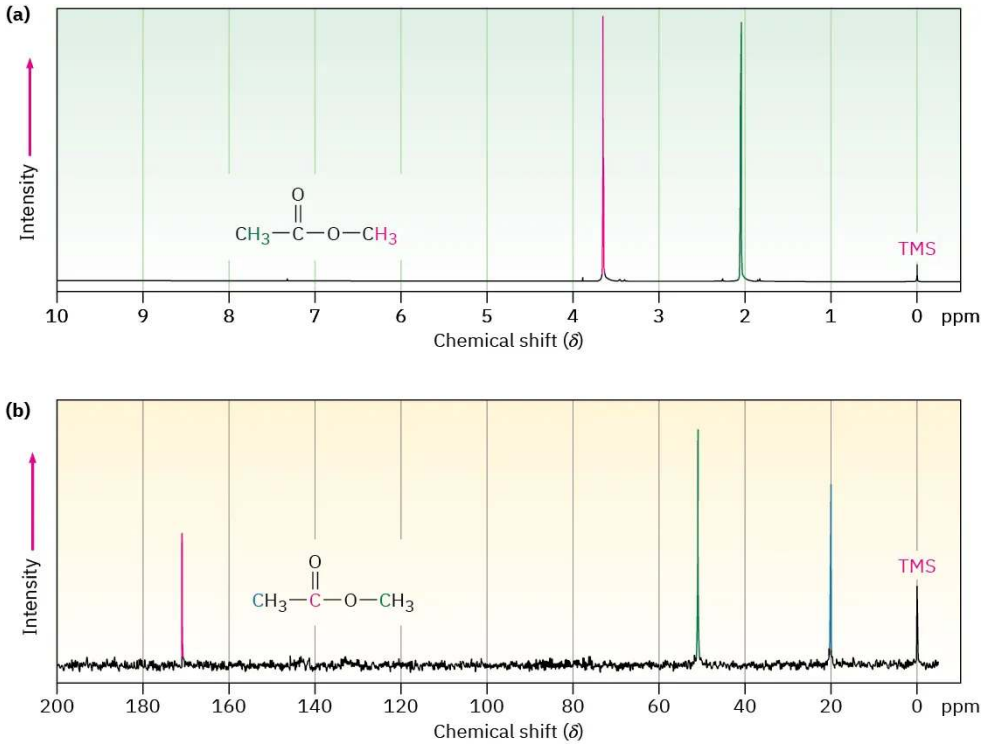


Figure 2.3.1: (a) The ^{1}H NMR spectrum and (b) the proton-decoupled ^{13}C NMR spectrum of methyl acetate, $CH_3CO_2CH_3$. The small peak labeled "TMS" at the far right of each spectrum is a calibration peak, as explained in the next section.

The ^{13}C NMR spectrum of methyl acetate in Figure 2.3.1b shows three peaks, one for each of the three chemically distinct carbon atoms in the molecule. The ^{1}H NMR spectrum in Figure 2.3.1a shows only two peaks, however, even though methyl acetate has six hydrogens. One peak is due to the $CH_3C{=}O$ hydrogens, and the other to the $-OCH_3$ hydrogens. Because the three hydrogens in each methyl group have the same electronic environment, they are shielded to the same extent and are said to be equivalent.

Chemically equivalent nuclei always show the same absorption. The two methyl groups themselves, however, are not equivalent, so the two sets of hydrogens absorb at different positions.

The operation of a basic NMR spectrometer is illustrated in Figure 2.3.2. An organic sample is dissolved in a suitable solvent (usually deuteriochloroform, $CDCl_3$, which has no hydrogens) and placed in a thin glass tube between the poles of a magnet. The strong magnetic field causes the ^1H and ^{13}C nuclei in the molecule to align in one of the two possible orientations, and the sample is irradiated with rf energy. If the frequency of the rf irradiation is held constant and the strength of the applied magnetic field is varied, each nucleus comes into resonance at a slightly different field strength. A sensitive detector monitors the absorption of rf energy, and its electronic signal is then amplified and displayed as a peak.

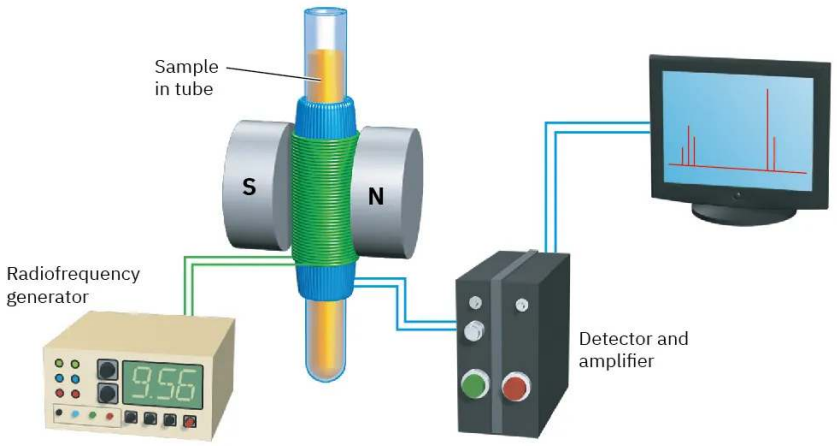
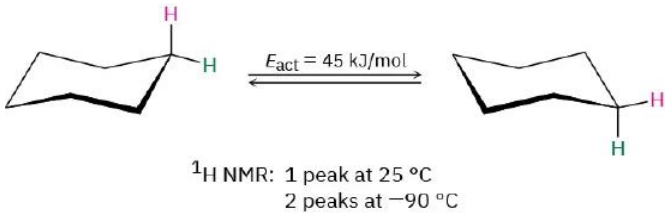


Figure 2.3.2: Schematic operation of a basic NMR spectrometer. A thin glass tube containing the sample solution is placed between the poles of a strong magnet and irradiated with rf energy.

NMR spectroscopy differs from IR spectroscopy (Section 12.6–Section 12.8) in that the timescales of the two techniques are quite different. The absorption of infrared energy by a molecule giving rise to a change in vibrational amplitude is an essentially instantaneous process (about 10^{-13} s), but the NMR process is much slower (about 10^{-3} s). This difference in timescales between IR and NMR spectroscopy is analogous to the difference between cameras operating at very fast and very slow shutter speeds. The fast camera (IR) takes an instantaneous picture and freezes the action. If two rapidly interconverting species are present, IR spectroscopy records the spectrum of both. The slow camera (NMR), however, takes a blurred, time-averaged picture. If two species interconverting faster than 10^3 times per second are present in a sample, NMR records only a single, averaged spectrum, rather than separate spectra of the two discrete species.

Because of this blurring effect, NMR spectroscopy can be used to measure the rates and activation energies of very fast chemical processes. In cyclohexane, for example, a ring-flip (Section 4.6) occurs so rapidly at room temperature that axial and equatorial hydrogens can't be distinguished by NMR; only a single, averaged ^1H NMR absorption is seen for cyclohexane at 25 °C. At –90 °C, however, the ring-flip is slowed down enough that two absorption peaks are visible, one for the six axial hydrogens and one for the six equatorial hydrogens. Knowing the temperature and the rate at which signal blurring begins to occur, it's possible to calculate that the activation energy for the cyclohexane ring-flip is 45 kJ/mol (10.8 kcal/mol).

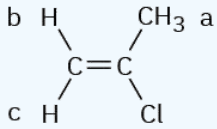


? Exercise 2.3.1

2-Chloropropene shows signals for three kinds of protons in its ^1H NMR spectrum. Explain.

Answer

The vinylic C − H protons are nonequivalent.



This page titled 2.3: The Nature of NMR Absorptions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **13.2: The Nature of NMR Absorptions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

2.4: Chemical Shifts

NMR spectra are displayed on charts that show the applied field strength increasing from left to right (Figure 2.4.1). Thus, the left part of the chart is the low-field, or **downfield**, side, and the right part is the high-field, or **upfield**, side. Nuclei that absorb on the downfield side of the chart require a lower field strength for resonance, implying that they have less shielding. Nuclei that absorb on the upfield side require a higher field strength for resonance, implying that they have more shielding.

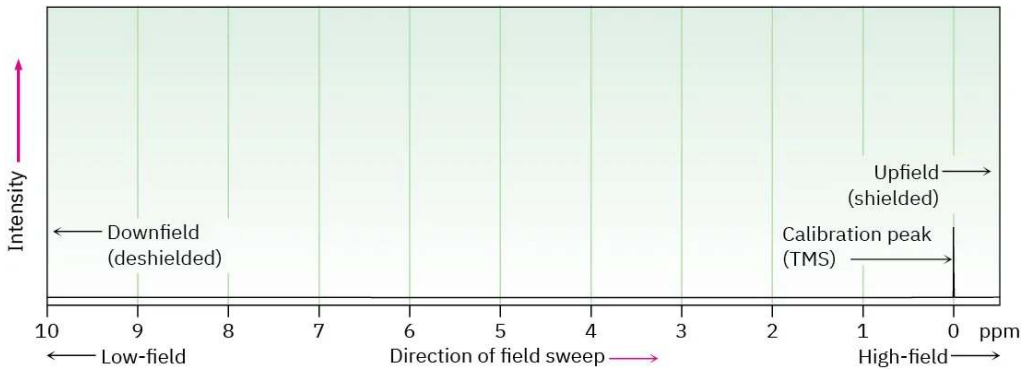


Figure 2.4.1: The NMR chart. The downfield, deshielded side is on the left, and the upfield, shielded side is on the right. The tetramethylsilane (TMS) absorption is used as reference point.

To define the position of an absorption, the NMR chart is calibrated and a reference point is used. In practice, a small amount of tetramethylsilane [TMS; $(CH_3)_4Si$] is added to the sample so that a reference absorption peak is produced when the spectrum is run. TMS is used as reference for both ^1H and ^{13}C measurements because in both cases it produces a single peak that occurs upfield of other absorptions normally found in organic compounds. The ^1H and ^{13}C spectra of methyl acetate in Figure 13.4 have the TMS reference peak indicated.The position on the chart at which a nucleus absorbs is called its **chemical shift**. The chemical shift of TMS is set as the zero point, and other absorptions normally occur downfield, to the left on the chart. NMR charts are calibrated using an arbitrary scale called the **delta (δ) scale**, where 1 δ equals 1 part-per-million (1 ppm) of the spectrometer operating frequency. For example, if we were measuring the ^1H NMR spectrum of a sample using an instrument operating at 200 MHz, 1 δ would be 1 part per million of 200,000,000 Hz, or 200 Hz. If we were measuring the spectrum using a 500 MHz instrument, 1 δ = 500 Hz. The following equation can be used for any absorption:

$$\delta = \frac{\text{Observed chemical shift (number of Hz away from TMS)}}{\text{Spectrometer frequency in}} \tag{2.4.1}$$

Although this method of calibrating NMR charts may seem complex, there's a good reason for it. As we saw earlier, the rf frequency required to bring a given nucleus into resonance depends on the spectrometer's magnetic field strength. But because there are many different kinds of spectrometers with many different magnetic field strengths available, chemical shifts given in frequency units (Hz) vary from one instrument to another. Thus, a resonance that occurs at 120 Hz downfield from TMS on one spectrometer might occur at 600 Hz downfield from TMS on another spectrometer with a more powerful magnet.

By using a system of measurement in which NMR absorptions are expressed in relative terms (parts per million relative to spectrometer frequency) rather than absolute terms (Hz), it's possible to compare spectra obtained on different instruments. *The chemical shift of an NMR absorption in δ units is constant, regardless of the operating frequency of the spectrometer.* A ^1H nucleus that absorbs at 2.0 δ on a 200 MHz instrument also absorbs at 2.0 δ on a 500 MHz instrument.

The range in which most NMR absorptions occur is quite narrow. Almost all ^1H NMR absorptions occur from 0 to 10 δ downfield from the proton absorption of TMS, and almost all ^{13}C absorptions occur from 1 to 220 δ downfield from the carbon absorption of TMS. Thus, there is a likelihood that accidental overlap of nonequivalent signals will occur. The advantage of using an instrument with higher field strength (say, 500 MHz) rather than lower field strength (200 MHz) is that different NMR absorptions are more widely separated at the higher field strength. The chances that two signals will accidentally overlap are therefore lessened, and interpretation of spectra becomes easier. For example, two signals that are only 20 Hz apart at 200 MHz (0.1 ppm) are 50 Hz apart at 500 MHz (still 0.1 ppm).

Exercise 2.4.1

The following ^{1}H NMR peaks were recorded on a spectrometer operating at 200 MHz. Convert each into δ units.

a. $CHCl_3$; 1454 Hz
b. CH_3Cl; 610 Hz
c. CH_3OH; 693 Hz
d. CH_2Cl_2; 1060 Hz

Answer

a. 7.27 δ
b. 3.05 δ
c. 3.46 δ
d. 5.30 δ

Exercise 2.4.2

When the ^{1}H NMR spectrum of acetone, CH_3COCH_3, is recorded on an instrument operating at 200 MHz, a single sharp resonance at 2.1 δ is seen.

a. How many hertz downfield from TMS does the acetone resonance correspond to?
b. If the ^{1}H NMR spectrum of acetone is recorded at 500 MHz, what would the position of the absorption be in δ units?
c. How many hertz downfield from TMS does this 500 MHz resonance correspond to?

Answer

a. 420 Hz
b. 2.1 δ
c. 1050 Hz

This page titled 2.4: Chemical Shifts is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **13.3: Chemical Shifts** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

2.5: Chemical Shifts in ^{1}H NMR Spectroscopy

As mentioned previously, differences in chemical shifts are caused by the small local magnetic field of electrons surrounding different nuclei. Nuclei that are more strongly shielded by electrons require a higher applied field to bring them into resonance so they absorb on the right side of the NMR chart. Nuclei that are less strongly shielded need a lower applied field for resonance so they absorb on the left of the NMR chart.

Most ^{1}H chemical shifts fall within the range 0 to 10 δ, which can be divided into the five regions shown in Figure 2.5.1. By remembering the positions of these regions, it's often possible to tell at a glance what kinds of protons a molecule contains.

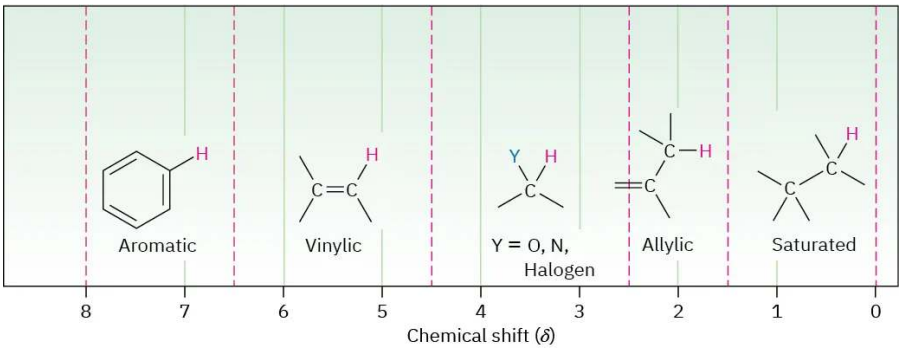
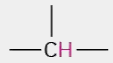
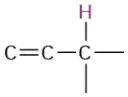
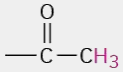
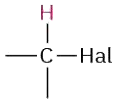
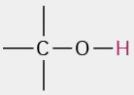
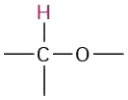
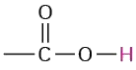


Figure 2.5.1: Regions of the ^{1}H NMR Spectrum

Figure 2.5.2 shows the correlation of ^{1}H chemical shift with electronic environment in more detail. In general, protons bonded to saturated, sp^3-hybridized carbons absorb at higher fields, whereas protons bonded to sp^2-hybridized carbons absorb at lower fields. Protons on carbons that are bonded to electronegative atoms, such as N, O, or halogen, also absorb at lower fields.

Figure 2.5.2: Correlation of ^{1}H Chemical Shifts with Environment

Type of hydrogen	Structure	Chemical shift (δ)
Reference	$Si(CH_3)_4$	0
Alkyl (primary)	—CH_3	0.7–1.3
Alkyl (secondary)	—CH_2—	1.2–1.6
Alkyl (tertiary)		1.4–1.8
Allylic		1.6–2.2
Methyl ketone		2.0–2.4
Aromatic methyl	Ar—CH_3	2.4–2.7
Alkynyl	—C ≡ C—H	2.5–3.0
Alkyl halide		2.5–4.0
Alcohol		2.5–5.0
Alcohol, ether		3.3–4.5
Vinylic		4.5–6.5
Aryl	Ar—H	6.5–8.0
Aldehyde		9.7–10.0
Carboxylic acid		11.0–12.0

Worked Example 2.5.1: Predicting Chemical Shifts in ^{1}H NMR Spectra

Methyl 2,2-dimethylpropanoate $(CH_3)_2CCO_2CH_3$ has two peaks in its ^{1}H NMR spectrum. What are their approximate chemical shifts?

Strategy

Identify the types of hydrogens in the molecule, and note whether each is alkyl, vinylic, or next to an electronegative atom. Then predict where each absorbs, using Figure 2.5.2 if necessary.

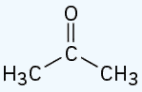
Solution

The $–OCH_3$ protons absorb around 3.5 to 4.0 δ because they are on carbon bonded to oxygen. The $(CH_3)_3C–$ protons absorb near 1.0 δ because they are typical alkane-like protons.

Exercise 2.5.1

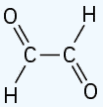
Each of the following compounds has a single ^{1}H NMR peak. Approximately where would you expect each compound to absorb?

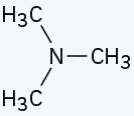
a.

b. 

c.

d. CH_2Cl_2

e. 

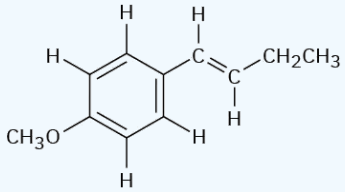
f. 

Answer

a. 1.43 δ
b. 2.17 δ
c. 7.37 δ
d. 5.30 δ
e. 9.70 δ
f. 2.12 δ

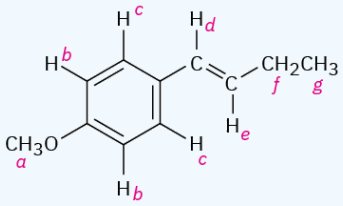
Exercise 2.5.2

Identify the different types of protons in the following molecule, and tell where you would expect each to absorb:



Answer

There are seven kinds of protons labeled. The types and expected range of absorption of each follow. ***a:*** ether, 3.5–4.5 δ; ***b:*** aryl, 6.5–8.0 δ; ***c:*** aryl, 6.5–8.0; ***d:*** vinylic, 4.5–6.5 δ; ***e:*** vinylic, 4.5–6.5 δ; ***f:*** alkyl (secondary), 1.2–1.6 δ; ***g:*** alkyl (primary), 0.7–1.3 δ.



This page titled 2.5: Chemical Shifts in ¹H NMR Spectroscopy is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **13.4: Chemical Shifts in ¹H NMR Spectroscopy** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

2.6: Integration of ^{1}H NMR Absorptions- Proton Counting

Look at the ^{1}H NMR spectrum of methyl 2,2-dimethylpropanoate in Figure 2.6.1. There are two peaks, corresponding to the two kinds of protons, but the peaks aren't the same size. The peak at 1.2 δ, due to the $(CH_3)_3C$– protons, is larger than the peak at 3.7 δ, due to the $–OCH_3$ protons.

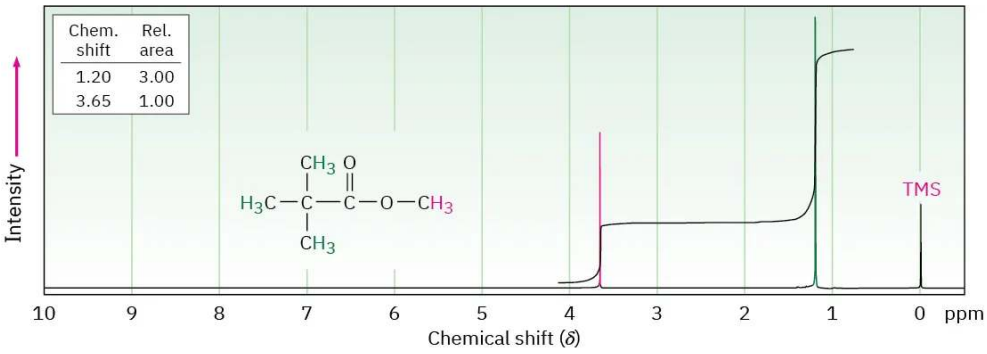


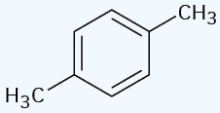
Figure 2.6.1: The ^{1}H NMR spectrum of methyl 2,2-dimethylpropanoate. Integrating the peaks in a stair-step manner shows that they have a 1 : 3 ratio, corresponding to the ratio of the numbers of protons (3 : 9) responsible for each peak. Modern instruments give a direct digital readout of relative peak areas.

The area under each peak is proportional to the number of protons causing that peak. By electronically measuring, or integrating, the area under each peak, it's possible to measure the relative numbers of the different kinds of protons in a molecule.

Modern NMR instruments provide a digital readout of relative peak areas, but an older, more visual method displays the integrated peak areas as a stair-step line, with the height of each step proportional to the area under the peak, and therefore proportional to the relative number of protons causing the peak. For example, the two steps for the peaks in methyl 2,2-dimethylpropanoate have a 1 : 3 (or 3 : 9) height ratio when integrated—exactly what we expect because the three $-OCH_3$ protons are equivalent and the nine $(CH_3)_3C$– protons are equivalent.

? Exercise 2.6.1

How many peaks would you expect in the ^{1}H NMR spectrum of 1,4-dimethylbenzene (*para*-xylene, or *p*-xylene)? What ratio of peak areas would you expect on integration of the spectrum? Refer to Figure 13.4.1 for approximate chemical shifts, and sketch what the spectrum would look like. (Remember from **Section 2.4** that aromatic rings have two resonance forms.)



***p*-Xylene**

Answer

Two peaks; 3 : 2 ratio

This page titled 2.6: Integration of ^{1}H NMR Absorptions- Proton Counting is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **13.5: Integration of ^{1}H NMR Absorptions- Proton Counting** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

2.7: Spin-Spin Splitting in ^{1}H NMR Spectra

In the ^{1}H NMR spectra we've seen thus far, each different kind of proton in a molecule has given rise to a single peak. It often happens, though, that the absorption of a proton splits into multiple peaks, called a **multiplet**. For example, in the ^{1}H NMR spectrum of bromoethane shown in Figure 2.7.1, the $–CH_2Br$ protons appear as four peaks (a *quartet*) centered at 3.42 δ and the $–CH_3$ protons appear as three peaks (a *triplet*) centered at 1.68 δ.

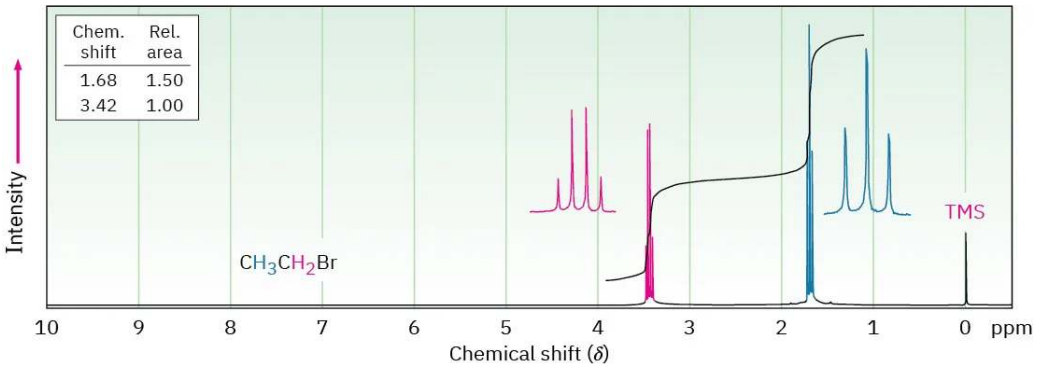


Figure 2.7.1: The ^{1}H NMR spectrum of bromoethane, CH_3CH_2Br. The $–CH_2Br$ protons appear as a quartet at 3.42 δ, and the $–CH_3$ protons appear as a triplet at 1.68 δ.

Called **spin–spin splitting**, multiple absorptions of a nucleus are caused by the interaction, or **coupling**, of the spins of nearby nuclei. In other words, the tiny magnetic field produced by one nucleus affects the magnetic field felt by a neighboring nucleus. Look at the $–CH_3$ protons in bromoethane, for example. The three equivalent $–CH_3$ protons are neighbored by two other magnetic nuclei—the two protons on the adjacent $–CH_2Br$ group. Each of the neighboring $–CH_2Br$ protons has its own nuclear spin, which can align either with or against the applied field, producing a tiny effect that is felt by the $–CH_3$ protons.

There are three ways in which the spins of the two $–CH_2Br$ protons can align, as shown in Figure 2.7.2. If both proton spins align with the applied field, the total effective field felt by the neighboring $–CH_3$ protons is slightly larger than it would be otherwise. Consequently, the applied field necessary to cause resonance is slightly reduced. Alternatively, if one of the $–CH_2Br$ proton spins aligns with the field and one aligns against the field, there is no effect on the neighboring $–CH_3$ protons. (This arrangement can occur in two ways, depending on which of the two proton spins aligns which way.) Finally, if both $–CH_2Br$ proton spins align against the applied field, the effective field felt by the $–CH_3$ protons is slightly smaller than it would be otherwise, and the applied field needed for resonance is slightly increased.

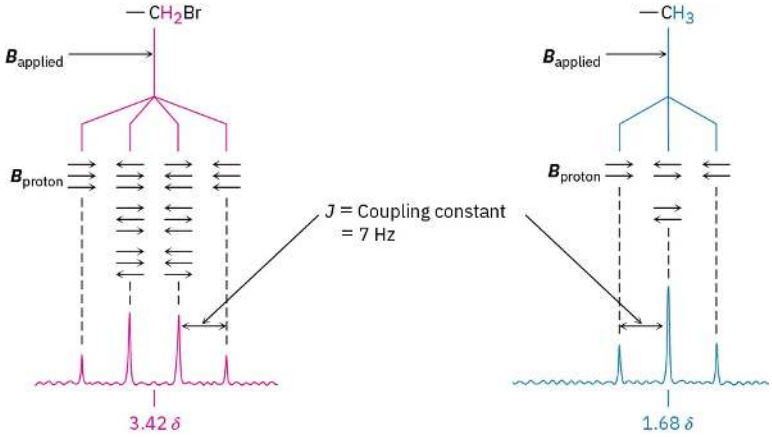


Figure 2.7.2: The origin of spin–spin splitting in bromoethane. The nuclear spins of neighboring protons, indicated by horizontal arrows, align either with or against the applied field, causing the splitting of absorptions into multiplets.

Any given molecule has only one of the three possible alignments of $–CH_2Br$ spins, but in a large collection of molecules, all three spin states are represented in a 1 : 2 : 1 statistical ratio. We therefore find that the neighboring $–CH_3$ protons come into resonance at three slightly different values of the applied field, and we see a 1 : 2 : 1 triplet in the NMR spectrum. One resonance is a little above

where it would be without coupling, one is at the same place it would be without coupling, and the third resonance is a little below where it would be without coupling.

In the same way that the $–CH_3$ absorption of bromoethane is split into a triplet, the $–CH_2Br$ absorption is split into a quartet. The three spins of the neighboring $–CH_3$ protons can align in four possible combinations: all three with the applied field, two with and one against (three ways), one with and two against (three ways), or all three against. Thus, four peaks are produced for the $–CH_2Br$ protons in a 1 : 3 : 3 : 1 ratio.

As a general rule, called the $n + 1$ rule, protons that have n equivalent neighboring protons show $n + 1$ peaks in their NMR spectrum. For example, the spectrum of 2-bromopropane in Figure 2.7.3 shows a *doublet* at 1.71 δ and a seven-line multiplet, or *septet*, at 4.28 δ. The septet is caused by splitting of the –CHBr– proton signal by six equivalent neighboring protons on the two methyl groups (n = 6 leads to 6 + 1 = 7 peaks). The doublet is due to signal splitting of the six equivalent methyl protons by the single –CHBr– proton (n = 1 leads to 2 peaks). Integration confirms the expected 6 : 1 ratio.

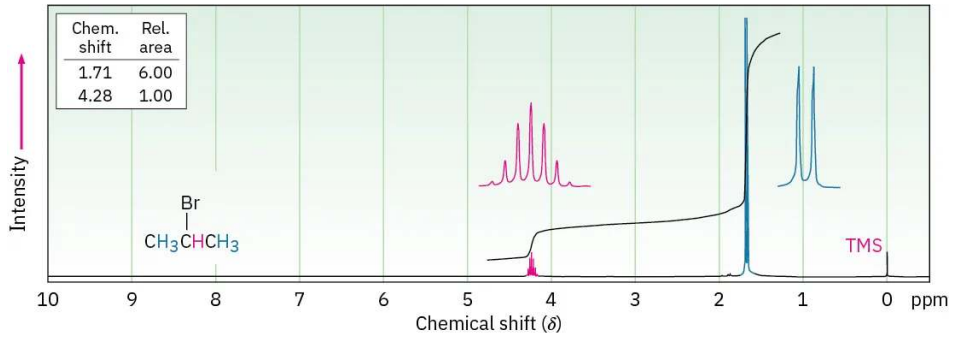


Figure 2.7.3: The ^1H NMR spectrum of 2-bromopropane. The $–CH_3$ proton signal at 1.71 δ is split into a doublet, and the –CHBr– proton signal at 4.28 δ is split into a septet. Note that the distance between peaks is the same in both multiplets. Note also that the two outer peaks of the septet are small enough to be nearly missed.

The distance between peaks in a multiplet is called the coupling constant and is denoted J. Coupling constants are measured in hertz and generally fall in the range 0 to 18 Hz. The exact value of the coupling constant between two neighboring protons depends on the geometry of the molecule, but a typical value for an open-chain alkane is J = 6 to 8 Hz. The same coupling constant is shared by both groups of hydrogens whose spins are coupled and is independent of spectrometer field strength. In bromoethane, for instance, the $–CH_2Br$ protons are coupled to the $–CH_3$ protons and appear as a quartet with J = 7 Hz. The $–CH_3$ protons appear as a triplet with the same J = 7 Hz coupling constant.

Because coupling is a reciprocal interaction between two adjacent groups of protons, it's sometimes possible to tell which multiplets in a complex NMR spectrum are related to each other. If two multiplets have the same coupling constant, they are probably related, and the protons causing those multiplets are therefore adjacent in the molecule.

The most commonly observed coupling patterns and the relative intensities of lines in their multiplets are listed in Table Figure 2.7.1. Note that it's not possible for a given proton to have five equivalent neighboring protons. (Why not?) A six-line multiplet, or sextet, is therefore found only when a proton has five nonequivalent neighboring protons that coincidentally happen to be coupled with an identical coupling constant J.

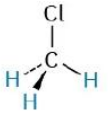
Table 2.7.1: Some Common Spin Multiplicities

Number of equivalent adjacent protons	Multiplet	Ratio of intensities
0	Singlet	1
1	Doublet	1 : 1
2	Triplet	1 : 2 : 1
3	Quartet	1 : 3 : 3 : 1
4	Quintet	1 : 4 : 6 : 4 : 1
6	Septet	1 : 6 : 15 : 20 : 15 : 6 : 1

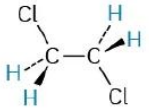
Spin–spin splitting in ^{1}H NMR can be summarized by three rules.

RULE 1

Chemically equivalent protons don't show spin–spin splitting. Equivalent protons may be on the same carbon or on different carbons, but their signals don't split.



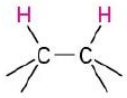
Three C–H protons are chemically equivalent; no splitting occurs.



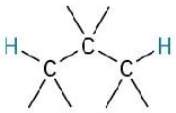
Four C–H protons are chemically equivalent; no splitting occurs.

RULE 2

The signal of a proton with *n* equivalent neighboring protons is split into a multiplet of *n* + 1 peaks with coupling constant *J*. Protons that are farther than two carbon atoms apart don't usually couple, although they sometimes show weak coupling when they are separated by a π bond.



Splitting observed



Splitting not usually observed

RULE 3

Two groups of protons coupled to each other have the same coupling constant, *J*. The spectrum of *para*-methoxypropiophenone in Figure 2.7.4 further illustrates these three rules. The downfield absorptions at 6.91 and 7.93 δ are due to the four aromatic-ring protons. There are two kinds of aromatic protons, each of which gives a signal that is split into a doublet by its neighbor. The –OCH_3 signal is unsplit and appears as a sharp singlet at 3.84 δ. The –CH_2– protons next to the carbonyl group appear at 2.93 δ in the region expected for protons on carbon next to an unsaturated center, and their signal is split into a quartet by coupling with the protons of the neighboring methyl group. The methyl protons appear as a triplet at 1.20 δ in the usual upfield region.

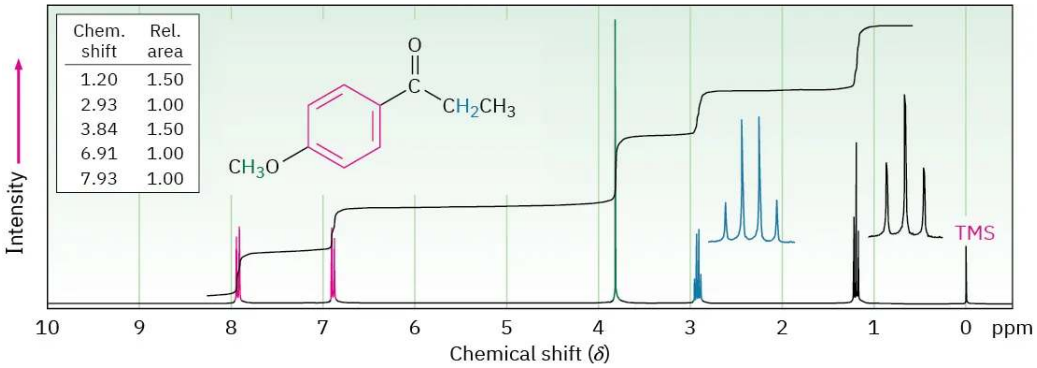


Figure 2.7.4: The ^{1}H NMR spectrum of *para*-methoxypropiophenone.

Worked Example 2.7.1: Assigning a Chemical Structure from a 1H NMR Spectrum

Propose a structure for a compound, $C_5H_{12}O$, that fits the following ^{1}H NMR data: 0.92 δ (3 H, triplet, J = 7 Hz), 1.20 δ (6 H, singlet), 1.50 δ (2 H, quartet, J = 7 Hz), 1.64 δ (1 H, broad singlet).

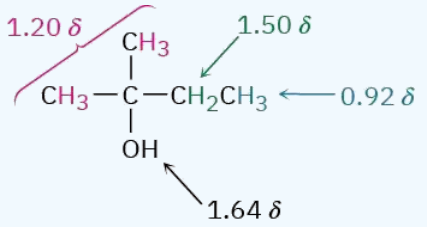
Strategy

It's best to begin solving structural problems by calculating a molecule's degree of unsaturation (we'll see this again in Worked Example 13.4). In the present instance, a formula of $C_5H_{12}O$ corresponds to a saturated, open-chain molecule, either an alcohol

or an ether.

To interpret the NMR information, let's look at each absorption individually. The three-proton absorption at 0.92 δ is due to a methyl group in an alkane-like environment, and the triplet-splitting pattern implies that the CH_3 is next to a CH_2. Thus, our molecule contains an ethyl group, CH_3CH_2–. The six-proton singlet at 1.20 δ is due to two equivalent alkane-like methyl groups attached to a carbon with no hydrogens, $(CH_3)_2C$, and the two-proton quartet at 1.50 δ is due to the CH_2 of the ethyl group. All 5 carbons and 11 of the 12 hydrogens in the molecule are now accounted for. The remaining hydrogen, which appears as a broad one-proton singlet at 1.64 δ, is probably due to an OH group, since there is no other way to account for it. Putting the pieces together gives the structure: 2-methyl-2-butanol.

Solution



2-Methyl-2-butanol

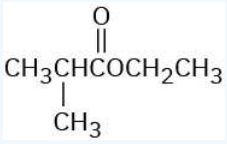
Exercise 2.7.1

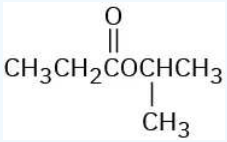
Predict the splitting patterns you would expect for each proton in the following molecules:

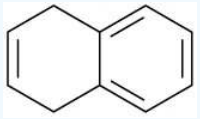
a. $CHBr_2CH_3$

b. $CH_3OCH_2CH_2Br$

c. $ClCH_2CH_2CH_2Cl$

d. 

e. 

f. 

Answer

a. $-CHBr_2$, quartet; $-CH_3$, doublet

b. CH_3O-, singlet; $-OCH_2-$, triplet; $-CH_2Br$, triplet

c. $ClCH_2-$, triplet; $-CH_2-$, quintet

d. CH_3-, triplet; $-CH_2-$, quartet; $-CH-$, septet; $(CH_3)_2$, doublet

e. CH_3-, triplet; $-CH_2-$, quartet; $-CH-$, septet; $(CH_3)_2$, doublet

f. =CH, triplet, $-CH_2-$, doublet, aromatic C−H, two multiplets

Exercise 2.7.2

Draw structures for compounds that meet the following descriptions:

a. C_2H_6O; one singlet

b. C_3H_7Cl; one doublet and one septet

c. $C_4H_8Cl_2O$; two triplets

d. $C_4H_8O_2$; one singlet, one triplet, and one quartet

Answer

a. CH_3OCH_3

b. $CH_3CH(Cl)CH_3$

c. $ClCH_2CH_2OCH_2CH_2Cl$

d. $CH_3CH_2CO_2CH_3$ or $CH_3CO_2CH_2CH_3$

? Exercise 2.7.3

The integrated ^1H NMR spectrum of a compound of formula $C_4H_{10}O$ is shown in Figure 2.7.5. Propose a structure.

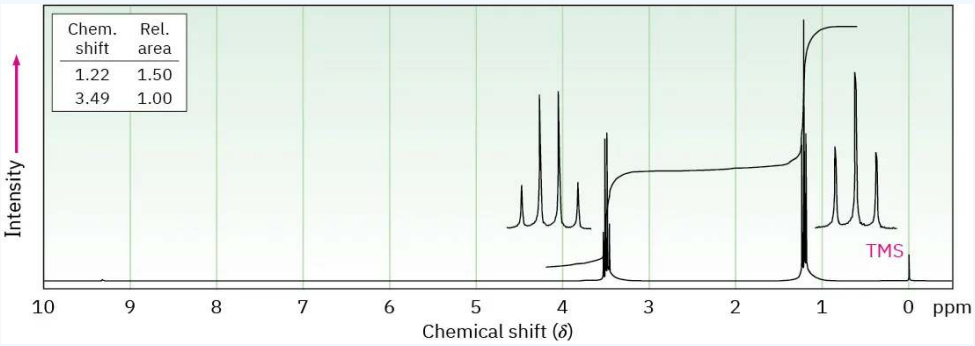


Figure 2.7.5 : An integrated ^1H NMR spectrum for Problem 11.

Answer

$CH_3CH_2OCH_2CH_3$

This page titled 2.7: Spin-Spin Splitting in ^1H NMR Spectra is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

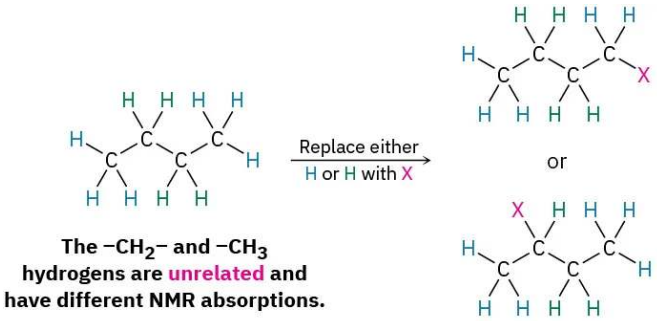
- **13.6: Spin-Spin Splitting in ^1H NMR Spectra** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

2.8: ^{1}H NMR Spectroscopy and Proton Equivalence

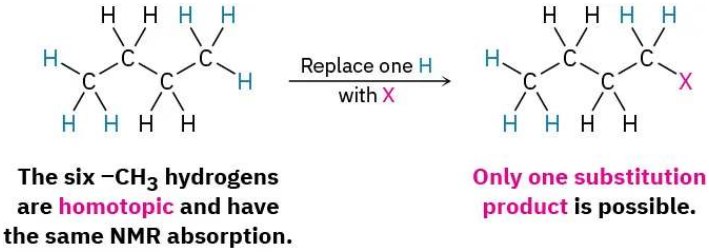
Because each electronically distinct hydrogen in a molecule has its own unique absorption, one use of ^{1}H NMR is to find out how many kinds of electronically nonequivalent hydrogens are present. In the ^{1}H NMR spectrum of methyl acetate shown previously, for instance, there are two signals, corresponding to the two kinds of nonequivalent protons present, $CH_3C{=}O$ protons and $–OCH_3$ protons.

For relatively small molecules, a quick look at the structure is often enough to decide how many kinds of protons are present and thus how many NMR absorptions might appear. If in doubt, though, the equivalence or nonequivalence of two protons can be determined by comparing the structures that would be formed if each hydrogen were replaced by an X group. There are four possibilities.

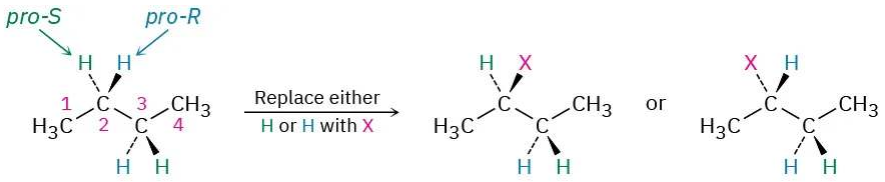
- One possibility is that the protons are chemically unrelated and thus nonequivalent. If so, the products formed on substitution of H by X would be different constitutional isomers. In butane, for instance, the $–CH_3$ protons are different from the $–CH_2–$ protons. They therefore give different products on substitution by X than the $–CH_2$ protons and would likely show different NMR absorptions.



- A second possibility is that the protons are chemically identical and thus electronically equivalent. If so, the same product would be formed regardless of which H is substituted by X. In butane, for instance, the six $–CH_3$ hydrogens on C1 and C4 are identical, would give the identical structure on substitution by X, and would show an identical NMR absorption. Such protons are said to be homotopic.



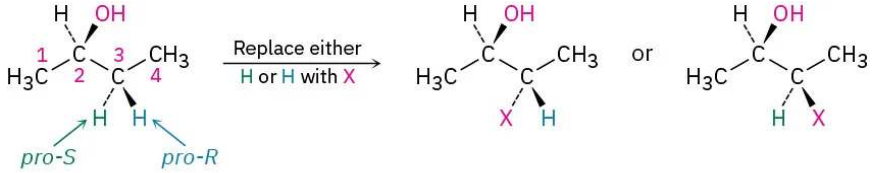
- The third possibility is a bit more subtle. Although they might at first seem homotopic, the two $–CH_2–$ hydrogens on C2 in butane (and the two $–CH_2–$ hydrogens on C3) are in fact not identical. Substitution by X of a hydrogen at C2 (or C3) would form a new chirality center, so different enantiomers (Section 5.1) would result, depending on whether the pro-*R* or pro-*S* hydrogen had been substituted (Section 5.11). Such hydrogens, whose substitution by X would lead to different enantiomers, are said to be enantiotopic. Enantiotopic hydrogens, even though not identical, are nevertheless electronically equivalent and thus have the same NMR absorption.



The two hydrogens on C2 (and on C3) are enantiotopic and have the same NMR absorption.

The two possible substitution products are enantiomers.

- The fourth possibility arises in chiral molecules, such as (*R*)-2-butanol. The two –CH_2– hydrogens at C3 are neither homotopic nor enantiotopic. Because substitution of a hydrogen at C3 would form a *second* chirality center, different diastereomers (Section 5.6) would result, depending on whether the pro-*R* or pro-*S* hydrogen had been substituted. Such hydrogens, whose substitution by X leads to different diastereomers, are said to be diastereotopic. Diastereotopic hydrogens are neither chemically nor electronically equivalent. They are completely different and would likely show different NMR absorptions.

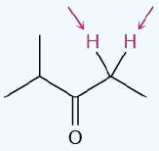


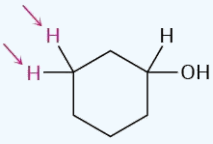
The two hydrogens on C3 are diastereotopic and have different NMR absorptions.

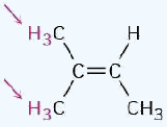
The two possible substitution products are diastereomers.

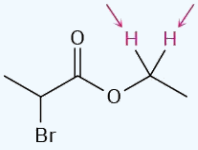
? Exercise 2.8.1

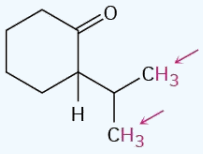
Identify the indicated sets of protons as unrelated, homotopic, enantiotopic, or diastereotopic:

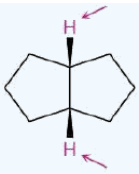
a.


b.


c.


d.


e.


f. 

Answer

a. Enantiotopic
b. Diastereotopic
c. Diastereotopic
d. Diastereotopic
e. Diastereotopic
f. Homotopic

Exercise 2.8.2

How many kinds of electronically nonequivalent protons are present in each of the following compounds, and thus how many NMR absorptions might you expect in each?

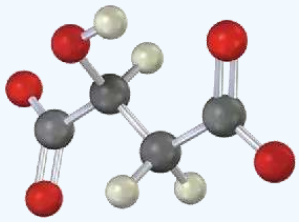
a. CH_3CH_2Br
b. $CH_3OCH_2CH(CH_3)_2$
c. $CH_3CH_2CH_2NO_2$
d. Methylbenzene
e. 2-Methyl-1-butene
f. *cis*-3-Hexene

Answer

a. 2
b. 4
c. 3
d. 4
e. 5
f. 3

Exercise 2.8.3

How many absorptions would you expect (*S*)-malate, an intermediate in carbohydrate metabolism, to have in its ^1H NMR spectrum? Explain.



(*S*)-Malate

Answer

4

This page titled 2.8: ^1H NMR Spectroscopy and Proton Equivalence is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **13.7: ^{1}H NMR Spectroscopy and Proton Equivalence** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

2.9: More Complex Spin-Spin Splitting Patterns

In the ^{1}H NMR spectra we've seen so far, the chemical shifts of different protons have been distinct and the spin–spin splitting patterns have been straightforward. It often happens, however, that different kinds of hydrogens in a molecule have accidentally overlapping signals. The spectrum of toluene (methylbenzene) in Figure 2.9.1, for example, shows that the five aromatic ring protons give a complex, overlapping pattern, even though they aren't all equivalent.

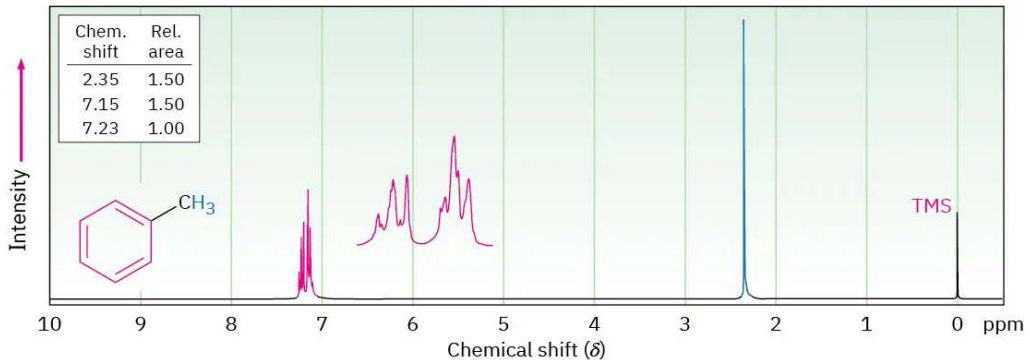


Figure 2.9.1: The ^{1}H NMR spectrum of toluene, showing the accidental overlap of the five nonequivalent aromatic ring protons.

Yet another complication in ^{1}H NMR spectroscopy arises when a signal is split by two or more *nonequivalent* kinds of protons, as is the case with *trans*-cinnamaldehyde, isolated from oil of cinnamon (Figure 2.9.2). Although the n + 1 rule predicts splitting caused by equivalent protons, splittings caused by nonequivalent protons are more complex.

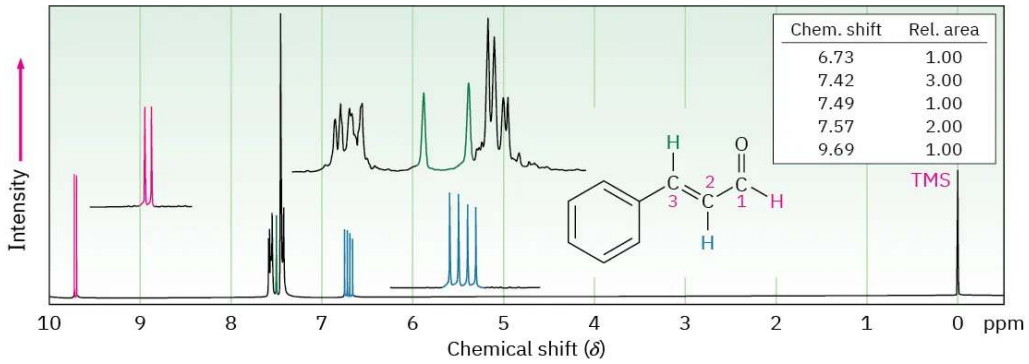


Figure 2.9.2: The ^{1}H NMR spectrum of *trans*-cinnamaldehyde. The signal of the proton at C2 (blue) is split into four peaks—a doublet of doublets—by the two nonequivalent neighboring protons.

To understand the ^{1}H NMR spectrum of *trans*-cinnamaldehyde, we have to isolate the different parts and look at the signal of each proton individually.

- The five aromatic proton signals (black in Figure 2.9.2) overlap into a complex pattern with a large peak at 7.42 δ and a broad absorption at 7.57 δ.
- The aldehyde proton signal at C1 (**red**) appears in the normal downfield position at 9.69 δ and is split into a doublet with J = 6 Hz by the adjacent proton at C2.
- The vinylic proton at C3 (**green**) is next to the aromatic ring and is therefore shifted downfield from the normal vinylic region. This C3 proton signal appears as a doublet centered at 7.49 δ. Because it has one neighbor proton at C2, its signal is split into a doublet, with J = 12 Hz.
- The C2 vinylic proton signal (**blue**) appears at 6.73 δ and shows an interesting, four-line absorption pattern. It is coupled to the two nonequivalent protons at C1 and C3 with two different coupling constants: $J_{1\text{-}2}$ = 6 Hz and $J_{2\text{-}3}$ = 12 Hz.

A good way to understand the effect of multiple coupling, such as that occurring for the C2 proton of *trans*-cinnamaldehyde, is to draw a *tree diagram*, like that in Figure 2.9.3. The diagram shows the individual effect of each coupling constant on the overall pattern. Coupling with the C3 proton splits the signal of the C2 proton in *trans*-cinnamaldehyde into a doublet with J =12 Hz. Further coupling with the aldehyde proton then splits each peak of the doublet into new doublets with J = 6 Hz, and we therefore observe a four-line spectrum for the C2 proton.

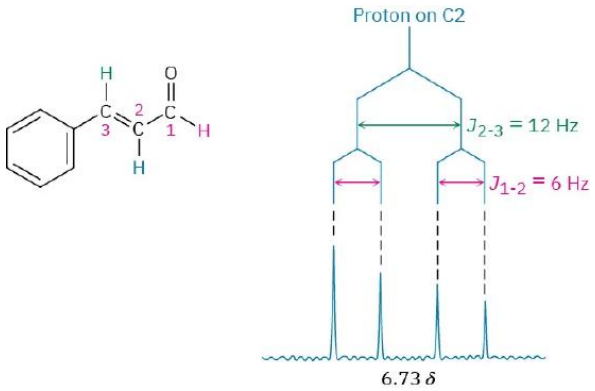
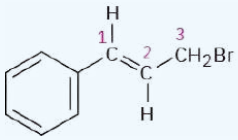


Figure 2.9.3: A tree diagram for the C2 proton of *trans*-cinnamaldehyde shows how it is coupled to the C1 and C3 protons with different coupling constants.

One further trait evident in the cinnamaldehyde spectrum is that the four peaks of the C2 proton signal are not all the same size. The two left-hand peaks are somewhat larger than the two right-hand peaks. Such a size difference occurs whenever coupled nuclei have similar chemical shifts—in this case, 7.49 δ for the C3 proton and 6.73 δ for the C2 proton. The peaks nearer the signal of the coupled partner are always larger, and the peaks farther from the signal of the coupled partner are always smaller. Thus, the left-hand peaks of the C2 proton multiplet at 6.73 δ are closer to the C3 proton absorption at 7.49 δ and are larger than the right-hand peaks. At the same time, the right-hand peak of the C3 proton doublet at 7.49 δ is larger than the left-hand peak because it is closer to the C2 proton multiplet at 6.73 δ. This skewing effect on multiplets can often be useful because it tells where to look in the spectrum to find the coupled partner: look in the direction of the larger peaks.

Exercise 2.9.1

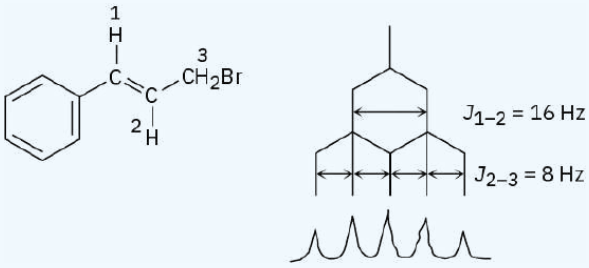
3-Bromo-1-phenyl-1-propene shows a complex NMR spectrum in which the vinylic proton at C2 is coupled with both the C1 vinylic proton (J = 16 Hz) and the C3 methylene protons (J = 8 Hz). Draw a tree diagram for the C2 proton signal, and account for the fact that a five-line multiplet is observed.



3-Bromo-1-phenyl-1-propene

Answer

J_{1-2} = 16 Hz; J_{2-3} = 8 Hz



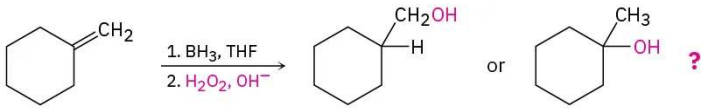
This page titled 2.9: More Complex Spin-Spin Splitting Patterns is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **13.8: More Complex Spin-Spin Splitting Patterns** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

2.10: Uses of ^{1}H NMR Spectroscopy

NMR is used to help identify the product of nearly every reaction run in the laboratory. For example, we said in Section 8.5 that hydroboration–oxidation of alkenes occurs with non-Markovnikov regiochemistry to yield the less highly substituted alcohol. With the help of NMR, we can now prove this statement.

Does hydroboration–oxidation of methylenecyclohexane yield cyclohexylmethanol or 1-methylcyclohexanol?



Methylenecyclohexane **Cyclohexylmethanol** **1-Methylcyclohexanol**

The ^{1}H NMR spectrum of the reaction product is shown in Figure 2.10.1a. The spectrum shows a two-proton peak at 3.40 δ, indicating that the product has a $–CH_2–$ group bonded to an electronegative oxygen atom ($–CH_2OH$). Furthermore, the spectrum shows no large three-proton singlet absorption near 1 δ, where we would expect the signal of a quaternary $–CH_3$ group to appear. (Figure 2.10.1b) gives the spectrum of 1-methylcyclohexanol, the alternative product.) Thus, it's clear that cyclohexylmethanol is the reaction product.

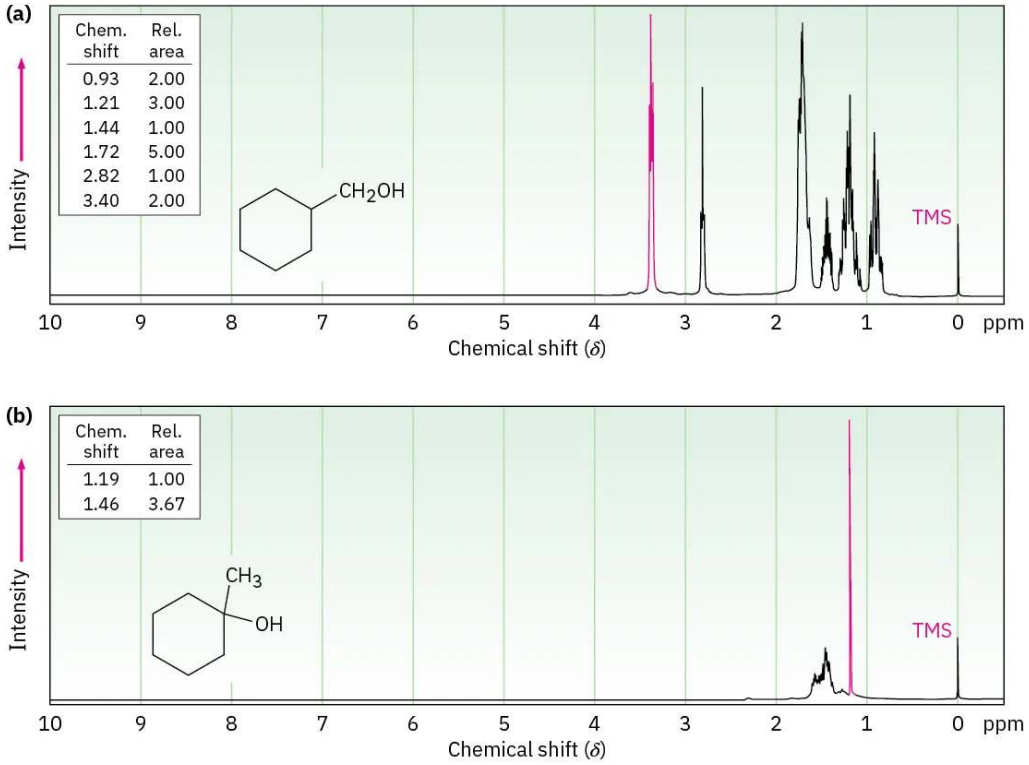


Figure 2.10.1: (a) The ^{1}H NMR spectrum of cyclohexylmethanol, the product from hydroboration–oxidation of methylenecyclohexane, and (b) the ^{1}H NMR spectrum of 1-methylcyclohexanol, the possible alternative reaction product.

? Exercise 2.10.1

How could you use ^{1}H NMR to determine the regiochemistry of electrophilic addition to alkenes? For example, does addition of HCl to 1-methylcyclohexene yield 1-chloro-1-methylcyclohexane or 1-chloro-2-methylcyclohexane?

Answer

1-Chloro-1-methylcyclohexane has a singlet methyl absorption.

This page titled 2.10: Uses of ¹H NMR Spectroscopy is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **13.9: Uses of ¹H NMR Spectroscopy** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

2.11: ^{13}C NMR Spectroscopy - Signal Averaging and FT-NMR

In some ways, it's surprising that carbon NMR is even possible. After all, ^{12}C, the most abundant carbon isotope, has no nuclear spin and can't be seen by NMR. Carbon-13 is the only naturally occurring carbon isotope with a nuclear spin, but its natural abundance is only 1.1%. Thus, only about 1 of every 100 carbon atoms in an organic sample can be observed by NMR. The problem of low abundance has been overcome, however, by the use of *signal averaging* and *Fourier-transform NMR* (FT–NMR). Signal averaging increases instrument sensitivity, and FT–NMR increases instrument speed.

The low natural abundance of ^{13}C means that any individual NMR spectrum is extremely "noisy." That is, the signals are so weak that they are cluttered with random background electronic noise, as shown in Figure 2.11.1a. If, however, hundreds or thousands of individual runs are added together by a computer and then averaged, a greatly improved spectrum results (Figure 2.11.1b). Background noise, because of its random nature, increases very slowly as the runs are added, while the nonzero signals stand out clearly. Unfortunately, the value of signal averaging is limited when using the method of NMR spectrometer operation described in Section 13.2, because it takes about 5 to 10 minutes to obtain a single spectrum. Thus, a faster way to obtain spectra is needed if signal averaging is to be used.

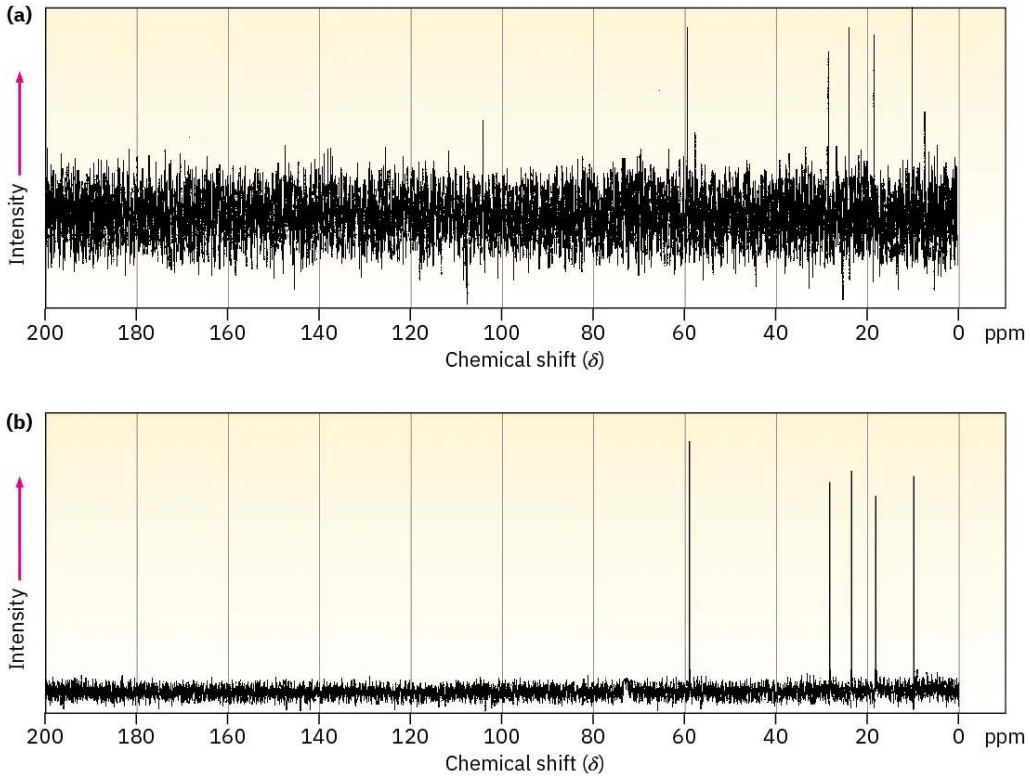


Figure 2.11.1: Carbon-13 NMR spectra of 1-pentanol, $CH_3CH_2CH_2CH_2CH_2OH$. Spectrum **(a)** is a single run, showing the large amount of background noise. Spectrum **(b)** is an average of 200 runs.

In the method of NMR spectrometer operation described in Section 13.2, the rf frequency is held constant while the strength of the magnetic field is varied so that all signals in the spectrum are recorded sequentially. In the FT–NMR technique used by modern spectrometers, however, all the signals are recorded simultaneously. A sample is placed in a magnetic field of constant strength and is irradiated with a short pulse of rf energy that covers the entire range of useful frequencies. All ^{1}H or ^{13}C nuclei in the sample resonate at once, giving a complex, composite signal that is mathematically manipulated using so-called Fourier transforms and then displayed in the usual way. Because all resonance signals are collected at once, it takes only a few seconds rather than a few minutes to record an entire spectrum.

Combining the speed of FT–NMR with the sensitivity enhancement of signal averaging is what gives modern NMR spectrometers their power. Literally thousands of spectra can be taken and averaged in a few hours, resulting in sensitivity so high that a ^{13}C NMR spectrum can be obtained from less than 0.1 mg of sample and a ^{1}H spectrum can be recorded from only a few *micro*grams.

One further question needs to be answered before moving forward with our discussion of ^{13}C NMR. Why is spin–spin splitting seen only for ^{1}H NMR? Why is there no splitting of *carbon* signals into multiplets in ^{13}C NMR? After all, you might expect that the spin of a given ^{13}C nucleus would couple with the spin of an adjacent magnetic nucleus, either ^{13}C or ^{1}H.

No coupling of a ^{13}C nucleus with nearby carbons is seen because their low natural abundance makes it unlikely that two ^{13}C nuclei will be adjacent. No coupling of a ^{13}C nucleus with nearby hydrogens is seen because ^{13}C spectra are normally recorded using *broadband decoupling*. At the same time that the sample is irradiated with a pulse of rf energy to cover the carbon resonance frequencies, it is also irradiated by a second band of rf energy covering all the hydrogen resonance frequencies. This second irradiation makes the hydrogens spin-flip so rapidly that their local magnetic fields average to zero and no coupling with carbon spins occurs.

This page titled 2.11: ^{13}C NMR Spectroscopy - Signal Averaging and FT-NMR is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **13.10: ^{13}C NMR Spectroscopy - Signal Averaging and FT-NMR** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

2.12: Characteristics of ^{13}C NMR Spectroscopy

At its simplest, ^{13}C NMR makes it possible to count the number of different carbon atoms in a molecule. Look at the ^{13}C NMR spectra of methyl acetate and 1-pentanol shown previously in Figure 13.4b and Figure 13.17b. In each case, a single sharp resonance line is observed for each different carbon atom.

Most ^{13}C resonances are between 0 and 220 ppm downfield from the TMS reference line, with the exact chemical shift of each ^{13}C resonance dependent on that carbon's electronic environment within the molecule. Figure 2.12.1 shows the correlation of chemical shift with environment.

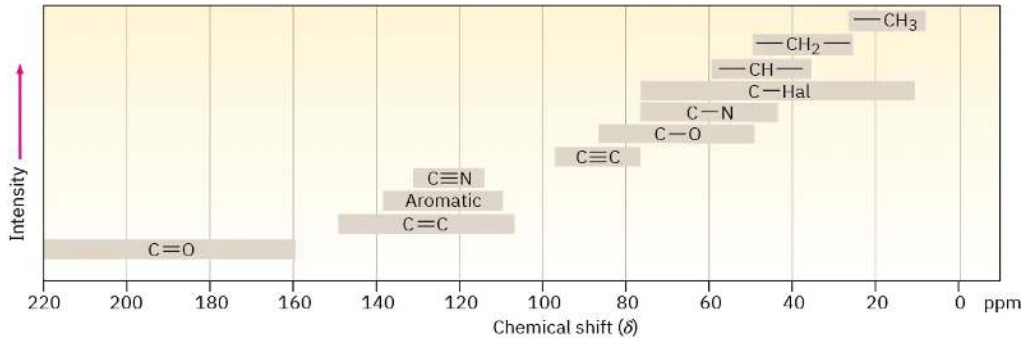


Figure 2.12.1: Chemical shift correlations for ^{13}C NMR.

The factors that determine chemical shifts are complex, but it's possible to make some generalizations from the data in Figure 2.12.1. One trend is that a carbon atom's chemical shift is affected by the electronegativity of nearby atoms. Carbons bonded to oxygen, nitrogen, or halogen absorb downfield (to the left) of typical alkane carbons. Because electronegative atoms attract electrons, they pull electrons away from neighboring carbon atoms, causing those carbons to be deshielded and to come into resonance at a lower field.

Another trend is that sp^3-hybridized carbons generally absorb from 0 to 90 δ, while sp^2 carbons absorb from 110 to 220 δ. Carbonyl carbons (C=O) are particularly distinct in ^{13}C NMR and are always found at the low-field end of the spectrum, from 160 to 220 δ. Figure 2.12.2 shows the ^{13}C NMR spectra of 2-butanone and *para*-bromoacetophenone and indicates the peak assignments. Note that the C=O carbons are at the left edge of the spectrum in each case.

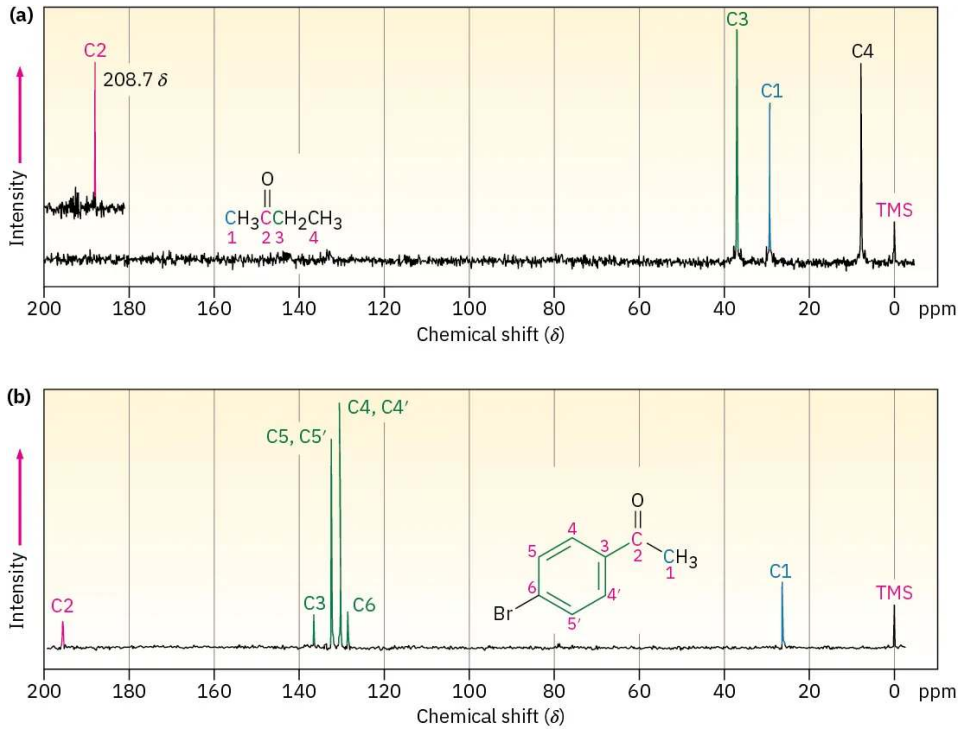
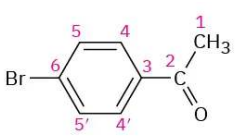
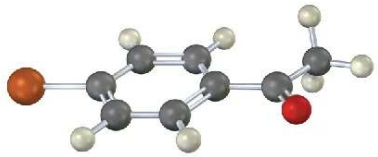


Figure 2.12.2: Carbon-13 NMR spectra of (a) 2-butanone and (b) *para*-bromoacetophenone.

The ^{13}C NMR spectrum of *para*-bromoacetophenone is interesting in several ways. Note particularly that only six carbon absorptions are observed, even though the molecule contains eight carbons. *para*-bromoacetophenone has a symmetry plane that makes ring carbons 4 and 4′, and ring carbons 5 and 5′ equivalent. (Remember from Section 2.4 that aromatic rings have two resonance forms.) Thus, the six ring carbons show only four absorptions in the range 128 to 137 δ.



***para*-Bromoacetophenone**



A second interesting point about both spectra in Figure 2.12.2 is that the peaks aren't uniform in size. Some peaks are larger than others even though they are one-carbon resonances (except for the two 2-carbon peaks of *para*-bromoacetophenone). This difference in peak size is a general feature of broadband-decoupled ^{13}C NMR spectra, and explains why we can't integrate ^{13}C NMR spectra in the same way we integrate the resonances in a ^{1}H NMR spectrum. The local environment of each carbon atom determines not only its chemical shift but also the time it takes for the nuclei to return to their equilibrium state after receiving a pulse of rf radiation and flipping their spins. Quaternary carbons, regardless of their hybridization state or substituents, typically give smaller resonances than primary, secondary, or tertiary carbons.

Worked Example 2.12.1: Predicting Chemical Shifts in ^{13}C NMR Spectra

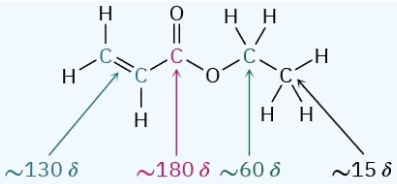
At what approximate positions would you expect ethyl acrylate, $H_2C{=}CHCO_2CH_2CH_3$, to show ^{13}C NMR absorptions?

Strategy

Identify the distinct carbons in the molecule, and note whether each is alkyl, vinylic, aromatic, or in a carbonyl group. Then predict where each absorbs, using Figure 2.12.1 as necessary.

Solution

Ethyl acrylate has five chemically distinct carbons: two different C=C, one C=O, one O–C, and one alkyl C. From Figure 2.12.1, the likely absorptions are

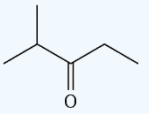


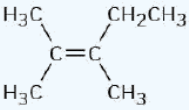
The actual absorptions are at 14.1, 60.5, 128.5, 130.3, and 166.0 δ.

Exercise 2.12.1

Predict the number of carbon resonance lines you would expect in the ^{13}C NMR spectra of the following compounds:

a. Methylcyclopentane
b. 1-Methylcyclohexene
c. 1,2-Dimethylbenzene
d. 2-Methyl-2-butene

e. 

f. 

Answer

a. 4
b. 7
c. 4
d. 5
e. 5
f. 7

Exercise 2.12.2

Propose structures for compounds that fit the following descriptions:

a. A hydrocarbon with seven lines in its ^{13}C NMR spectrum
b. A six-carbon compound with only five lines in its ^{13}C NMR spectrum
c. A four-carbon compound with three lines in its ^{13}C NMR spectrum

Answer

a. 1,3-Dimethylcyclopentene
b. 2-Methylpentane
c. 1-Chloro-2-methylpropane

Exercise 2.12.3

Classify the resonances in the ^{13}C NMR spectrum of methyl propanoate, $CH_3CH_2CO_2CH_3$ (Figure 2.12.3).

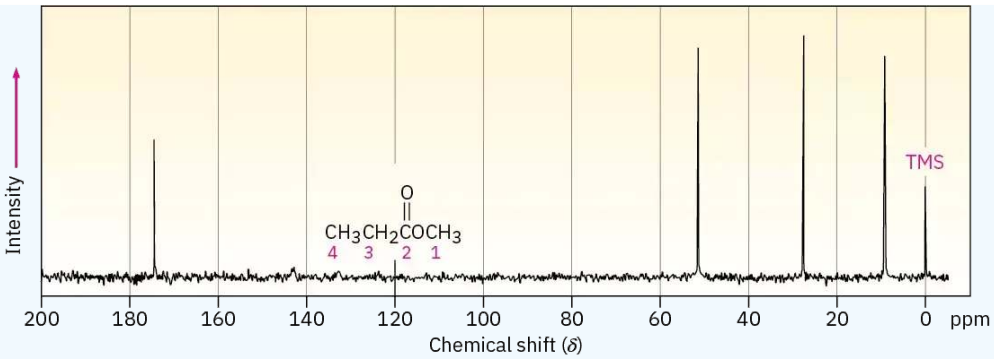


Figure 2.12.3 13C NMR spectrum of methyl propanoate

Answer

$-CH_3$, 9.3 δ; $-CH_2-$, 27.6 δ; C=O, 174.6 δ; $-OCH_3$, 51.4 δ

This page titled 2.12: Characteristics of ^{13}C NMR Spectroscopy is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **13.11: Characteristics of ^{13}C NMR Spectroscopy** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

2.13: DEPT ^{13}C NMR Spectroscopy

Numerous techniques developed in recent years have made it possible to obtain enormous amounts of information from ^{13}C NMR spectra. Among these techniques is one called *DEPT–NMR*, for *distortionless enhancement by polarization transfer*, which makes it possible to distinguish between signals due to CH_3, CH_2, CH, and quaternary carbons. That is, the number of hydrogens attached to each carbon in a molecule can be determined.

A DEPT experiment is usually done in three stages, as shown in Figure 2.13.1 for 6-methyl-5-hepten-2-ol. The first stage is to run an ordinary spectrum (called a broadband-decoupled spectrum) to locate the chemical shifts of all carbons. Next, a second spectrum called a DEPT-90 is run, using special conditions under which only signals due to CH carbons appear. Signals due to CH_3, CH_2, and quaternary carbons are absent. Finally, a third spectrum called a DEPT-135 is run, using conditions under which CH_3 and CH resonances appear as positive signals, CH_2 resonances appear as negative signals—that is, as peaks below the baseline—and quaternary carbons are again absent.

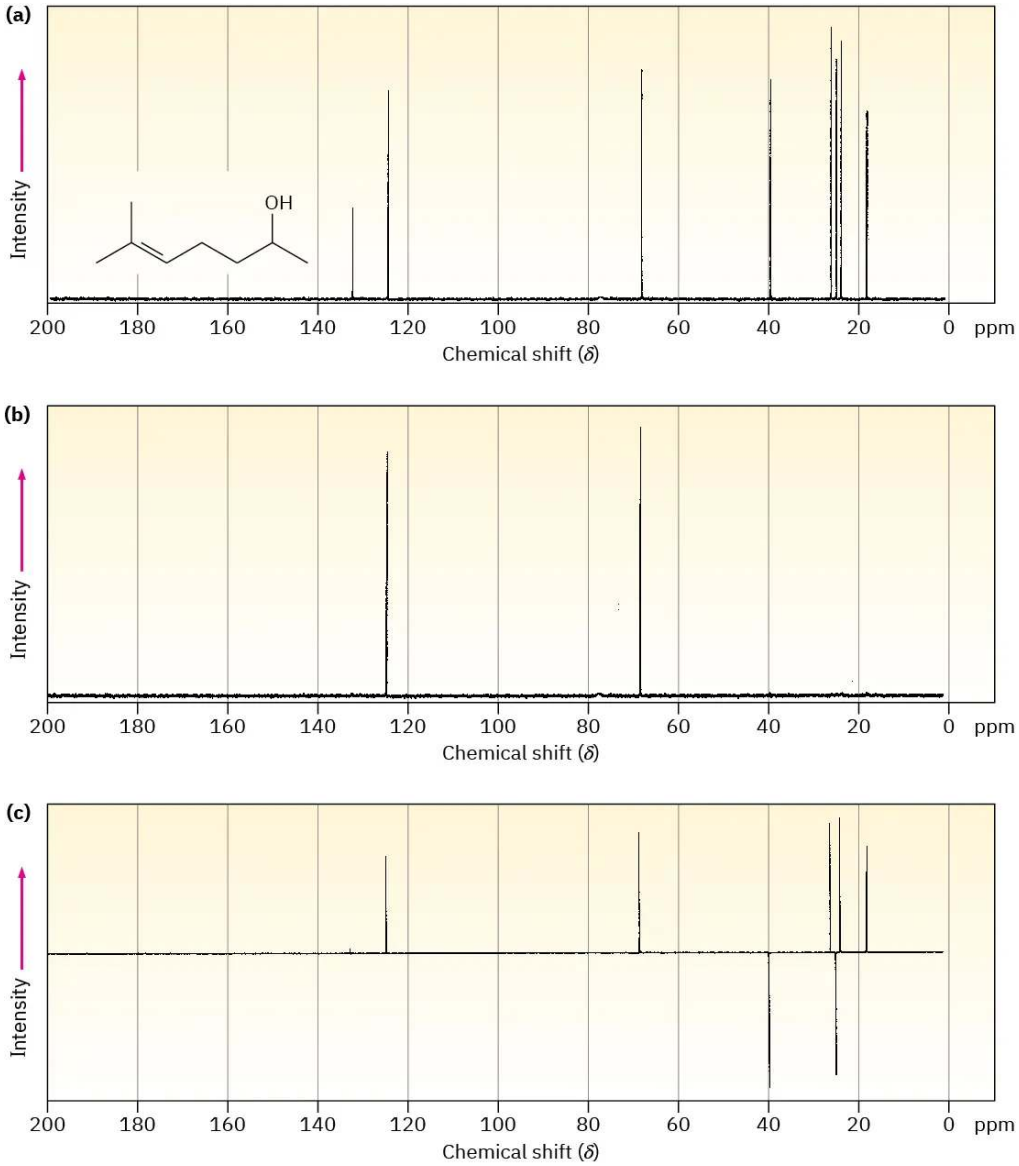
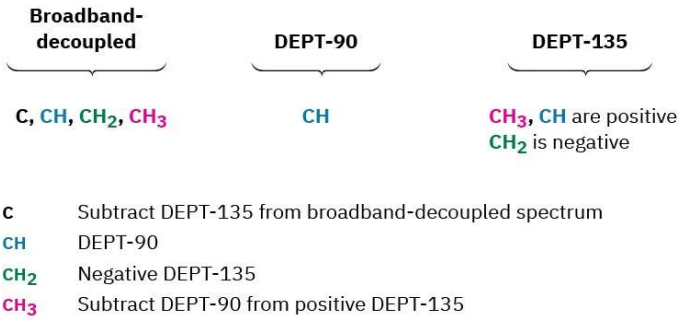


Figure 2.13.1: DEPT–NMR spectra for 6-methyl-5-hepten-2-ol. Part **(a)** is an ordinary broadband-decoupled spectrum, which shows signals for all eight carbons. Part **(b)** is a DEPT-90 spectrum, which shows only signals for the two CH carbons. Part **(c)** is a DEPT-135 spectrum, which shows positive signals for the two CH and three CH_3 carbons and negative signals for the two CH_2 carbons.

Putting together the information from all three spectra makes it possible to tell the number of hydrogens attached to each carbon. The CH carbons are identified in the DEPT-90 spectrum, the CH_2 carbons are identified as negative peaks in the DEPT-135 spectrum, the CH_3 carbons are identified by subtracting the CH peaks from the positive peaks in the DEPT-135 spectrum, and quaternary carbons are identified by subtracting all peaks in the DEPT-135 spectrum from the peaks in the broadband-decoupled spectrum.



Worked Example 2.13.1: Assigning a Chemical Structure from a 13C NMR Spectrum

Propose a structure for an alcohol, $C_4H_{10}O$, that has the following ^{13}C NMR spectral data:

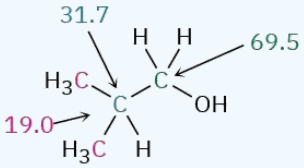
- Broadband decoupled ^{13}C NMR: 19.0, 31.7, 69.5 δ;
- DEPT-90: 31.7 δ;
- DEPT-135: positive peak at 19.0 δ, negative peak at 69.5 δ.

Strategy

As noted in Section 7.2, it usually helps with compounds of known formula but unknown structure to calculate the compound's degree of unsaturation. In the present instance, a formula of $C_4H_{10}O$ corresponds to a saturated, open-chain molecule.

To gain information from the ^{13}C data, let's begin by noting that the unknown alcohol has four carbon atoms, yet has only three NMR absorptions, which implies that two of the carbons must be equivalent. Looking at chemical shifts, two of the absorptions are in the typical alkane region (19.0 and 31.7 δ), while one is in the region of a carbon bonded to an electronegative atom (69.5 δ)—oxygen in this instance. The DEPT-90 spectrum tells us that the alkyl carbon at 31.7 δ is tertiary (CH); the DEPT-135 spectrum tells us that the alkyl carbon at 19.0 δ is a methyl (CH_3) and that the carbon bonded to oxygen (69.5 δ) is secondary (CH_2). The two equivalent carbons are probably both methyls bonded to the same tertiary carbon, $(CH_3)_2CH$–. We can now put the pieces together to propose a structure: 2-methyl-1-propanol.

Solution



2-Methyl-1-propanol

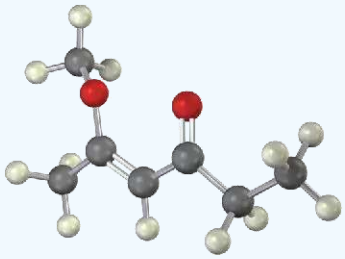
Exercise 2.13.1

Assign a chemical shift to each carbon in 6-methyl-5-hepten-2-ol (Figure 2.13.1).

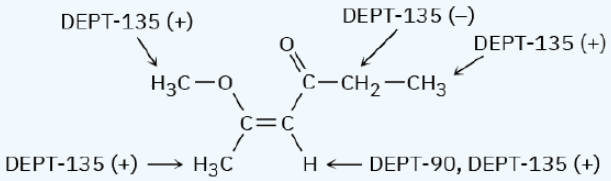
Answer

Exercise 2.13.2

Estimate the chemical shift of each carbon in the following molecule. Predict which carbons will appear in the DEPT-90 spectrum, which will give positive peaks in the DEPT-135 spectrum, and which will give negative peaks in the DEPT-135 spectrum.



Answer

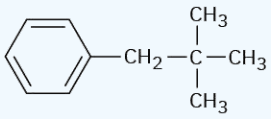


Exercise 2.13.3

Propose a structure for an aromatic hydrocarbon, $C_{11}H_{16}$, that has the following ^{13}C NMR spectral data:

Broadband decoupled: 29.5, 31.8, 50.2, 125.5, 127.5, 130.3, 139.8 δ
DEPT-90: 125.5, 127.5, 130.3 δ
DEPT-135: positive peaks at 29.5, 125.5, 127.5, 130.3 δ; negative peak at 50.2 δ

Answer



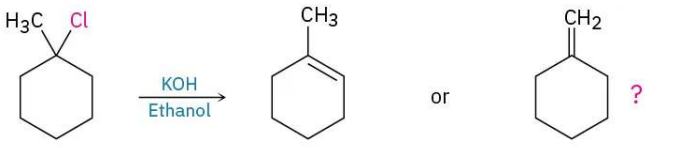
This page titled 2.13: DEPT ^{13}C NMR Spectroscopy is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **13.12: DEPT ^{13}C NMR Spectroscopy** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

2.14: Uses of ^{13}C NMR Spectroscopy

The information derived from ^{13}C NMR spectroscopy is extraordinarily useful for structure determination. Not only can we count the number of nonequivalent carbon atoms in a molecule, we can also get information about the electronic environment of each carbon and find how many protons are attached to each. As a result, we can address many structural questions that go unanswered by IR spectroscopy or mass spectrometry.

Here's an example: how do we know that the E2 reaction of an alkyl halide follows Zaitsev's rule (Section 11.7)? Does treatment of 1-chloro-1-methylcyclohexane with a strong base give predominantly the trisubstituted alkene 1-methylcyclohexene or the disubstituted alkene methylenecyclohexane?



1-Chloro-1-methylcyclohexane **1-Methylcyclohexene** **Methylenecyclohexane**

1-Methylcyclohexene will have five sp^3-carbon resonances in the 20 to 50 δ range and two sp^2-carbon resonances in the 100 to 150 δ range. Methylenecyclohexane, however, because of its symmetry, will have only three sp^3-carbon resonance peaks and two sp^2-carbon peaks. The spectrum of the actual reaction product, shown in Figure 2.14.1, clearly identifies 1-methylcyclohexene as the product of this E2 reaction.

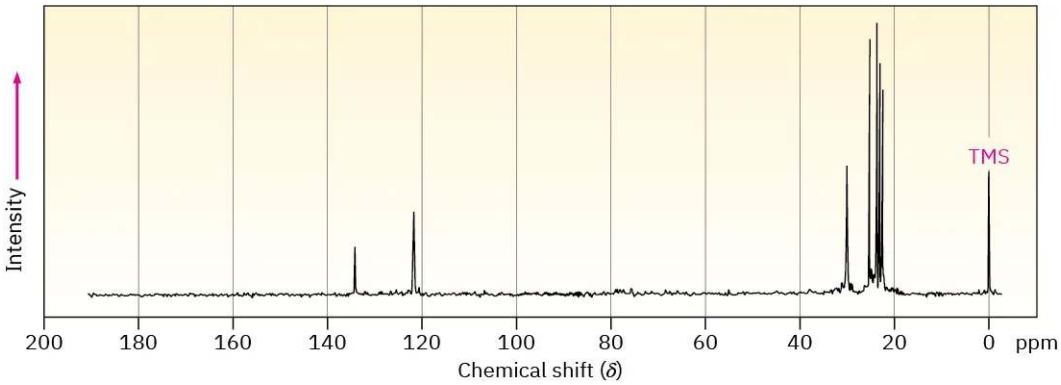


Figure 2.14.1: The ^{13}C NMR spectrum of 1-methylcyclohexene, the E2 reaction product from treatment of 1-chloro-1-methylcyclohexane with base.

? Exercise 2.14.1

We saw in Section 9.3 that addition of HBr to a terminal alkyne leads to the Markovnikov addition product, with the Br bonding to the more highly substituted carbon. How could you use ^{13}C NMR to identify the product of the addition of 1 equivalent of HBr to 1-hexyne?

Answer

A DEPT-90 spectrum would show two absorptions for the non-Markovnikov product (RCH=CHBr) but no absorptions for the Markovnikov product (RBrC=CH_2).

This page titled 2.14: Uses of ^{13}C NMR Spectroscopy is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **13.13: Uses of ^{13}C NMR Spectroscopy** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

2.15: Chemistry Matters—Magnetic Resonance Imaging (MRI)

As practiced by organic chemists, NMR spectroscopy is a powerful method of structure determination. A small amount of sample, typically a few milligrams or less, is dissolved in a small amount of solvent, the solution is placed in a thin glass tube, and the tube is placed into the narrow (1–2 cm) gap between the poles of a strong magnet. Imagine, though, that a much larger NMR instrument were available. Instead of a few milligrams, the sample size could be tens of kilograms; instead of a narrow gap between magnet poles, the gap could be large enough for a whole person to climb into so that an NMR spectrum of body parts could be obtained. That large instrument is exactly what's used for *magnetic resonance imaging (MRI)*, a diagnostic technique of enormous value to the medical community.

Like NMR spectroscopy, MRI takes advantage of the magnetic properties of certain nuclei, typically hydrogen, and of the signals emitted when those nuclei are stimulated by radiofrequency energy. Unlike what happens in NMR spectroscopy, though, MRI instruments use data manipulation techniques to look at the three-dimensional *location* of magnetic nuclei in the body rather than at the chemical nature of the nuclei. As noted, most MRI instruments currently look at hydrogen, present in abundance wherever there is water or fat in the body.

Figure 2.15.1 If you're a runner, you really don't want this to happen to you. The MRI of this left knee shows bone formation in the tissue in a patient with osteochondroma. (credit: "Osteochondroma MRI" by Michael R Carmont, Sian Davies, Daniel Gey van Pittius and Robin Rees/Wikimedia Commons, CC BY 2.0)

The signals detected by MRI vary with the density of hydrogen atoms and with the nature of their surroundings, allowing identification of different types of tissue and even allowing the visualization of motion. For example, the volume of blood leaving the heart in a single stroke can be measured, and heart motion can be observed. Soft tissues that don't show up well on X-ray images can be seen clearly, allowing diagnosis of brain tumors, strokes, and other conditions. This technique is also valuable in diagnosing damage to knees or other joints and is a noninvasive alternative to surgical explorations.

Several types of atoms in addition to hydrogen can be detected by MRI, and the applications of images based on ^{31}P atoms are being explored. This approach holds great promise for studies of metabolism.

This page titled 2.15: Chemistry Matters—Magnetic Resonance Imaging (MRI) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **13.14: Chemistry Matters—Magnetic Resonance Imaging (MRI)** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

2.16: Key Terms

- chemical shift
- coupling
- coupling constant (J)
- delta (δ) scale
- DEPT-NMR
- diastereotopic
- downfield
- enantiotopic
- FT–NMR
- homotopic
- integration
- multiplet
- n + 1 rule
- nuclear magnetic resonance (NMR) spectroscopy
- shielding
- spin–spin splitting
- upfield

This page titled 2.16: Key Terms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **13.15: Key Terms** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

2.17: Summary

Nuclear magnetic resonance spectroscopy, or **NMR**, is the most valuable of the numerous spectroscopic techniques used for structure determination. Although we focused in this chapter on NMR applications with small molecules, more advanced NMR techniques are also used in biological chemistry to study protein structure and folding.

When magnetic nuclei, such as ^{1}H and ^{13}C, are placed in a strong magnetic field, their spins orient either with or against the field. On irradiation with radiofrequency (rf) waves, energy is absorbed and the nuclei "spin-flip" from the lower energy state to the higher energy state. This absorption of rf energy is detected, amplified, and displayed as an NMR spectrum.

Each electronically distinct ^{1}H or ^{13}C nucleus in a molecule comes into resonance at a slightly different value of the applied field, thereby producing a unique absorption signal. The exact position of each peak is called the **chemical shift**. Chemical shifts are caused by electrons setting up tiny local magnetic fields that **shield** a nearby nucleus from the applied field.

The NMR chart is calibrated in **delta units (δ)**, where 1 δ = 1 ppm of spectrometer frequency. Tetramethylsilane (TMS) is used as a reference point because it shows both ^{1}H and ^{13}C absorptions at unusually high values of applied magnetic field. The TMS absorption occurs on the right-hand (**upfield**) side of the chart and is arbitrarily assigned a value of 0 δ.

^{13}C spectra are run on Fourier-transform NMR (**FT–NMR**) spectrometers using broadband decoupling of proton spins so that each chemically distinct carbon shows a single unsplit resonance line. As with ^{1}H NMR, the chemical shift of each ^{13}C signal provides information about a carbon's chemical environment in the sample. In addition, the number of protons attached to each carbon can be determined using the DEPT–NMR technique.

In ^{1}H NMR spectra, the area under each absorption peak can be electronically **integrated** to determine the relative number of hydrogens responsible for each peak. In addition, neighboring nuclear spins can **couple**, causing the **spin–spin splitting** of NMR peaks into **multiplets**. The NMR signal of a hydrogen neighbored by n equivalent adjacent hydrogens splits into n + 1 peaks (the ***n* + 1 rule**) with **coupling constant *J***.

This page titled 2.17: Summary is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

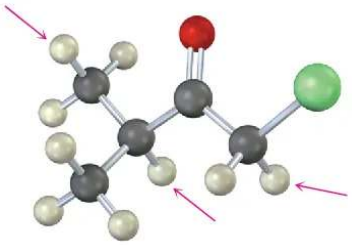
- **13.16: Summary** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

2.18: Additional Problems

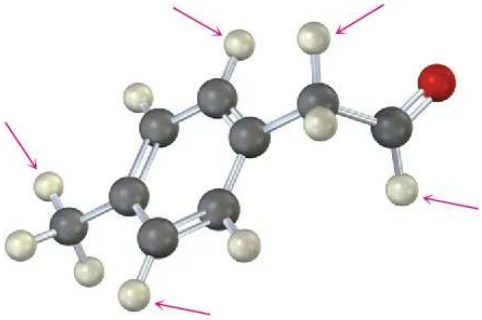
13 • Additional Problems

Visualizing Chemistry

PROBLEM 13-24 Into how many peaks would you expect the ^{1}H NMR signals of the indicated protons to be split? (Green = Cl.)

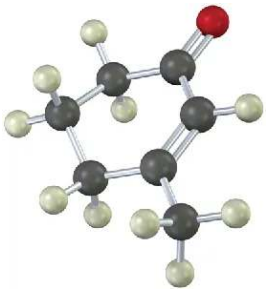


(a)

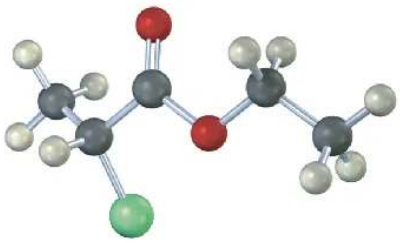


(b)

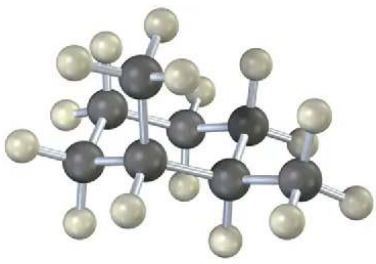
PROBLEM 13-25 How many absorptions would you expect the following compound to have in its ^{1}H and ^{13}C NMR spectra?



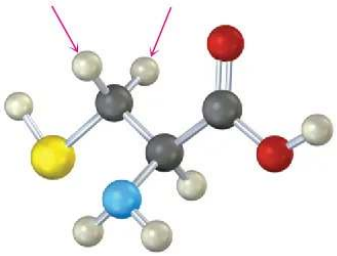
PROBLEM 13-26 Sketch what you might expect the ^{1}H and ^{13}C NMR spectra of the following compound to look like (green = Cl):



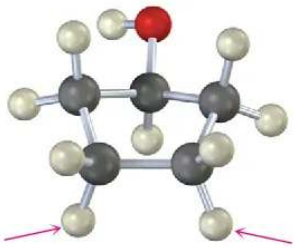
PROBLEM 13-27 How many electronically nonequivalent kinds of protons and how many kinds of carbons are present in the following compound? Don't forget that cyclohexane rings can ring-flip.



PROBLEM 13-28 Identify the indicated protons in the following molecules as unrelated, homotopic, enantiotopic, or diastereotopic.



(a) Cysteine



(b)

Chemical Shifts and NMR Spectroscopy

PROBLEM 13-29 Identify the indicated protons in the following molecules as unrelated, homotopic, enantiotopic, or diastereotopic. (a) <p">The following ^{1}H NMR absorptions were obtained on a spectrometer operating at 200 MHz and are given in hertz downfield from the TMS standard. Convert the absorptions to δ units.

(a) 436 Hz (b) 956 Hz (c) 1504 Hz

PROBLEM 13-30 The following ^{1}H NMR absorptions were obtained on a spectrometer operating at 300 MHz. Convert the chemical shifts from δ units to hertz downfield from TMS. (a) 2.1 δ (b) 3.45 δ (c) 6.30 δ (d) 7.70 δ

PROBLEM 13-31 When measured on a spectrometer operating at 200 MHz, chloroform ($CHCl_3$) shows a single sharp absorption at 7.3 δ. (a)

How many parts per million downfield from TMS does chloroform absorb?

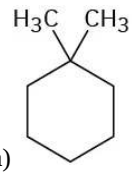
(b) How many hertz downfield from TMS would chloroform absorb if the measurement were carried out on a spectrometer operating at 360 MHz? (c) What would be the position of the chloroform absorption in δ units when measured on a 360 MHz spectrometer?

PROBLEM 13-32 Why do you suppose accidental overlap of signals is much more common in ^{1}H NMR than in ^{13}C NMR?

PROBLEM 13-33 Is a nucleus that absorbs at 6.50 δ more shielded or less shielded than a nucleus that absorbs at 3.20 δ? Does the nucleus that absorbs at 6.50 δ require a stronger applied field or a weaker applied field to come into resonance than the one that absorbs at 3.20 δ?

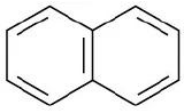
^{1}H NMR Spectroscopy

PROBLEM 13-34 How many types of nonequivalent protons are present in each of the following molecules?

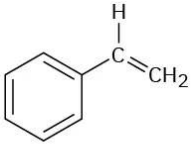


(a)

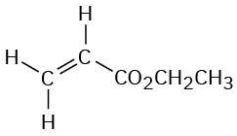
(b) $CH_3CH_2CH_2OCH_3$



(c) Naphthalene



(d) Styrene

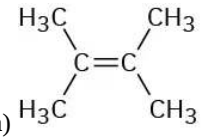


(e) Ethyl acrylate

PROBLEM 13-35 The following compounds all show a single line in their ^{1}H NMR spectra. List them in order of expected increasing chemical shift:

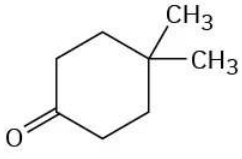
CH_4, CH_2Cl_2, cyclohexane, CH_3COCH_3, $H_2C=CH_2$, benzene

PROBLEM 13-36 How many signals would you expect each of the following molecules to have in its ^{1}H and ^{13}C spectra?

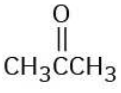


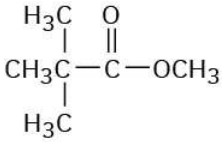
(a)

(b)

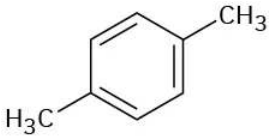


(c)

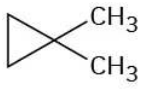




(d)



(e)



(f)

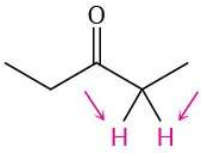
Problem 13-37 Propose structures for compounds with the following formulas that show only one peak in their ^{1}H NMR spectra:
(a) C_5H_{12} **(b)** C_5H_{10} **(c)** $C_4H_8O_2$

PROBLEM 13-38 Predict the splitting pattern for each kind of hydrogen in the following molecules:

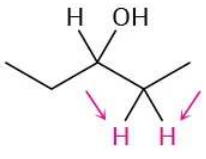
(a) $(CH_3)_3CH$ **(b)** $CH_3CH_2CO_2CH_3$ **(c)** *trans*-2-Butene

PROBLEM 13-39 Predict the splitting pattern for each kind of hydrogen in isopropyl propanoate, $CH_3CH_2CO_2CH(CH_3)_2$.

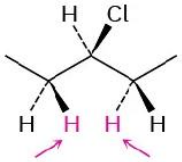
PROBLEM 13-40 Identify the indicated sets of protons as unrelated, homotopic, enantiotopic, or diastereotopic:



(a)

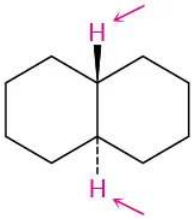


(b)

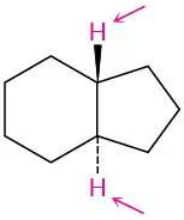


(c)

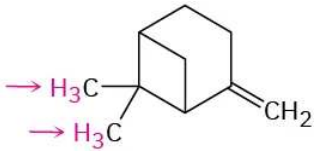
PROBLEM 13-41 Identify the indicated sets of protons as unrelated, homotopic, enantiotopic, or diastereotopic:



(a)

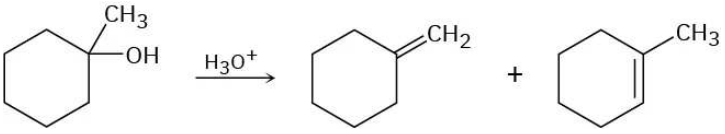


(b)

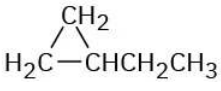


(c)

PROBLEM 13-42 The acid-catalyzed dehydration of 1-methylcyclohexanol yields a mixture of two alkenes. How could you use ^{1}H NMR to help you decide which was which?



PROBLEM 13-43 1H NMR to distinguish between the following pairs of isomers? (a)

(a) $CH_3CH{=}CHCH_2CH_3$ and  **(b)**

(b) $CH_3CH_2OCH_2CH_3$ and $CH_3OCH_2CH_2CH_3$

(c) $CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_3$ and $CH_3CH_2\overset{O}{\overset{\|}{C}}CH_3$

(d) $H_2C{=}C(CH_3)\overset{O}{\overset{\|}{C}}CH_3$ and $CH_3CH{=}CH\overset{O}{\overset{\|}{C}}CH_3$

PROBLEM 13-44 Propose structures for compounds that fit the following ^{1}H NMR data:

(a) $C_5H_{10}O$

0.95 δ (6 H, doublet, J = 7 Hz)

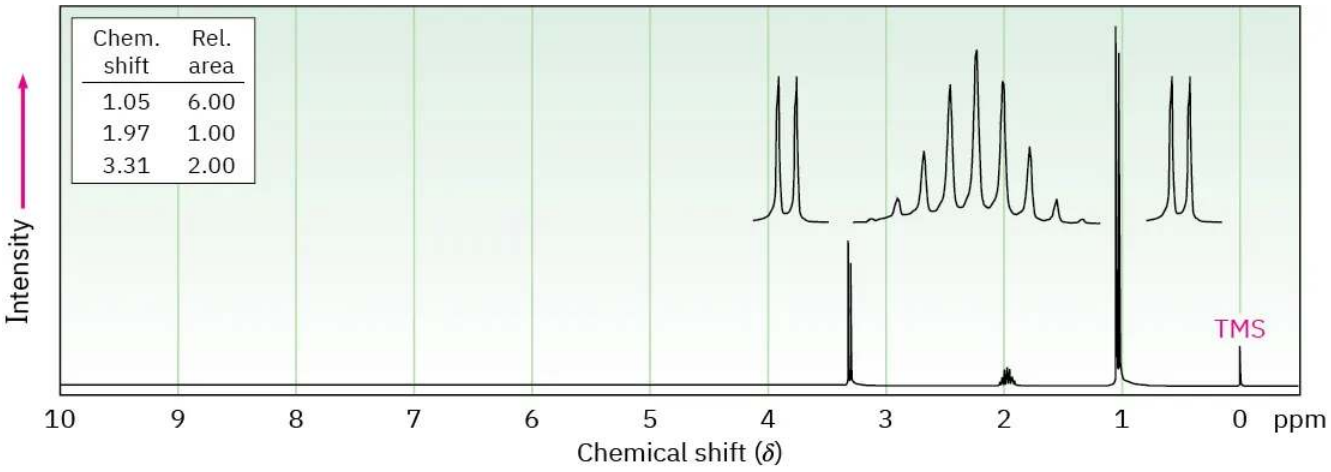
2.10 δ (3 H, singlet)
2.43 δ (1 H, multiplet)

(b) C_3H_5Br

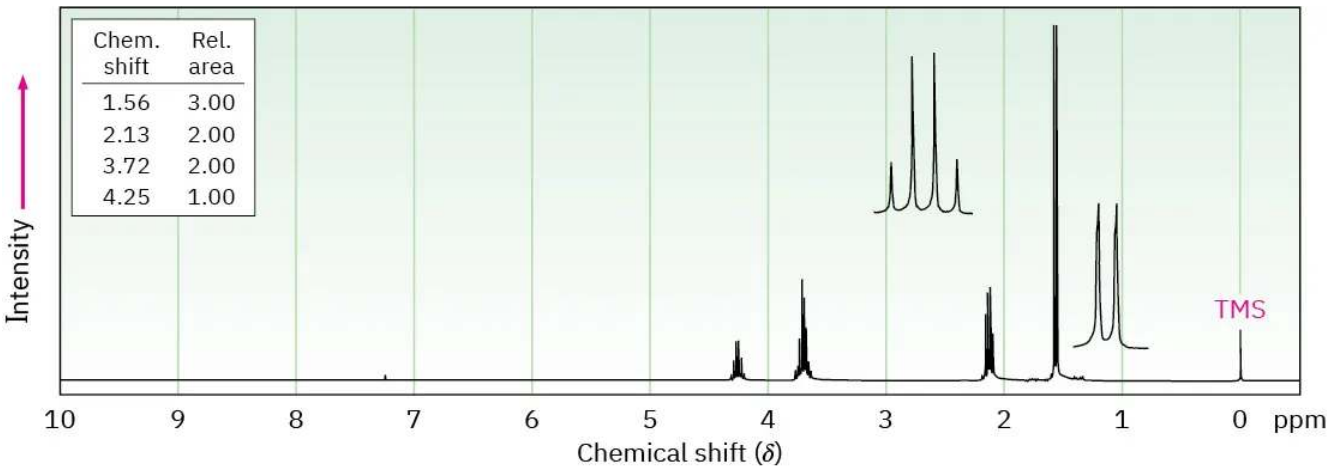
2.32 δ (3 H, singlet)
2.32 δ (3 H, singlet)
2.32 δ (3 H, singlet)

PROBLEM 13-45 Propose structures for the two compounds whose <<sup">1H NMR spectra are shown.

(a)C_4H_9Br



(b) $C_4H_8Cl_2$



^{13}C NMR Spectroscopy

PROBLEM 13-46 How many ^{13}C NMR absorptions would you expect for *cis*-1,3-dimethylcyclohexane? For *trans*-1,3-dimethylcyclohexane? Explain.

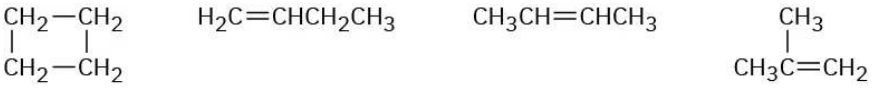
PROBLEM 13-47 How many absorptions would you expect to observe in the <sup">13C NMR spectra of the following compounds?

(a)1,1-Dimethylcyclohexane **(b)** $CH_3CH_2OCH_3$ **(c)***tert*-Butylcyclohexane

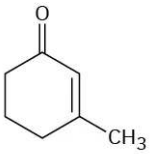
(d) 3-Methyl-1-pentyne **(e)** *cis*-1,2-Dimethylcyclohexane **(f)** Cyclohexanone

PROBLEM 13-48 Suppose you ran a DEPT-135 spectrum for each substance in Problem 13.47. Which carbon atoms in each molecule would show positive peaks, and which would show negative peaks?

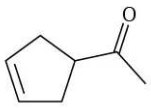
PROBLEM 13-49 How could you use ^{1}H and ^{13}C NMR to help distinguish the following isomeric compounds of the formula C_4H_8?



PROBLEM 13-50 How could you use ^{1}H NMR, ^{13}C NMR, and IR spectroscopy to help you distinguish between the following structures?

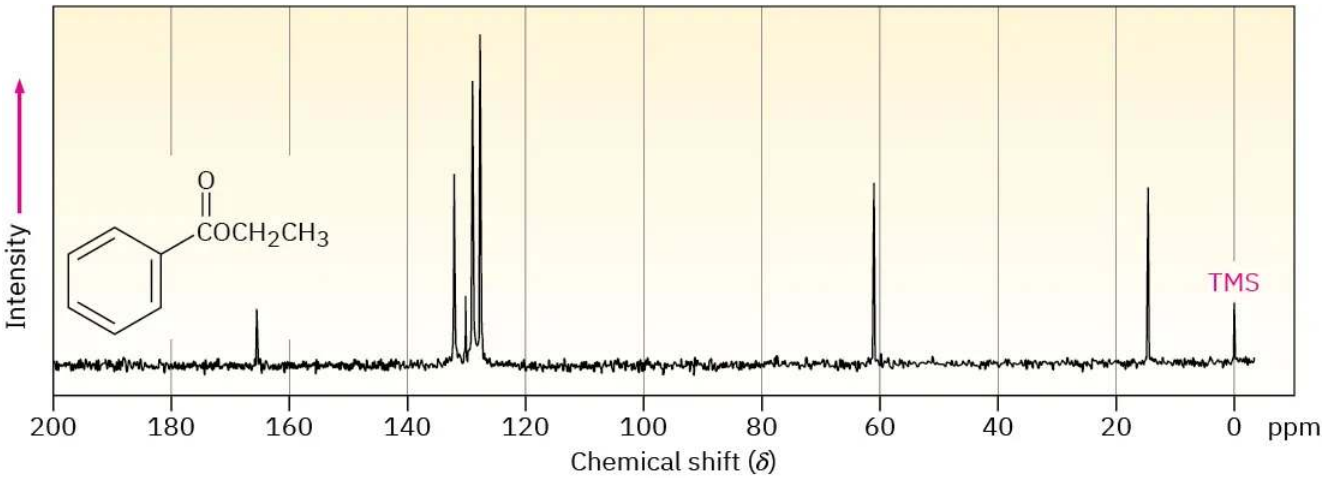


3-Methyl-2-cyclohexenone



3-Cyclopentenyl methyl ketone

PROBLEM 13-51 Assign as many resonances as you can to specific carbon atoms in the ^{13}C NMR spectrum of ethyl benzoate.

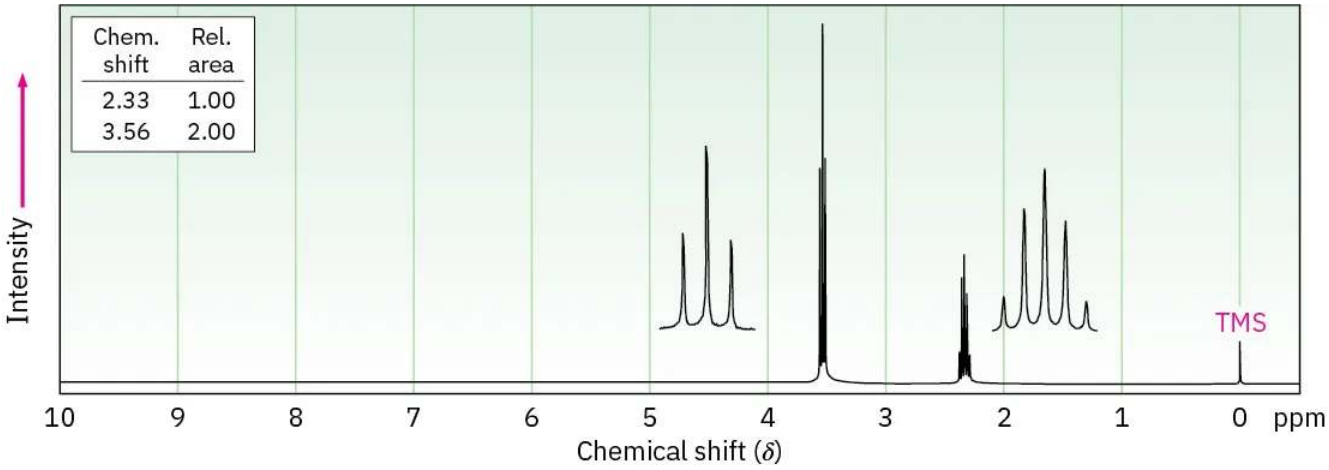


General Problems

PROBLEM 13-52 Assume that you have a compound with the formula C_3H_6O.

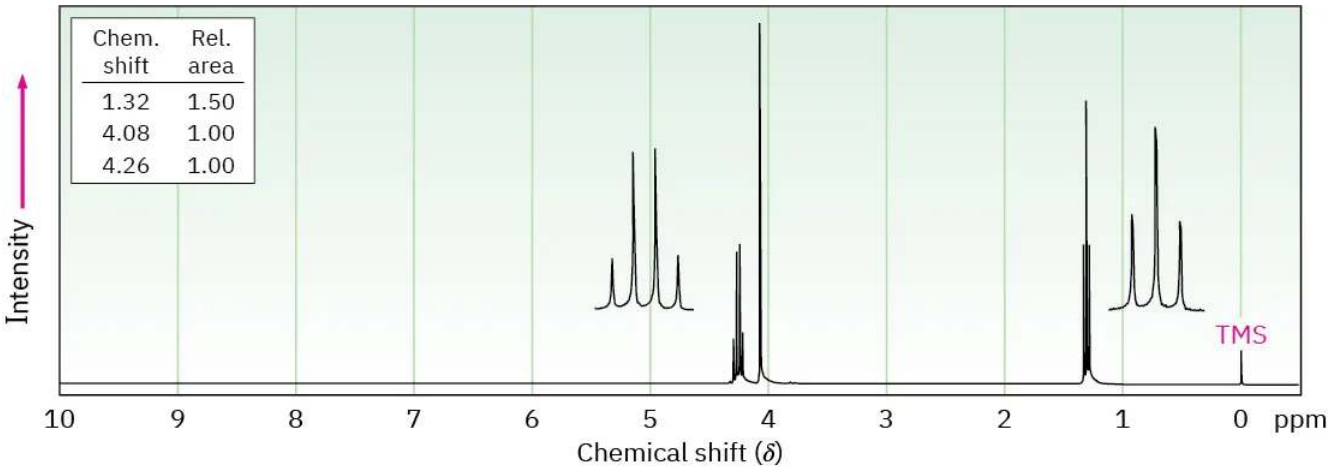
(a) How many double bonds and/or rings does your compound contain? (b) Propose as many structures as you can that fit the molecular formula. (c) If your compound shows an infrared absorption peak at 1715 cm^{-1}, what functional group does it have? (d) If your compound shows a single ^{1}H NMR absorption peak at 2.1 δ, what is its structure?

PROBLEM 13-53 The compound whose ^{1}H NMR spectrum is shown has the molecular formula $C_3H_6Br_2$. Propose a structure.



https://chem.libretexts.org/@go/page/564157

PROBLEM 13-54 The compound whose ^{1}H NMR spectrum is shown has the molecular formula $C_4H_7O_2Cl$ and has an infrared absorption peak at 1740 cm^{-1}. Propose a structure.



PROBLEM 13-55 Propose structures for compounds that fit the following <sup">1H NMR data:

(a) **$C_4H_6Cl_2$**

2.18 δ (3 H, singlet)
4.16 δ (2 H, doublet, J = 7 Hz)
5.71 δ (1 H, triplet, J = 7 Hz)

(b) $C_{10}H_{14}$

1.30 δ (9 H, singlet)
7.30 δ (5 H, singlet)

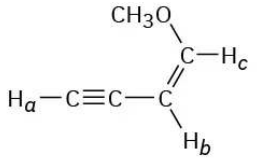
(c) C_4H_7BrO

2.11 δ (3 H, singlet)
3.52 δ (2 H, triplet, J = 6 Hz)
4.40 δ (2 H, triplet, J = 6 Hz)

(d) $C_9H_{11}Br$

2.15 δ (2 H, quintet, J = 7 Hz)
2.75 δ (2 H, triplet, J = 7 Hz)
3.38 δ (2 H, triplet, J = 7 Hz)
7.22 δ (5 H, singlet)

PROBLEM 13-56 Long-range coupling between protons more than two carbon atoms apart is sometimes observed when π bonds intervene. An example is found in 1-methoxy-1-buten-3-yne. Not only does the acetylenic proton, H_a, couple with the vinylic proton H_b, it also couples with the vinylic proton H_c, four carbon atoms away. The data are:



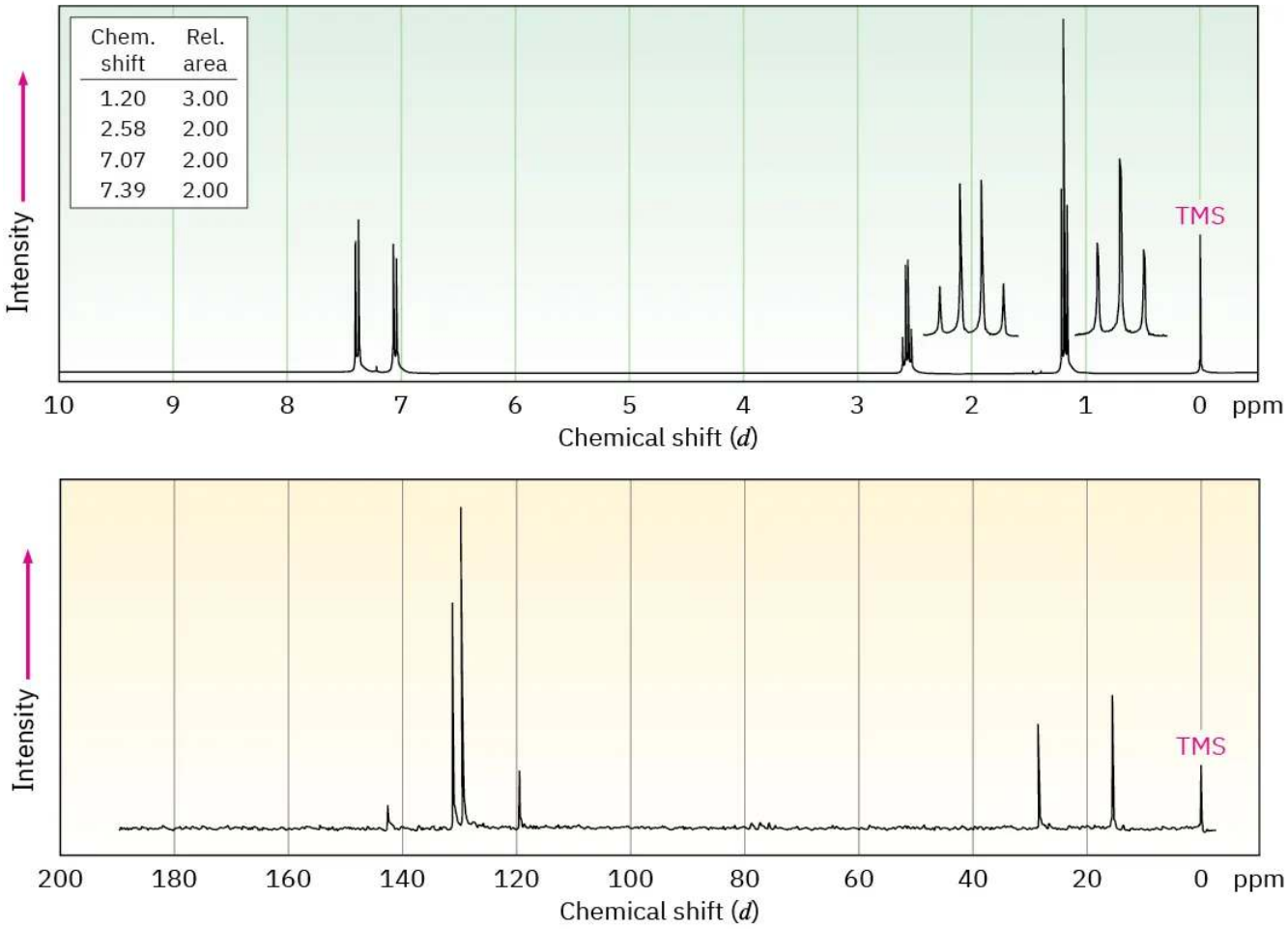
H_a (3.08 δ) H_b (4.52 δ) H_c (6.35 δ)

$J_{a\text{-}b}$ = 3 Hz $J_{a\text{-}c}$ = 1 Hz $J_{b\text{-}c}$ = 7 Hz

1-Methoxy-1-buten-3-yne

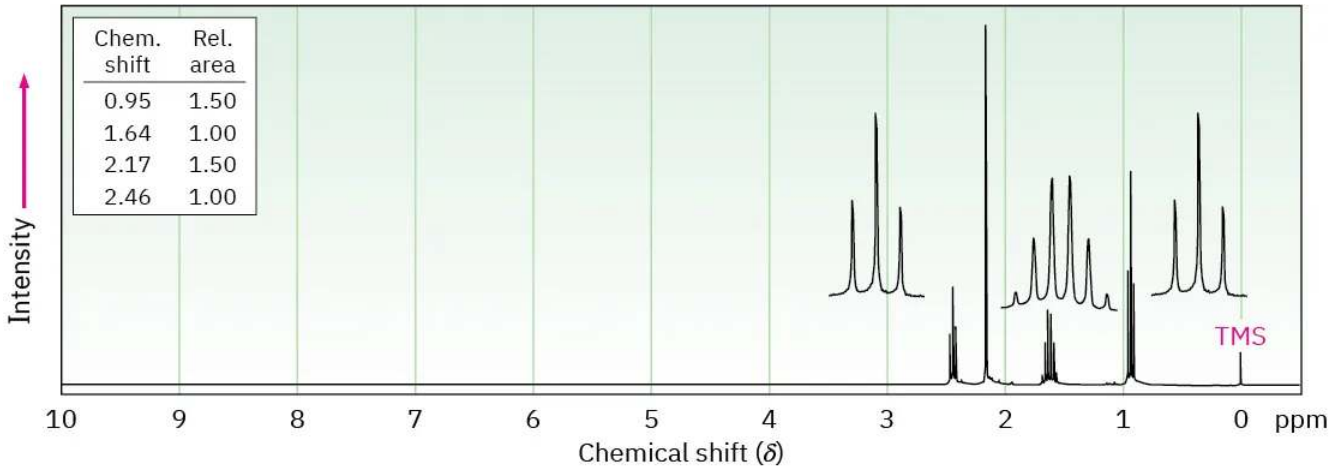
Construct tree diagrams that account for the observed splitting patterns of H_a, H_b, and H_c.

PROBLEM 13-57 The ^{1}H and ^{13}C NMR spectra of compound **A**, C_8H_9Br, are shown. Propose a structure for **A**, and assign peaks in the spectra to your structure.

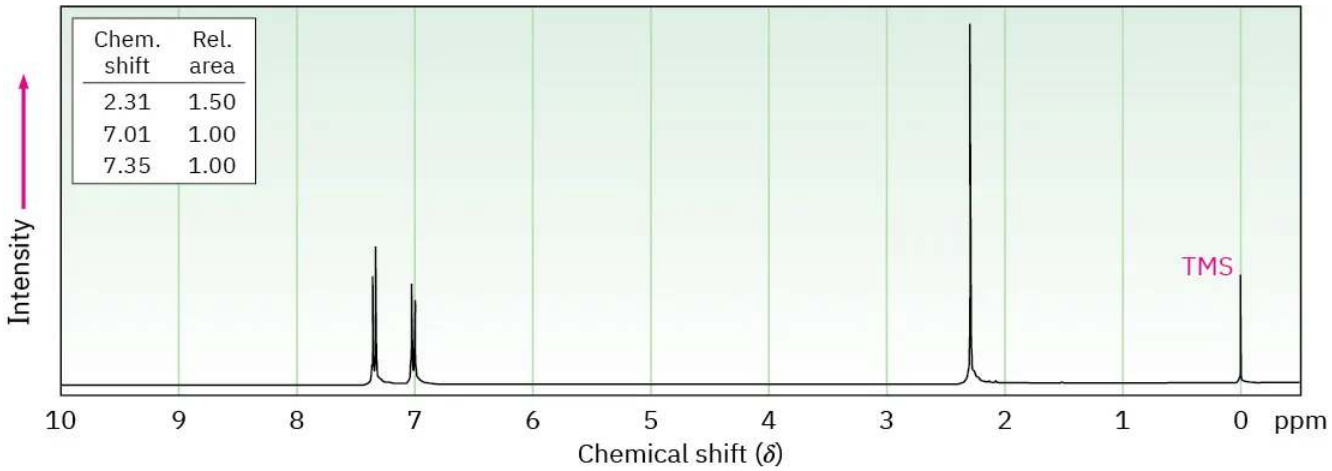


PROBLEM 13-58 Propose structures for the three compounds whose <sup">1H NMR spectra are shown.

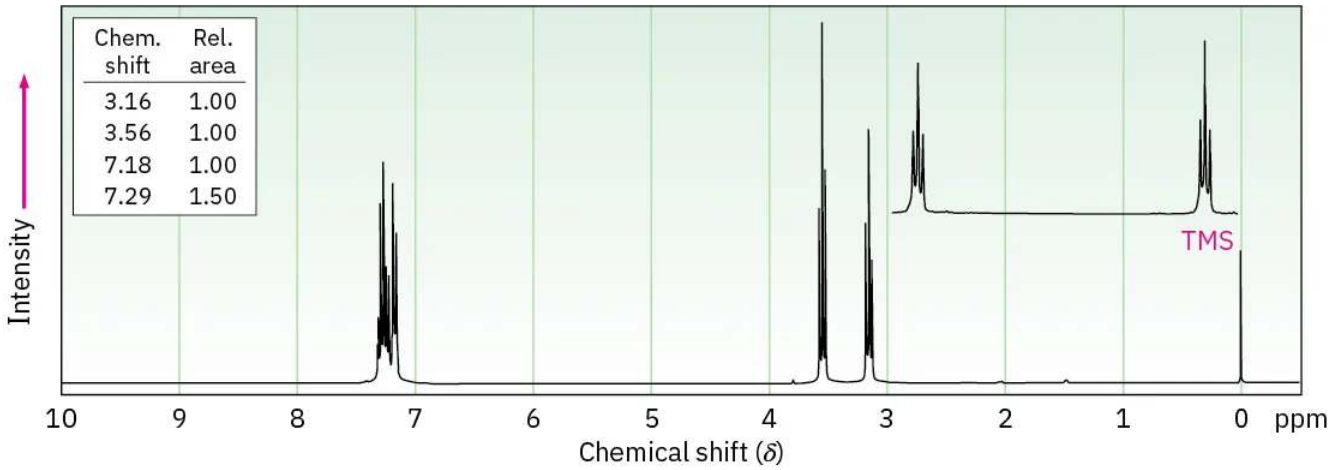
(a) **$C_5H_{10}O$**



(b) C_7H_7Br

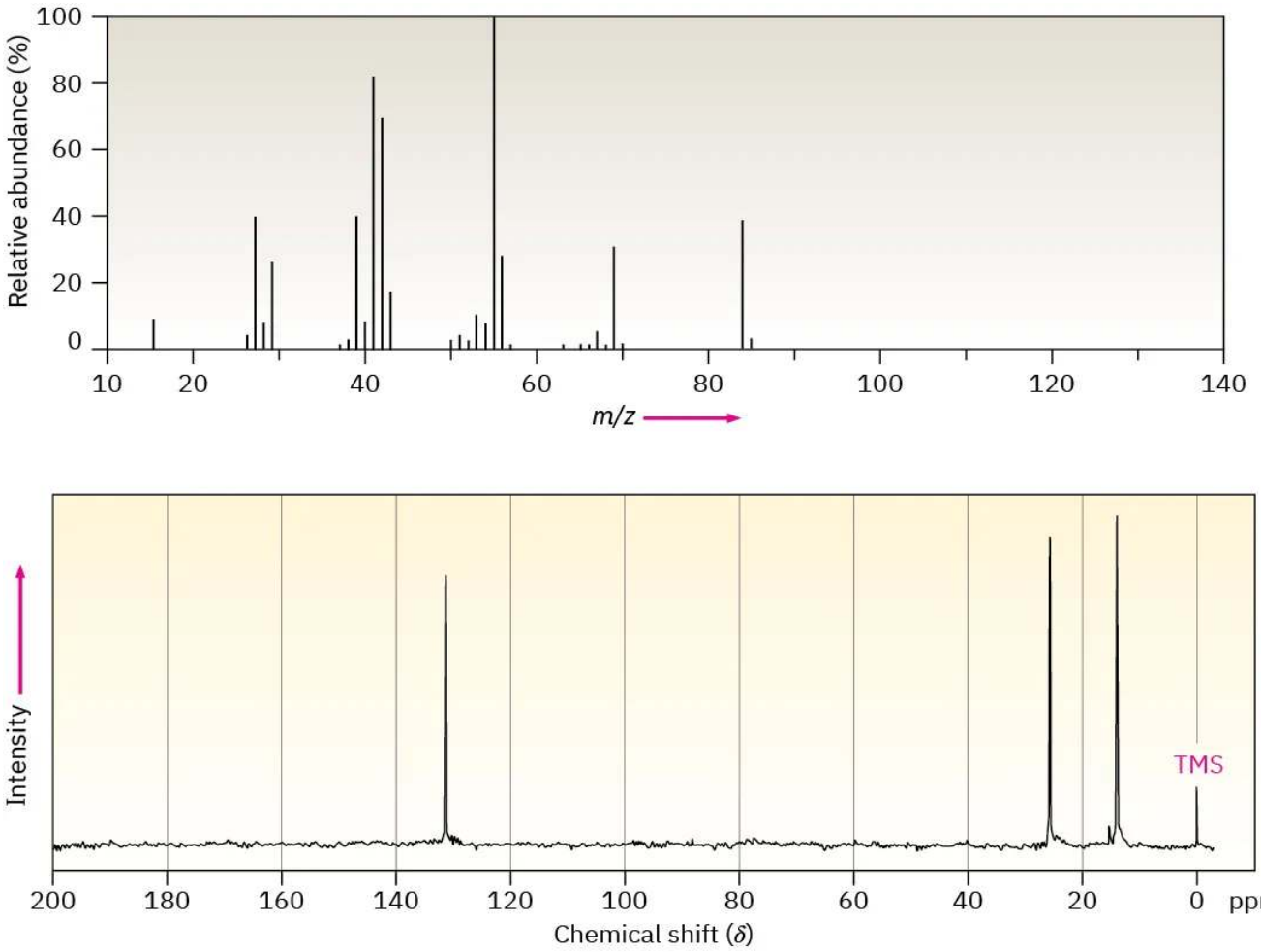


(c) C_8H_9Br



PROBLEM 13-59 The mass spectrum and ^{13}C NMR spectrum of a hydrocarbon are shown. Propose a structure for this hydrocarbon, and explain the spectral data.

https://chem.libretexts.org/@go/page/564157



PROBLEM 13-60 Compound **A**, a hydrocarbon with M^+ = 96 in its mass spectrum, has the following ^{13}C spectral data. On reaction with BH_3, followed by treatment with basic H_2O_2, **A** is converted into **B**, whose ^{13}C spectral data are also given. Propose structures for **A** and **B**.

Compound A

Broadband-decoupled ^{13}C NMR: 26.8, 28.7, 35.7, 106.9, 149.7 δ
DEPT-90: no peaks
DEPT-135: no positive peaks ; negative peaks at 26.8, 28.7, 35.7, 106.9 δ

Compound B

Broadband-decoupled ^{13}C NMR: 26.1, 26.9, 29.9, 40.5, 68.2 δ
DEPT-90: 40.5 δ
DEPT-135: positive peak at 40.5 δ; negative peaks at 26.1, 26.9, 29.9, 68.2 δ

PROBLEM 13-61 Propose a structure for compound **C**, which has M^+ = 86 in its mass spectrum, an IR absorption at 3400 cm^{-1}, and the following ^{13}C NMR spectral data:

Compound C

Broadband-decoupled ^{13}C NMR: 30.2, 31.9, 61.8, 114.7, 138.4 δ
DEPT-90: 138.4 δ
DEPT-135: positive peak at 138.4 δ; negative peaks at 30.2, 31.9, 61.8, 114.7 δ

PROBLEM 13-62 Compound **D** is isomeric with compound **C** (Problem 13.61) and has the following ^{13}C NMR spectral data. Propose a structure.

Compound D

Broadband-decoupled ^{13}C NMR: 9.7, 29.9, 74.4, 114.4, 141.4 δ
DEPT-90: 74.4, 141.4 δ
DEPT-135: positive peaks at 9.7, 74.4, 141.4 δ; negative peaks at 29.9, 114.4 δ

PROBLEM 13-63 Propose a structure for compound **E**, $C_7H_{12}O_2$, which has the following ^{13}C NMR spectral data:

Compound E

Broadband-decoupled ^{13}C NMR: 19.1, 28.0, 70.5, 129.0, 129.8, 165.8 δ
DEPT-90: 28.0, 129.8 δ
DEPT-135: positive peaks at 19.1, 28.0, 129.8 δ; negative peaks at 70.5, 129.0 δ

PROBLEM 13-64 Compound **F**, a hydrocarbon with M^+ = 96 in its mass spectrum, undergoes reaction with HBr to yield compound **G**. Propose structures for **F** and **G**, whose ^{13}C NMR spectral data are given below.

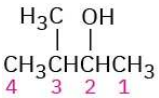
Compound F

Broadband-decoupled ^{13}C NMR: 27.6, 29.3, 32.2, 132.4 δ
DEPT-90: 132.4 δ
DEPT-135: positive peak at 132.4 δ; negative peaks at 27.6, 29.3, 32.2 δ

Compound G

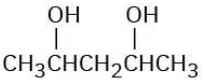
Broadband-decoupled ^{13}C NMR: 25.1, 27.7, 39.9, 56.0 δ
DEPT-90: 56.0 δ
DEPT-135: positive peak at 56.0 δ; negative peaks at 25.1, 27.7, 39.9 δ

PROBLEM 13-65 3-Methyl-2-butanol has five signals in its ^{13}C NMR spectrum at 17.90, 18.15, 20.00, 35.05, and 72.75 δ. Why are the two methyl groups attached to C3 nonequivalent? Making a molecular model should be helpful.



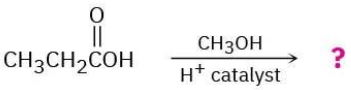
3-Methyl-2-butanol

PROBLEM 13-66 A ^{13}C NMR spectrum of commercially available 2,4-pentanediol, shows *five* peaks at 23.3, 23.9, 46.5, 64.8, and 68.1 δ. Explain.



2,4-Pentanediol

PROBLEM 13-67 Carboxylic acids (RCO_2H) react with alcohols (R′OH) in the presence of an acid catalyst. The reaction product of propanoic acid with methanol has the following spectroscopic properties. Propose a structure.



Propanoic acid

MS: M^+ = 88

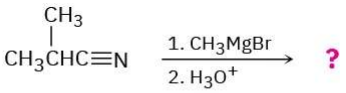
IR: 1735 cm^{-1}

^1H NMR: 1.11 δ (3 H, triplet, J = 7 Hz); 2.32 δ (2 H, quartet, J = 7 Hz);

3.65 δ (3 H, singlet)

^{13}C NMR: 9.3, 27.6, 51.4, 174.6 δ

PROBLEM 13-68 Nitriles (RC Math input error MgBr). The reaction product from 2-methylpropanenitrile with methylmagnesium bromide has the following spectroscopic properties. Propose a structure.



2-Methylpropanenitrile

MS: $M^+ = 86$

IR: 1715 cm^{-1}

^1H NMR: 1.05 δ (6 H, doublet, J = 7 Hz); 2.12 δ (3 H, singlet);

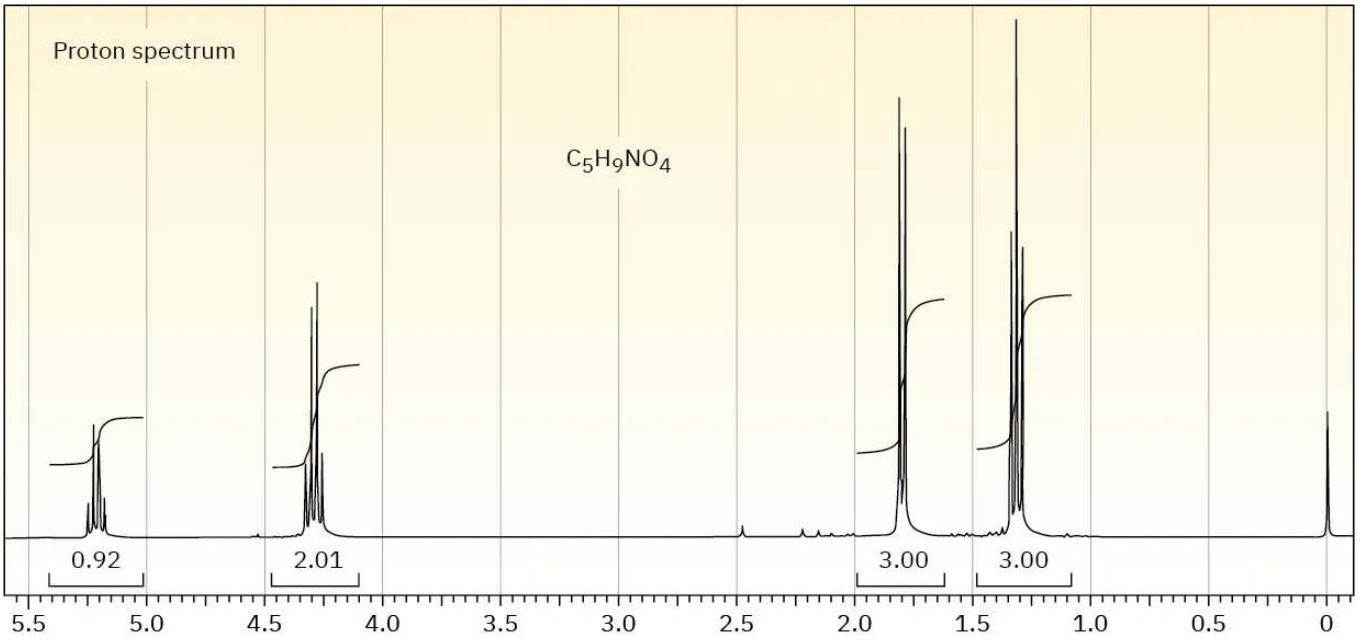
2.67 δ (1 H, septet, J = 7 Hz)

^{13}C NMR: 18.2, 27.2, 41.6, 211.2 δ

PROBLEM 13-69 The proton NMR spectrum is shown for a compound with the formula $C_5H_9NO_4$. The infrared spectrum displays strong bands at 1750 and 1562 cm^{-1} and a medium-intensity band at 1320 cm^{-1}. The normal carbon-13 and the DEPT experimental results are tabulated. Draw the structure of this compound.

Normal Carbon (ppm)	DEPT-135	DEPT-90
14	Positive	No peak
16	Positive	No peak
63	Negative	No peak
83	Positive	Positive
165	No peak	No peak

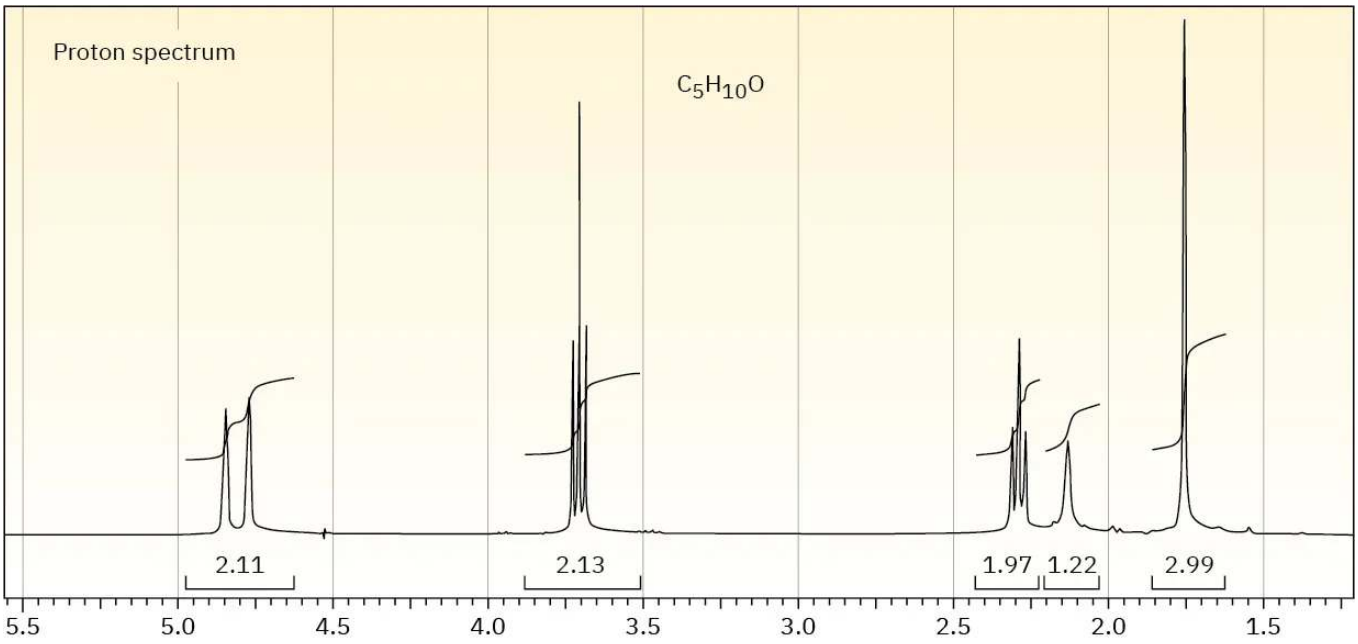
Normal CarbonDEPT-135DEPT-90 14 ppm Positive No peak 16 Positive No peak 63 Negative No peak 83 Positive Positive 165 No peak No peak



PROBLEM 13-70 The proton NMR spectrum of a compound with the formula $C_5H_{10}O$ is shown. The normal carbon-13 and the DEPT experimental results are tabulated. The infrared spectrum shows a broad peak at about 3340 cm^{-1} and a medium-sized peak

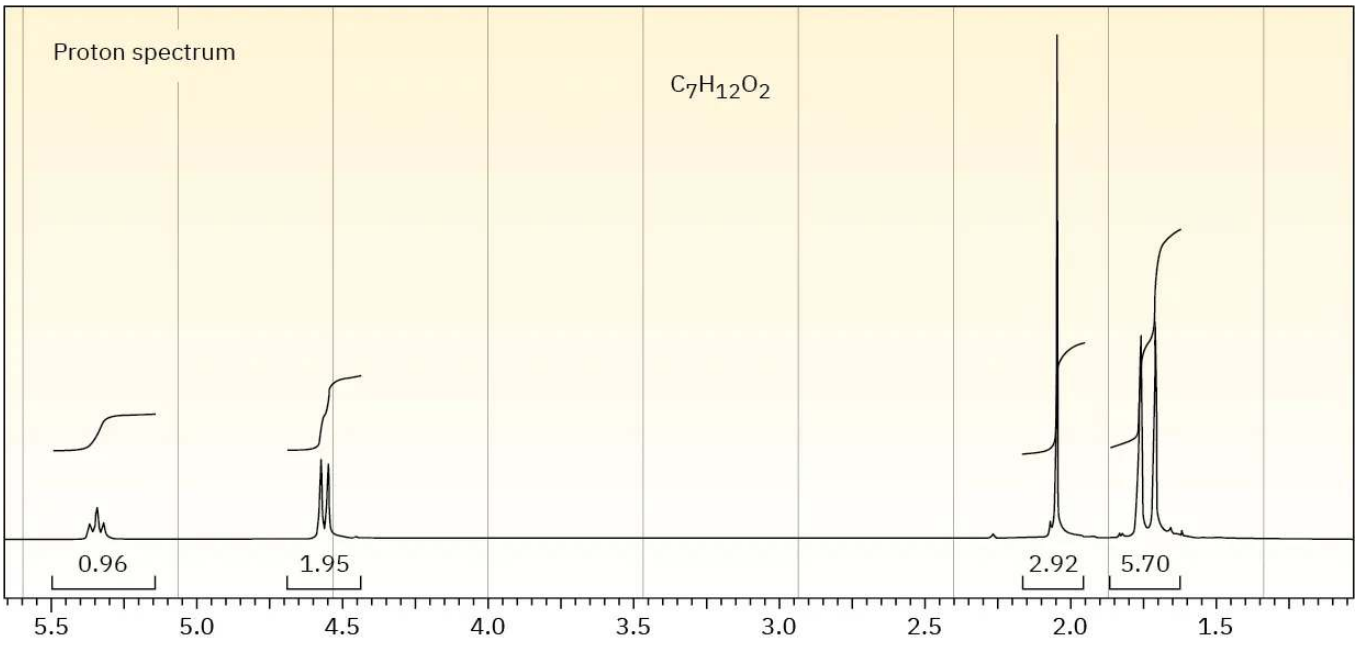
at about 1651 cm^{-1}. Draw the structure of this compound.

Normal Carbon (ppm)	DEPT-135	DEPT-90
22.2	Positive	No peak
40.9	Negative	No peak
60.2	Negative	No peak
112.5	Negative	No peak
142.3	No peak	No peak



PROBLEM 13-71 The proton NMR spectrum of a compound with the formula $C_7H_{12}O_2$ is shown. The infrared spectrum displays a strong band at 1738 cm^{-1} and a weak band at 1689 cm^{-1}. The normal carbon-13 and the DEPT experimental results are tabulated. Draw the structure of this compound.

Normal Carbon (ppm)	DEPT-135	DEPT-90
18	Positive	No peak
21	Positive	No peak
26	Positive	No peak
61	Negative	No peak
119	Positive	Positive
139	No peak	No peak
171	No peak	No peak



This page titled 2.18: Additional Problems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **13.17: Additional Problems** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

CHAPTER OVERVIEW

3: Conjugated Compounds and Ultraviolet Spectroscopy

Learning Objectives

After you have completed Chapter 14, you should be able to

1. fulfillall of the detailed objectives listed under each individual section.
2. use the reactions discussed, along with those from previous chapters, when designing multi-step syntheses.
3. use the reactions and concepts discussed to solve road-map problems.
4. use ultraviolet-spectral data, in conjunction with other spectral data, to elucidate the structure of an unknown compound.
5. define, and use in context, the key terms introduced.

You have already studied the chemistry of compounds that contain one carbon-carbon double bond. In this chapter, you will focus your attention on compounds that contain two or more such bonds. In particular you will study the properties of those compounds that contain two carbon-carbon double bonds which are separated by one carbon-carbon single bond. These compounds are called “conjugated dienes.”

To understand the properties exhibited by conjugated dienes, you must first examine their bonding in terms of the molecular orbital theory introduced in Section 1.11. Then, you must learn how the products of a reaction are dependent on both thermodynamic and kinetic considerations. Which of these two factors is the most important can sometimes determine which of two possible products will predominate when a reaction is carried out under specific conditions. Although we shall not make extensive use of ultraviolet spectroscopy, this technique can often provide important information when conjugated compounds are being investigated. In general, ultraviolet spectroscopy is less useful than the other spectroscopic techniques introduced earlier.

3.1: Why This Chapter?
3.2: Stability of Conjugated Dienes- Molecular Orbital Theory
3.3: Electrophilic Additions to Conjugated Dienes- Allylic Carbocations
3.4: Kinetic vs. Thermodynamic Control of Reactions
3.5: The Diels-Alder Cycloaddition Reaction
3.6: Characteristics of the Diels-Alder Reaction
3.7: Diene Polymers - Natural and Synthetic Rubbers
3.8: Ultraviolet Spectroscopy
3.9: Interpreting Ultraviolet Spectra- The Effect of Conjugation
3.10: Conjugation, Color, and the Chemistry of Vision
3.11: Chemistry Matters—Photolithography
3.12: Key Terms
3.13: Summary
3.14: Summary of Reactions
3.15: Additional Problems

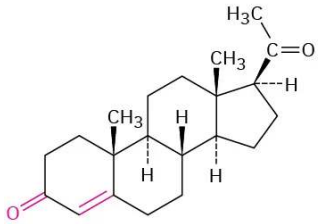
This page titled 3: Conjugated Compounds and Ultraviolet Spectroscopy is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

3.1: Why This Chapter?

Conjugated compounds of many different sorts are common in nature. Many of the pigments responsible for the brilliant colors of fruits, flowers, and even animals have numerous alternating single and double bonds. *β*-Carotene, for instance, the orange pigment responsible for the color of carrots and an important source of vitamin A, is a conjugated *polyene* with 11 double bonds. Conjugated *enones* (alk*ene* + ket*one*) are common structural features of many biologically important molecules such as progesterone, the hormone that prepares the uterus for implantation of a fertilized ovum. Cyclic conjugated molecules such as benzene are a major field of study in themselves. In this chapter, we'll look at some of the distinctive properties of conjugated molecules and at the reasons for those properties.

Figure 3.1.1: Saffron, derived from stigmas of the saffron crocus, is the world's most expensive spice. Its color is caused by the presence of alternating single and double bonds. (credit: modification of work "Welcome to My World! ~ Huron River Watershed" by j van cise photos/Flickr, CC BY 2.0)

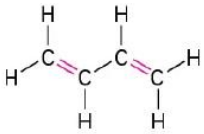
β-Carotene
(orange pigment and vitamin A precursor)



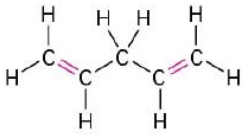
Progesterone, a conjugated enone

Benzene,
a cyclic conjugated molecule

Most of the unsaturated compounds we looked at in the previous chapters on alkenes had only one double bond, but many compounds have numerous sites of unsaturation. If the different unsaturations are well separated in a molecule, they react independently, but if they're close together, they may interact. In particular, compounds that have alternating single and double bonds—so-called conjugated compounds—have some distinctive characteristics. The conjugated diene 1,3-butadiene, for instance, has some properties quite different from those of the nonconjugated 1,4-pentadiene.



1,3-Butadiene (conjugated; alternating double and single bonds)



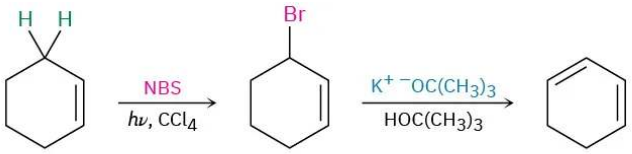
1,4-Pentadiene (nonconjugated; nonalternating double and single bonds)

This page titled 3.1: Why This Chapter? is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **14.0: Why This Chapter?** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

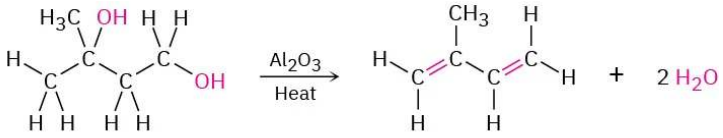
3.2: Stability of Conjugated Dienes- Molecular Orbital Theory

Conjugated dienes can be prepared by some of the methods previously discussed for preparing alkenes (Section 11.7–Section 11.11). The base-induced elimination of HX from an allylic halide is one such reaction.



Cyclohexene **3-Bromocyclohexene** **1,3-Cyclohexadiene (76%)**

Simple conjugated dienes used in polymer synthesis include 1,3-butadiene, chloroprene (2-chloro-1,3-butadiene), and isoprene (2-methyl-1,3-butadiene). Isoprene has been prepared industrially by several methods, including the acid-catalyzed double dehydration of 3-methyl-1,3-butanediol.



3-Methyl-1,3-butanediol **Isoprene**
2-Methyl-1,3-butadiene

One of the properties that distinguishes conjugated from nonconjugated dienes is that the central single bond is shorter than might be expected. The C2–C3 single bond in 1,3-butadiene, for instance, has a length of 147 pm, some 6 pm shorter than the C2–C3 bond in butane (153 pm).

1,3-Butadiene **Butane**

Another distinctive property of conjugated dienes is their unusual stability, as evidenced by their heats of hydrogenation (Table 3.2.1). We saw in Section 7.6 that monosubstituted alkenes, such as 1-butene, have $\Delta H^{\circ}_{\text{hydrog}}$ near –126 kJ/mol (–30.1 kcal/mol), whereas disubstituted alkenes, such as 2-methylpropene, have $\Delta H^{\circ}_{\text{hydrog}}$ near –119 kJ/mol (–28.4 kcal/mol), which is approximately 7 kJ/mol less negative. We concluded from these data that more highly substituted alkenes are more stable than less substituted ones. That is, more highly substituted alkenes release less heat on hydrogenation because they contain less energy to start with. A similar conclusion can be drawn for conjugated dienes.

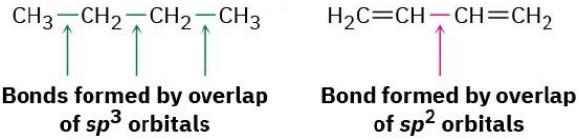
Table 3.2.1: Heats of Hydrogenation for Some Alkenes and Dienes

Alkene or diene	Product	$\Delta H^\circ_{\text{hydrog}}$	
		(kJ/mol)	(kcal/mol)
$CH_3CH_2CH{=}CH_2$	$CH_3CH_2CH_2CH_3$	–126	–30.1
$CH_3C(CH_3){=}CH_2$	$CH_3CH(CH_3)CH_3$	–119	–28.4
$H_2C{=}CHCH_2CH{=}CH_2$	$CH_3CH_2CH_2CH_2CH_3$	–253	–60.5
$H_2C{=}CH{-}CH{=}CH_2$	$CH_3CH_2CH_2CH_3$	–236	–56.4
$H_2C{=}CH{-}C(CH_3){=}CH_2$	$CH_3CH_2CH(CH_3)CH_3$	–229	–54.7

Because a monosubstituted alkene has a $\Delta H^\circ_{\text{hydrog}}$ of approximately –126 kJ/mol, we might expect that a compound with two monosubstituted double bonds would have a $\Delta H^\circ_{\text{hydrog}}$ approximately twice that value, or –252 kJ/mol. Nonconjugated dienes, such as 1,4-pentadiene ($\Delta H^\circ_{\text{hydrog}}$ =−253 kJ/mol), meet this expectation, but the conjugated diene 1,3-butadiene ($\Delta H^\circ_{\text{hydrog}}$=−236 kJ/mol) does not. 1,3-Butadiene is approximately 16 kJ/mol (3.8 kcal/mol) more stable than expected.

	$\Delta H^\circ_{\text{hydrog}}$ (kJ/mol)	
$H_2C{=}CHCH_2CH{=}CH_2$	−126 + (−126) = −252	Expected
1,4-Pentadiene	−253	Observed
	1	Difference
$H_2C{=}CHCH{=}CH_2$	−126 + (−126) = −252	Expected
1,3-Butadiene	−236	Observed
	−16	Difference

What accounts for the stability of conjugated dienes? According to valence bond theory (Section 1.5 and Section 1.8), their stability is due to orbital hybridization. Typical C–C single bonds, like those in alkanes, result from σ overlap of sp^3 orbitals on both carbons, but in a conjugated diene, the central C–C single bond results from σ overlap of sp^2 orbitals on both carbons. Because sp^2 orbitals have more *s* character (33% *s*) than sp^3 orbitals (25% *s*), the electrons in sp^2 orbitals are closer to the nucleus and the bonds they form are somewhat shorter and stronger. Thus, the "extra" stability of a conjugated diene results in part from the greater amount of *s* character in the orbitals forming the C–C single bond.



According to molecular orbital theory (Section 1.11), the stability of conjugated dienes arises because of an interaction between the π orbitals of the two double bonds. To review briefly, when two *p* atomic orbitals combine to form a π bond, two π molecular orbitals (MOs) result. One is lower in energy than the starting *p* orbitals and is therefore bonding; the other is higher in energy, has a node between nuclei, and is antibonding. The two π electrons occupy the low-energy, bonding orbital, resulting in formation of a stable bond between atoms (Figure 3.2.1).

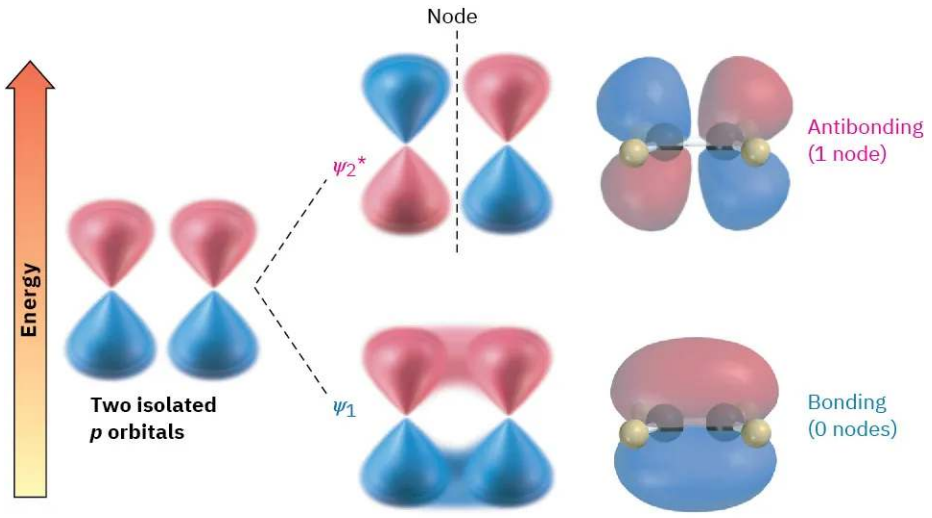


Figure 3.2.1: Two *p* orbitals combine to form two π molecular orbitals. Both electrons occupy the low-energy, bonding orbital, leading to a net lowering of energy and formation of a stable bond. The asterisk on ψ_2^* indicates an antibonding orbital.

Now let's combine four adjacent *p* atomic orbitals, as occurs in a conjugated diene. In so doing, we generate a set of four π molecular orbitals, two of which are bonding and two of which are antibonding (Figure 3.2.2). The four π electrons occupy the two bonding orbitals, leaving the antibonding orbitals vacant.

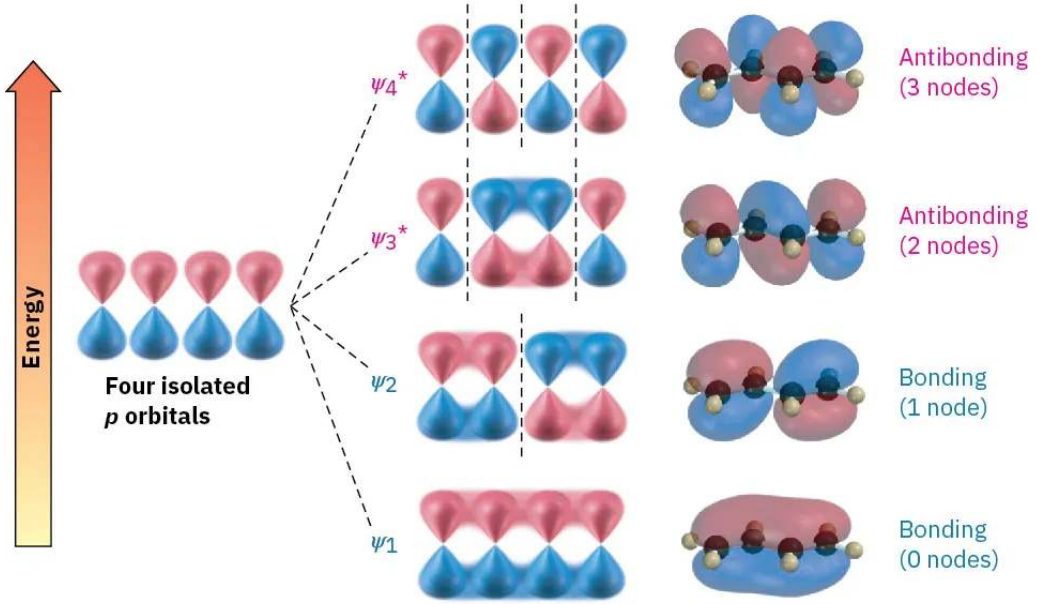


Figure 3.2.2: Four π molecular orbitals in 1,3-butadiene. Note that the number of nodes between nuclei increases as the energy level of the orbital increases.

The lowest-energy π molecular orbital (denoted ψ_1, Greek psi) has no nodes between the nuclei and is therefore bonding. The π MO of next-lowest energy, ψ2, has one node between nuclei and is also bonding. Above ψ_1 and ψ_2 in energy are the two antibonding π MOs, ψ_3^* and ψ_4^*. (The asterisks indicate antibonding orbitals.) Note that the number of nodes between nuclei increases as the energy level of the orbital increases. The ψ_3^* orbital has two nodes between nuclei, and ψ_4^*, the highest-energy MO, has three nodes between nuclei.

Comparing the π molecular orbitals of 1,3-butadiene (two conjugated double bonds) with those of 1,4-pentadiene (two isolated double bonds) shows why the conjugated diene is more stable. In a conjugated diene, the lowest-energy π MO (ψ_1) has a favorable bonding interaction between C2 and C3 that is absent in a nonconjugated diene. As a result, there is a certain amount of double-bond character to the C2–C3 single bond, making that bond both stronger and shorter than a typical single bond. Electrostatic potential maps show clearly the additional electron density in the central single bond (Figure 3.2.3).

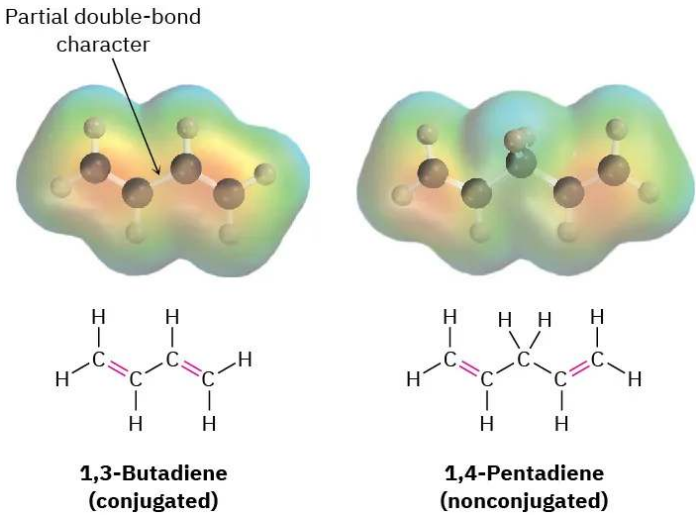


Figure 3.2.3: Electrostatic potential maps of 1,3-butadiene (conjugated) and 1,4-pentadiene (nonconjugated). Additional **electron density** is present in the central C−C bond of 1,3-butadiene, corresponding to partial double-bond character.

In describing 1,3-butadiene, we say that the π electrons are spread out, or *delocalized*, over the entire π framework, rather than localized between two specific nuclei. Delocalization allows the bonding electrons to be closer to more nuclei, thus leading to lower energy and greater stability.

Exercise 3.2.1

Allene, $H_2C{=}C{=}CH_2$, has a heat of hydrogenation of –298 kJ/mol (–71.3 kcal/mol). Rank a conjugated diene, a nonconjugated diene, and an allene in order of stability.

Answer

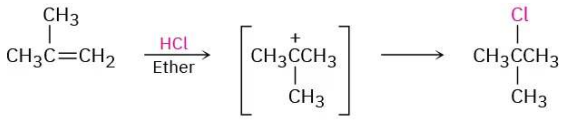
Expected $\Delta H^\circ_{\text{hydrog}}$ for allene is −252 kJ/mol. Allene is less stable than a nonconjugated diene, which is less stable than a conjugated diene.

This page titled 3.2: Stability of Conjugated Dienes- Molecular Orbital Theory is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

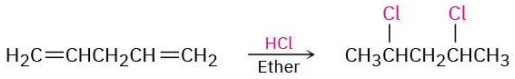
- **14.1: Stability of Conjugated Dienes- Molecular Orbital Theory** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

3.3: Electrophilic Additions to Conjugated Dienes- Allylic Carbocations

One of the most striking differences between conjugated dienes and typical alkenes is their behavior in electrophilic addition reactions. To review briefly, the addition of an electrophile to a carbon–carbon double bond is a general reaction of alkenes (Section 7.7). Markovnikov regiochemistry is observed because the more stable carbocation is formed as an intermediate. Thus, addition of HCl to 2-methylpropene yields 2-chloro-2-methylpropane rather than 1-chloro-2-methylpropane, and addition of 2 equivalents of HCl to the nonconjugated diene 1,4-pentadiene yields 2,4-dichloropentane.

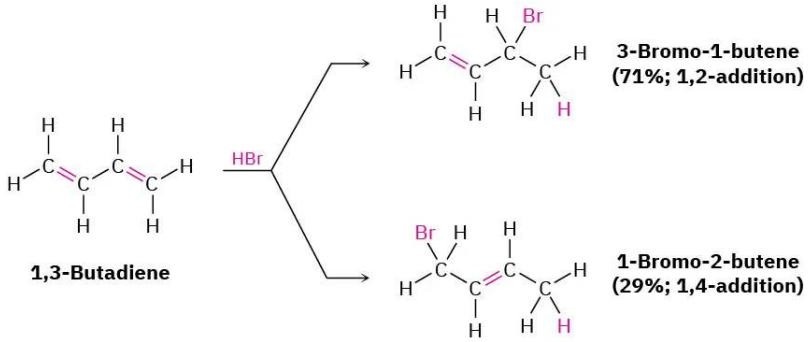


2-Methylpropene **Tertiary carbocation** **2-Chloro-2-methylpropane**



1,4-Pentadiene (nonconjugated) **2,4-Dichloropentane**

Conjugated dienes also undergo electrophilic addition reactions readily, but mixtures of products are invariably obtained. Addition of HBr to 1,3-butadiene, for instance, yields a mixture of two products (not counting cis–trans isomers). 3-Bromo-1-butene is the typical Markovnikov product of 1,2-addition to a double bond, but 1-bromo-2-butene seems unusual. The double bond in this product has moved to a position between carbons 2 and 3, and HBr has added to carbons 1 and 4, a result described as 1,4-addition.



1,3-Butadiene

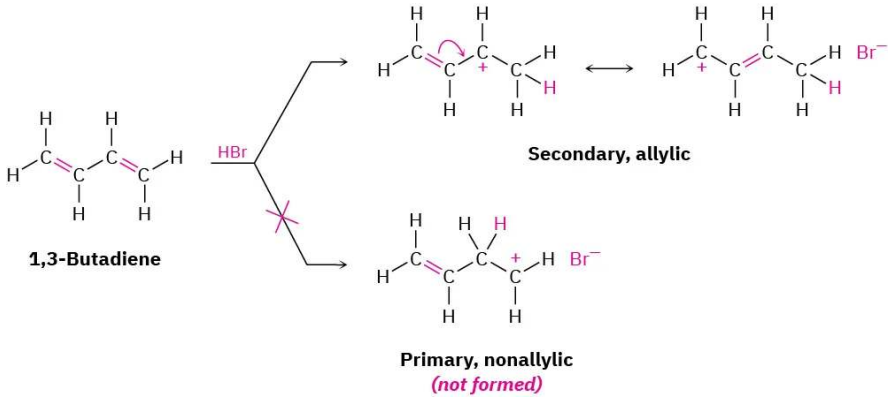
3-Bromo-1-butene (71%; 1,2-addition)

1-Bromo-2-butene (29%; 1,4-addition)

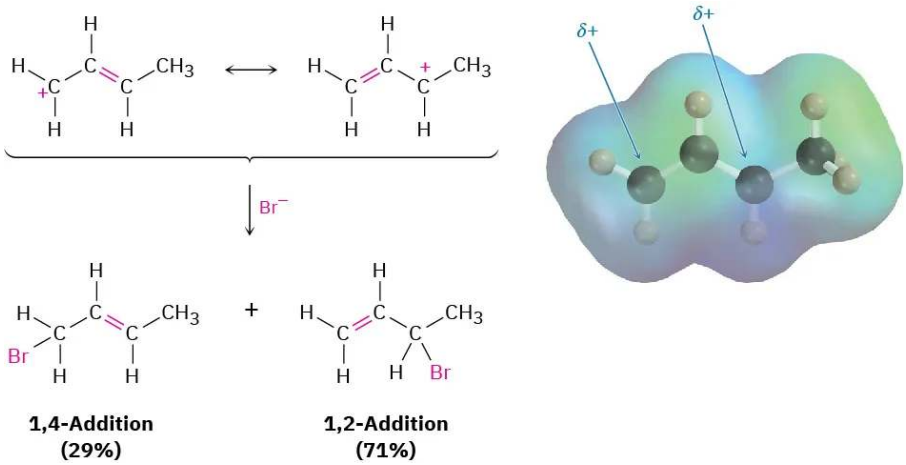
Many other electrophiles besides HBr add to conjugated dienes, and mixtures of products are usually formed. For example, Br_2 adds to 1,3-butadiene to give a mixture of 3,4-dibromo-1-butene and 1,4-dibromo-2-butene.

1,3-Butadiene **3,4-Dibromo-1-butene (55%; 1,2-addition)** **1,4-Dibromo-2-butene (45%; 1,4-addition)**

How can we account for the formation of 1,4-addition products? The answer is that allylic carbocations are involved as intermediates (recall that the word *allylic* means “next to a double bond”). When 1,3-butadiene reacts with an electrophile such as H^+, two carbocation intermediates are possible—a primary nonallylic carbocation and a secondary allylic cation. Because an allylic cation is stabilized by resonance between two forms (Section 11.5), it is more stable and forms faster than a nonallylic carbocation.



When the allylic cation reacts with Br^- to complete the electrophilic addition, the reaction can occur either at C1 or at C3 because both carbons share the positive charge (Figre 3.3.1). Thus, a mixture of 1,2- and 1,4-addition products results. You might recall that a similar product mixture was seen for NBS bromination of alkenes in Section 10.3, a reaction that proceeds through an allylic *radical*.



Figre 3.3.1: An electrostatic potential map of the allylic carbocation produced by protonation of 1,3-butadiene shows that the positive charge is shared by carbons 1 and 3. Reaction of Br^- with the more positive carbon **(C3)** predominantly yields the 1,2-addition product.

✔ Worked Example 3.3.1: Predicting the Product of an Electrophilic Addition Reaction of a Conjugated Diene

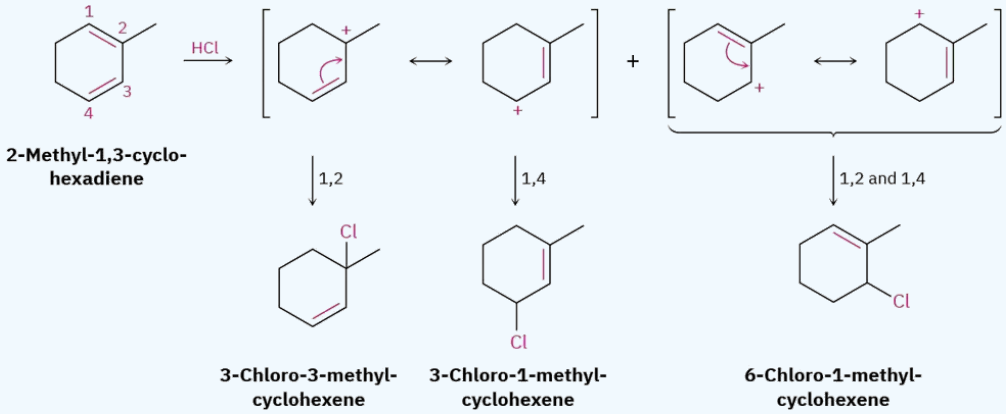
Give the structures of the likely products from reaction of 1 equivalent of HCl with 2-methyl-1,3-cyclohexadiene. Show both 1,2 and 1,4 adducts.

Strategy

Electrophilic addition of HCl to a conjugated diene involves the formation of allylic carbocation intermediate. Thus, the first step is to protonate the two ends of the diene and draw the resonance forms of the two allylic carbocations that result. Then, allow each resonance form to react with Cl^-, generating a maximum of four possible products.

In the present instance, protonation of the C1–C2 double bond gives a carbocation that can react further to give the 1,2 adduct 3-chloro-3-methylcyclohexene and the 1,4 adduct 3-chloro-1-methylcyclohexene. Protonation of the C3–C4 double bond gives a symmetrical carbocation, whose two resonance forms are equivalent. Thus, the 1,2 adduct and the 1,4 adduct have the same structure: 6-chloro-1-methylcyclohexene. Of the two possible modes of protonation, the first is more likely because it yields a more stable, tertiary allylic cation rather than a less-stable, secondary allylic cation.

Solution



Exercise 3.3.1

Give the structures of both 1,2 and 1,4 adducts resulting from reaction of 1 equivalent of HCl with 1,3-pentadiene.

Answer

1-Chloro-2-pentene, 3-chloro-1-pentene, 4-chloro-2-pentene

Exercise 3.3.2

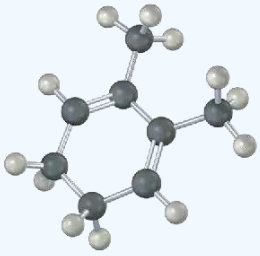
Look at the possible carbocation intermediates produced during addition of HCl to 1,3-pentadiene (the problem above), and predict which 1,2 adduct predominates. Which 1,4 adduct predominates?

Answer

4-Chloro-2-pentene predominates in both.

Exercise 3.3.3

Give the structures of both 1,2 and 1,4 adducts resulting from reaction of 1 equivalent of HBr with the following compound:



Answer

1,2 Addition: 6-bromo-1,6-dimethylcyclohexene 1,4 Addition: 3-bromo-1,2-dimethylcyclohexene.

This page titled 3.3: Electrophilic Additions to Conjugated Dienes- Allylic Carbocations is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **14.2: Electrophilic Additions to Conjugated Dienes- Allylic Carbocations** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

3.4: Kinetic vs. Thermodynamic Control of Reactions

Electrophilic addition to a conjugated diene at or below room temperature normally leads to a mixture of products in which the 1,2 adduct predominates over the 1,4 adduct. When the same reaction is carried out at higher temperatures, however, the product ratio often changes and the 1,4 adduct predominates. For example, addition of HBr to 1,3-butadiene at 0 °C yields a 71 : 29 mixture of 1,2 and 1,4 adducts, but the same reaction carried out at 40 °C yields a 15 : 85 mixture. Furthermore, when the product mixture formed at 0 °C is heated to 40 °C in the presence of HBr, the ratio of adducts slowly changes from 71 : 29 to 15 : 85. Why?

1,3-Butadiene **1,2 Adduct** **1,4 Adduct**

At 0 °C:	71%	29%
At 40 °C:	15%	85%

To understand the effect of temperature on product distribution, let's briefly review what we said in Section 6.7 about rates and equilibria. Imagine a reaction that can give either or both of two products, **B** and **C**.

Let's assume that B forms faster than C (in other words, $\Delta G_B^{\ddagger} < \Delta G_C^{\ddagger}$) but that C is more stable than B (in other words, $\Delta G_C^o > \Delta G_B^o$). An energy diagram for the two processes might look like that shown in Figure 3.4.1.

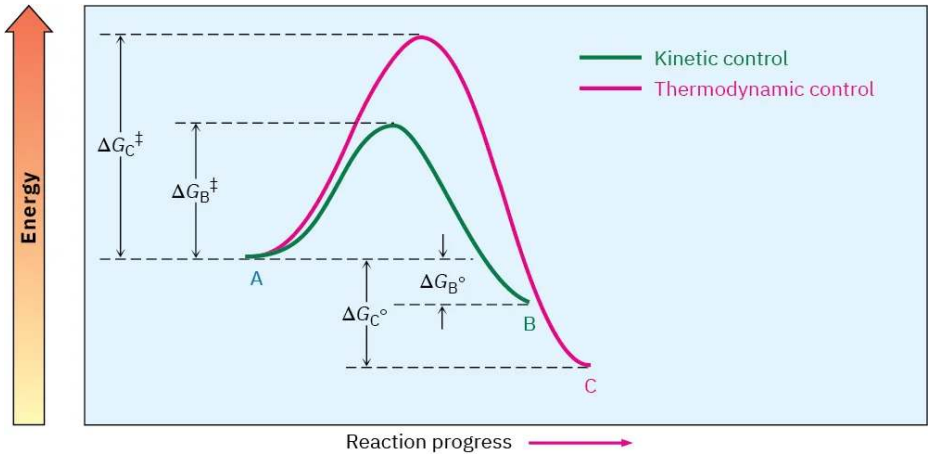
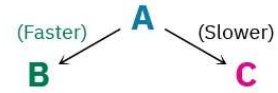


Figure 3.4.1: An energy diagram for two competing reactions in which the less stable product B forms faster than the more stable product C.

Let's first carry out the reaction at a lower temperature so that both processes are irreversible and no equilibrium is reached. Because **B** forms faster than **C**, **B** is the major product. It doesn't matter that **C** is more stable than **B**, because the two are not in equilibrium. *The product of an irreversible reaction depends only on relative rates, not on stability.* Such reactions are said to be under kinetic control.

Kinetic control
(Lower temperature; irreversible)



Now let's carry out the same reaction at some higher temperature so that both processes are readily reversible and an equilibrium is reached. Because **C** is more stable than **B**, **C** is the major product obtained. It doesn't matter that **C** forms more slowly than **B**, because the two are in equilibrium. *The product of a readily reversible reaction depends only on stability, not on relative rates.* Such reactions are said to be under equilibrium control, or thermodynamic control.

We can now explain the effect of temperature on the electrophilic addition reactions of conjugated dienes. At low temperature (0 °C), HBr adds to 1,3-butadiene under kinetic control to give a 71 : 29 mixture of products, with the more rapidly formed 1,2 adduct predominating. Because these low-temperature conditions don't allow the reaction to reach equilibrium, the product that forms faster predominates. At higher temperature (40 °C), however, the reaction occurs under thermodynamic control to give a 15 : 85 mixture of products, with the more stable 1,4 adduct predominating. The higher temperature allows the addition process to become reversible, so an equilibrium mixture of products results. Figure 3.4.2 shows this situation in an energy diagram.

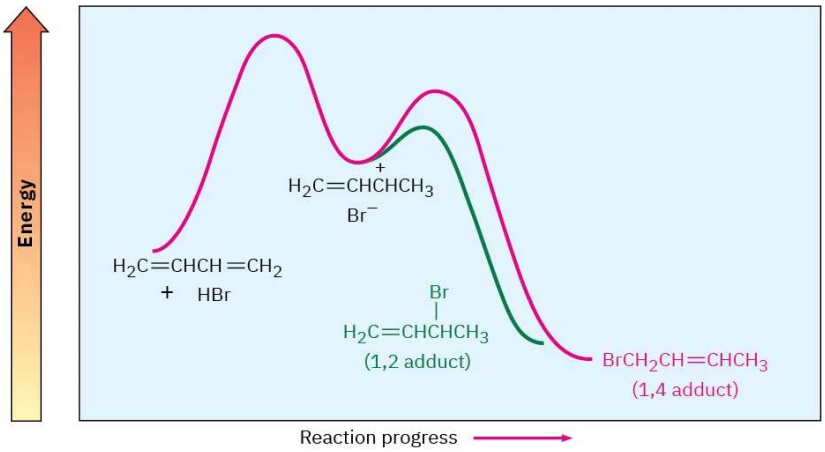


Figure 3.4.2: Energy diagram for the electrophilic addition of HBr to 1,3-butadiene. The 1,2 adduct is the kinetic product because it forms faster, but the 1,4 adduct is the thermodynamic product because it is more stable.

The electrophilic addition of HBr to 1,3-butadiene is a good example of how a change in experimental conditions can change the product of a reaction. The concept of thermodynamic control versus kinetic control is a useful one that we can sometimes take advantage of in the laboratory.

? Exercise 3.4.1

The 1,2 adduct and the 1,4 adduct formed by reaction of HBr with 1,3-butadiene are in equilibrium at 40 °C. Propose a mechanism by which the interconversion of products takes place.

Answer

Interconversion occurs by S_N1 dissociation to a common intermediate cation.

? Exercise 3.4.2

Why do you suppose 1,4 adducts of 1,3-butadiene are generally more stable than 1,2 adducts?

Answer

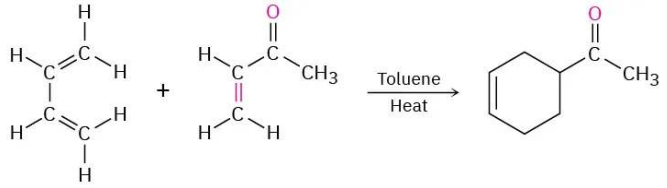
The double bond is more highly substituted.

This page titled 3.4: Kinetic vs. Thermodynamic Control of Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **14.3: Kinetic vs. Thermodynamic Control of Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

3.5: The Diels-Alder Cycloaddition Reaction

Perhaps the most striking difference between conjugated and nonconjugated dienes is that conjugated dienes undergo an addition reaction with alkenes to yield substituted cyclohexene products. For example, 1,3-butadiene and 3-buten-2-one give 3-cyclohexenyl methyl ketone.



1,3-Butadiene **3-Buten-2-one** **3-Cyclohexenyl methyl ketone (96%)**

This process, named the Diels–Alder cycloaddition reaction after its discoverers, is extremely useful in the laboratory because it forms two carbon–carbon bonds in a single step and is one of the few general methods available for making cyclic molecules. (As the name implies, a *cycloaddition* reaction is one in which two reactants add together to give a cyclic product.) The 1950 Nobel Prize in Chemistry was awarded to Otto Diels and Kurt Alder in recognition of the importance of their discovery.

The mechanism of Diels–Alder cycloaddition is different from that of other reactions we've studied because it is neither polar nor radical. Rather, the Diels–Alder reaction is a *pericyclic* process. Pericyclic reactions, which we'll discuss in more detail in Chapter 30, take place in a single step by a cyclic redistribution of bonding electrons. The two reactants simply join together through a cyclic transition state in which the two new C–C bonds form at the same time.

We can picture a Diels–Alder addition as occurring by head-on (σ) overlap of the two alkene *p* orbitals with the two *p* orbitals on carbons 1 and 4 of the diene (Figure 3.5.1). This is, of course, a cyclic orientation of the reactants.

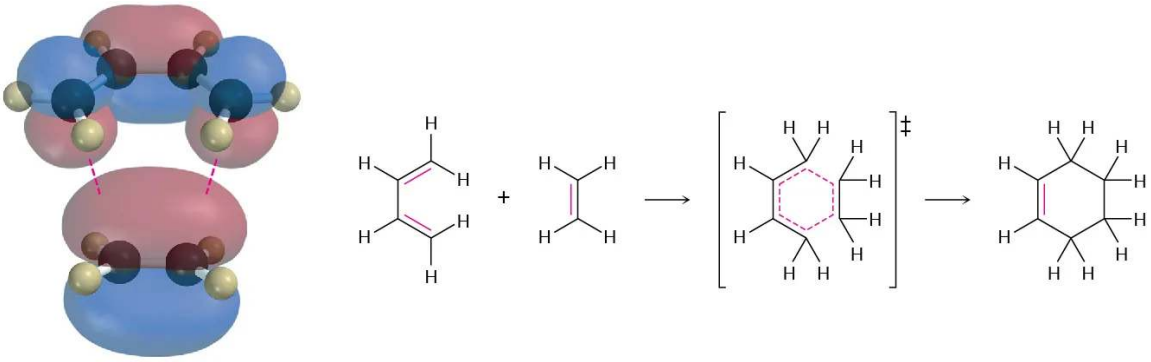


Figure 3.5.1: Mechanism of the Diels–Alder cycloaddition reaction. The reaction occurs in a single step through a cyclic transition state in which the two new C−C bonds form simultaneously.

In the Diels–Alder transition state, the two alkene carbons and carbons 1 and 4 of the diene rehybridize from sp^2 to sp^3 to form two new single bonds, while carbons 2 and 3 of the diene remain sp^2-hybridized to form the new double bond in the cyclohexene product. We'll study this mechanism in more detail in **Section 30.5** but will concentrate for the present on learning about the characteristics and uses of the Diels–Alder reaction.

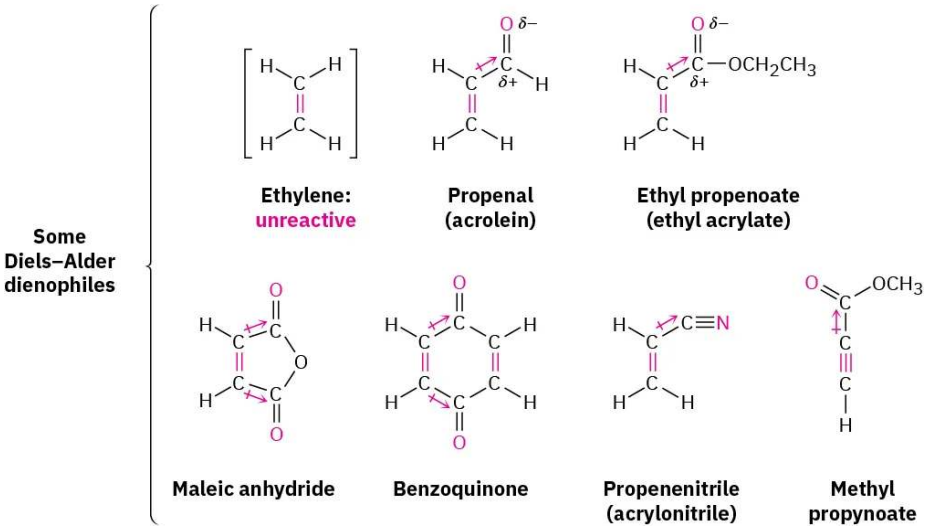
This page titled 3.5: The Diels-Alder Cycloaddition Reaction is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Amar Patel (OpenStax) via source content that was edited to the style and standards of the LibreTexts platform.

- **14.4: The Diels-Alder Cycloaddition Reaction** by Amar Patel is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

3.6: Characteristics of the Diels-Alder Reaction

The Dienophile

The Diels–Alder cycloaddition reaction occurs most rapidly if the alkene component, called the dienophile (“diene lover”), has an electron-withdrawing substituent group. Thus, ethylene itself reacts sluggishly, but propenal, ethyl propenoate, maleic anhydride, benzoquinone, propenenitrile, and similar compounds are highly reactive. Note also that alkynes, such as methyl propynoate, can act as Diels–Alder dienophiles.



In all cases, the double or triple bond of the dienophile is adjacent to the positively polarized carbon of an electron-withdrawing substituent. As a result, the double-bond carbons in these substances are substantially less electron-rich than the carbons in ethylene, as indicated by the electrostatic potential maps in Figure 3.6.1.

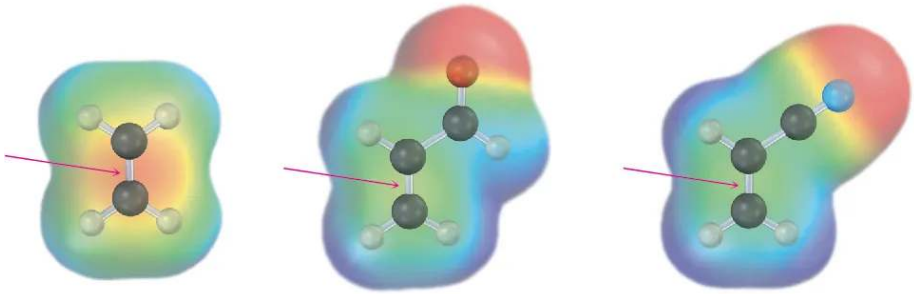
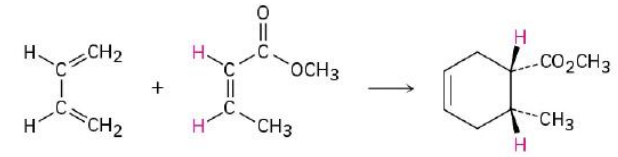
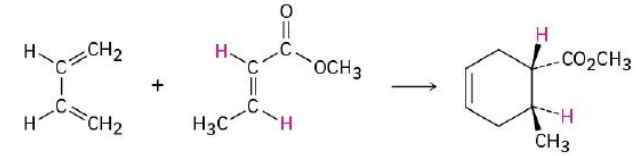


Figure 3.6.1: Electrostatic potential maps of ethylene, propenal, and propenenitrile show that electron-withdrawing groups make the double-bond carbons less electron-rich.

One of the most useful features of the Diels–Alder reaction is that it is stereospecific, meaning that a single product stereoisomer is formed. Furthermore, the stereochemistry of the dienophile is retained. If we carry out cycloaddition with methyl *cis*-2-butenoate, only the cis-substituted cyclohexene product is formed. With methyl *trans*-2-butenoate, only the trans-substituted cyclohexene product is formed.

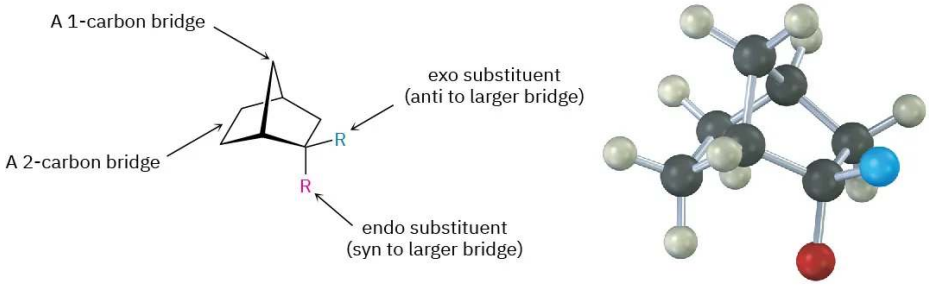


1,3-Butadiene Methyl (*Z*)-2-butenoate Cis product

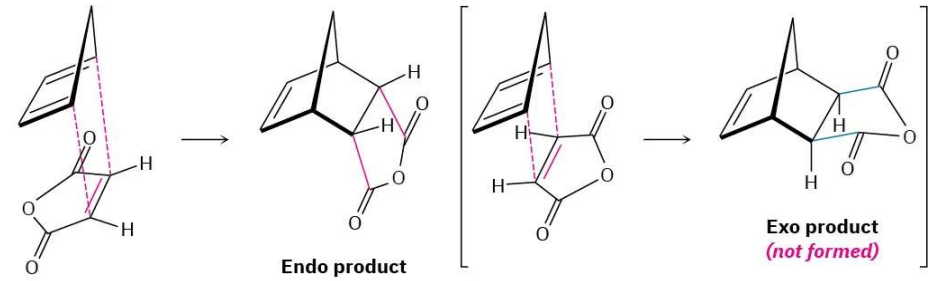


1,3-Butadiene Methyl (*E*)-2-butenoate Trans product

Another stereochemical feature of the Diels–Alder reaction is that the diene and dienophile partners orient so that the endo product, rather than the alternative exo product, is formed. The words *endo* and *exo* are used to indicate relative stereochemistry when referring to bicyclic structures like substituted norbornanes (Section 4.9). A substituent on one bridge is said to be endo if it is syn (cis) to the larger of the other two bridges and is said to be exo if it is anti (trans) to the larger of the other two.



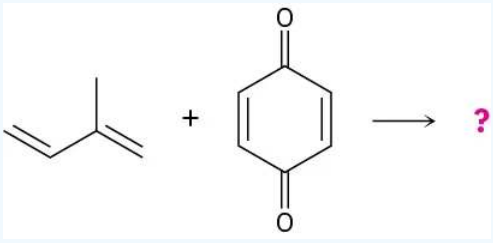
Endo products result from Diels–Alder reactions because the amount of orbital overlap between diene and dienophile is greater when the reactants lie directly on top of one another, so that the electron-withdrawing substituent on the dienophile is underneath the diene double bonds. In the reaction of 1,3-cyclopentadiene with maleic anhydride, for instance, the following result is obtained:



Maleic anhydride Endo product Exo product *(not formed)*

Worked Example 3.6.1: Predicting the Product of a Diels–Alder Reaction

Predict the product of the following Diels–Alder reaction:

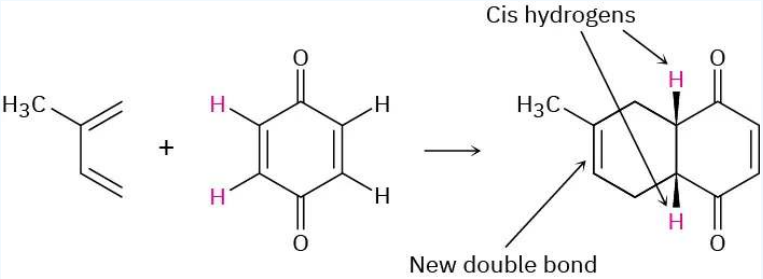


https://chem.libretexts.org/@go/page/564164

Strategy

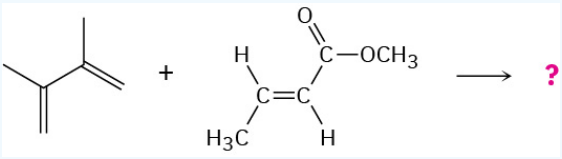
Draw the diene so that the ends of its two double bonds are near the dienophile double bond. Then form two single bonds between the partners, convert the three double bonds into single bonds, and convert the former single bond of the diene into a double bond. Because the dienophile double bond is cis to begin with, the two attached hydrogens must remain cis in the product.

Solution

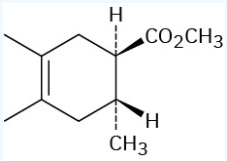


? Exercise 3.6.1

Predict the product of the following Diels–Alder reaction:

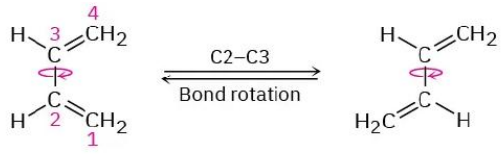


Answer



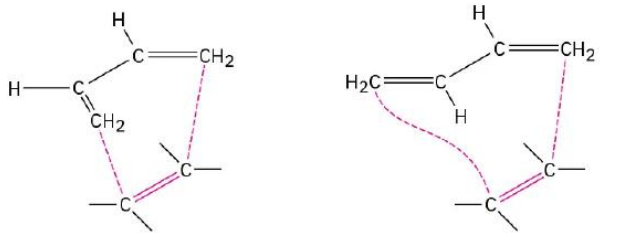
The Diene

Just as the dienophile component has certain constraints that affect its reactivity, so too does the conjugated diene component. The diene must adopt what is called an *s*-cis conformation, meaning "cis-like" about the single bond, to undergo a Diels–Alder reaction. Only in the *s*-cis conformation are carbons 1 and 4 of the diene close enough to react through a cyclic transition state.



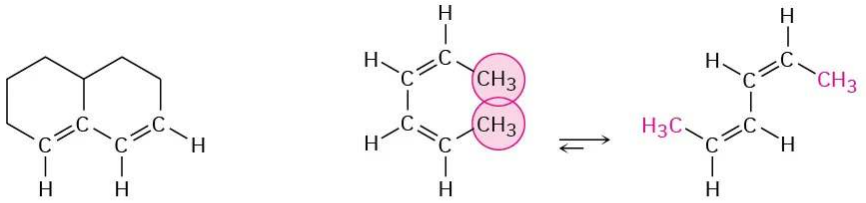
s-Cis conformation **s-Trans conformation**

In the alternative *s*-trans conformation, the ends of the diene partner are too far apart to overlap with the dienophile *p* orbitals.



Successful reaction | No reaction (ends too far apart)

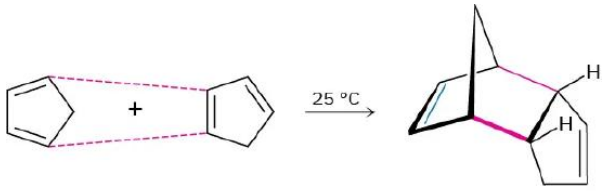
Two examples of dienes that can't adopt an *s*-cis conformation, and thus don't undergo Diels–Alder reactions, are shown in Figure 3.6.2. In the bicyclic diene, the double bonds are rigidly fixed in an *s*-trans arrangement by geometric constraints of the rings. In (2*Z*,4*Z*)-2,4-hexadiene, steric strain between the two methyl groups prevents the molecule from adopting *s*-cis geometry.



A bicyclic diene (rigid *s*-trans diene) | **Severe steric strain in *s*-cis form** | **(2*Z*,4*Z*)-2,4-Hexadiene (*s*-trans, more stable)**

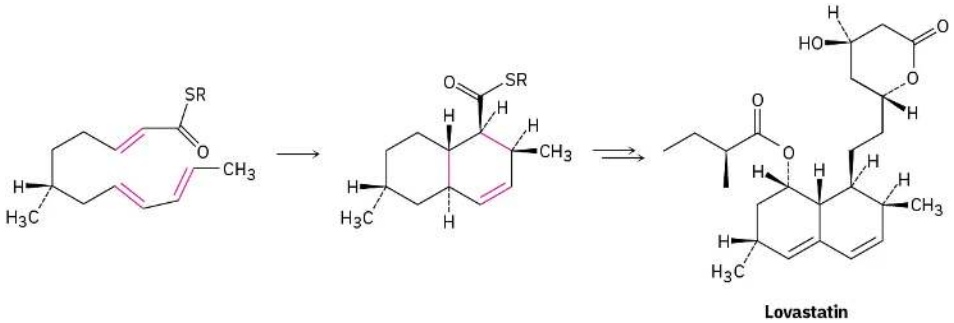
Figure 3.6.2: Two dienes that can't achieve an *s*-cis conformation and thus can't undergo Diels–Alder reactions.

In contrast to these unreactive dienes that can't achieve an *s*-cis conformation, other dienes are fixed only in the correct *s*-cis geometry and are therefore highly reactive in Diels–Alder cycloaddition. 1,3-Cyclopentadiene, for example, is so reactive that it reacts with itself. At room temperature, 1,3-cyclopentadiene *dimerizes*. One molecule acts as diene and a second molecule acts as dienophile in a self-Diels–Alder reaction.



1,3-Cyclopentadiene (*s*-cis) | **Bicyclopentadiene**

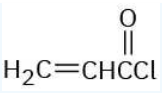
Biological Diels–Alder reactions are also known but are uncommon. One example occurs in the biosynthesis of the cholesterol-lowering drug lovastatin (trade name Mevacor) isolated from the bacterium *Aspergillus terreus*. The key step is the *intramolecular* Diels–Alder reaction of a triene, in which the diene and dienophile components are within the same molecule.

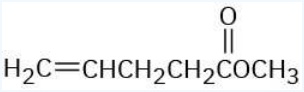


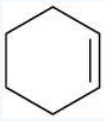
Lovastatin

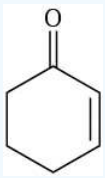
? Exercise 3.6.2

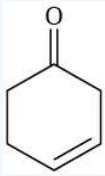
Which of the following alkenes would you expect to be good Diels–Alder dienophiles?

a. 

b. 

c. 

d. 

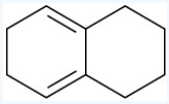
e. 

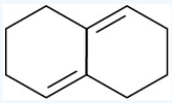
Answer

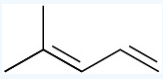
Good dienophiles: (a), (d)

Exercise 3.6.3

Which of the following dienes have an *s*-cis conformation, and which have an *s*-trans conformation? Of the *s*-trans dienes, which can readily rotate to *s*-cis?

a. 

b. 

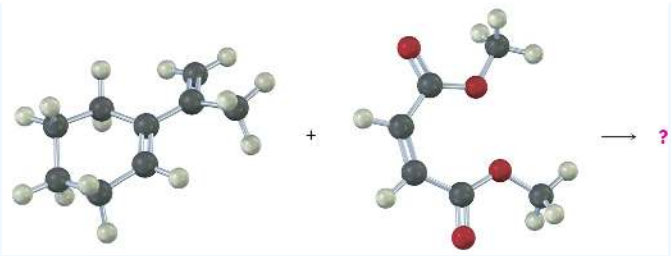
c. 

Answer

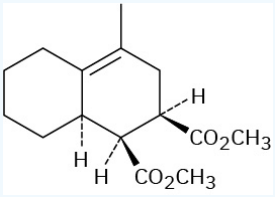
Compound **(a)** is *s*-cis. Compound **(c)** can rotate to *s*-cis.

Exercise 3.6.4

Predict the product of the following Diels–Alder reaction:



Answer

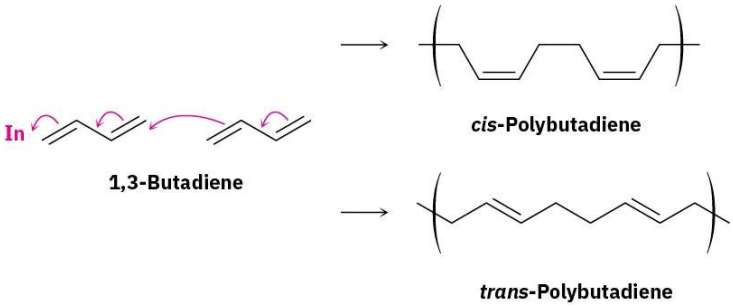


This page titled 3.6: Characteristics of the Diels-Alder Reaction is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

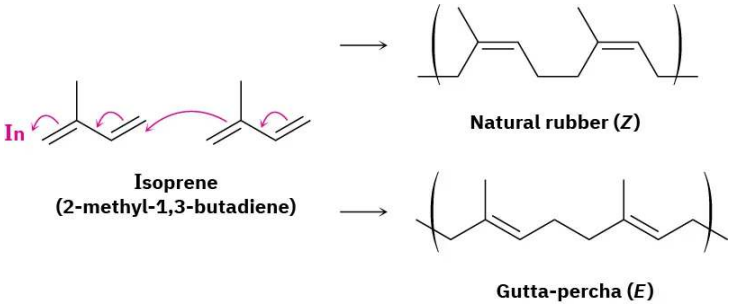
- **14.5: Characteristics of the Diels-Alder Reaction** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

3.7: Diene Polymers - Natural and Synthetic Rubbers

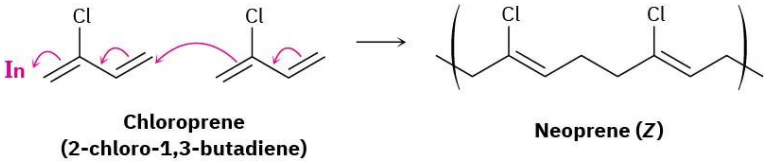
Conjugated dienes can be polymerized just as simple alkenes can (Section 8.10). Diene polymers are structurally more complex than simple alkene polymers, however, because double bonds occur every four carbon atoms along the chain, leading to the possibility of cis–trans isomers. The initiator (In) for the reaction can be either a radical, as occurs in ethylene polymerization, or an acid. Note that the polymerization is a 1,4 addition of the growing chain to a conjugated diene monomer.



Rubber is a naturally occurring diene polymer of isoprene (2-methyl-1,3-butadiene) and is produced by more than 400 different plants. The major source is the so-called rubber tree, *Hevea brasiliensis*, from which the crude material, called *latex*, is harvested as it drips from a slice made through the bark. The double bonds of rubber have *Z* stereochemistry, but gutta-percha, the *E* isomer of rubber, also occurs naturally. Harder and more brittle than rubber, gutta-percha has a variety of applications, including use in dental endodontics and as the covering on some golf balls.



A number of different synthetic rubbers are produced commercially by diene polymerization. Both *cis*- and *trans*-polyisoprene can be made, and the synthetic rubber thus produced is similar to the natural material. Chloroprene (2-chloro-1,3-butadiene) is polymerized to yield neoprene, an excellent, although expensive, synthetic rubber with good weather resistance. Neoprene is used in the production of industrial hoses and gloves, among other things.



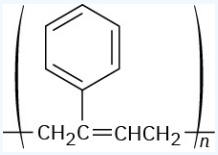
Both natural and synthetic rubbers are too soft and tacky to be useful until they are hardened by heating with elemental sulfur, a process called *vulcanization.* Vulcanization cross-links the rubber chains by forming carbon–sulfur bonds between them, thereby hardening and stiffening the polymer. The exact degree of hardening can be varied, yielding material soft enough for automobile tires or hard enough for bowling balls *(ebonite).*

The unusual ability of rubber to stretch and then contract to its original shape is due to the irregular structure of the polymer chains caused by the double bonds. These double bonds introduce bends and kinks into the polymer chains, thereby preventing neighboring chains from nestling together. When stretched, the randomly coiled chains straighten out and orient along the direction of the pull but are kept from sliding over one another by the cross-links. When the tension is released, the polymer reverts to its original random state.

Exercise 3.7.1

Draw a segment of the polymer that might be prepared from 2-phenyl-1,3-butadiene.

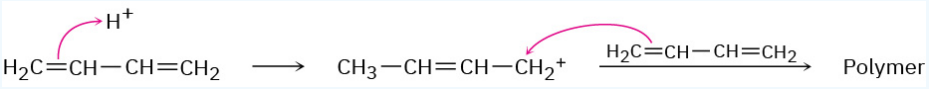
Answer



Exercise 3.7.2

Show the mechanism of the acid-catalyzed polymerization of 1,3-butadiene.

Answer



This page titled 3.7: Diene Polymers - Natural and Synthetic Rubbers is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **14.6: Diene Polymers - Natural and Synthetic Rubbers** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

3.8: Ultraviolet Spectroscopy

As we've seen, mass spectrometry, infrared spectroscopy, and nuclear magnetic resonance spectroscopy are techniques of structure determination applicable to all organic molecules. In addition to these three generally useful methods, there is a fourth—ultraviolet (UV) spectroscopy—that is applicable only to conjugated compounds. UV is less commonly used than the other three spectroscopic techniques because of the specialized information it gives, so we'll only discuss it briefly.

Mass spectrometry	Molecular size and formula
IR spectroscopy	Functional groups present
NMR spectroscopy	Carbon–hydrogen framework
UV spectroscopy	**Conjugated π electron systems**

The ultraviolet region of the electromagnetic spectrum extends from the short-wavelength end of the visible region (4×10^{-7} m) to the long-wavelength end of the X-ray region (10^{-8} m), but the narrow range from 2×10^{-7} m to 4×10^{-7} m is the part of greatest interest to organic chemists. Absorptions in this region are usually measured in nanometers (nm), where 1 nm = 10^{-9} m. Thus, the ultraviolet range of interest is from 200 to 400 nm (Figure 3.8.1).

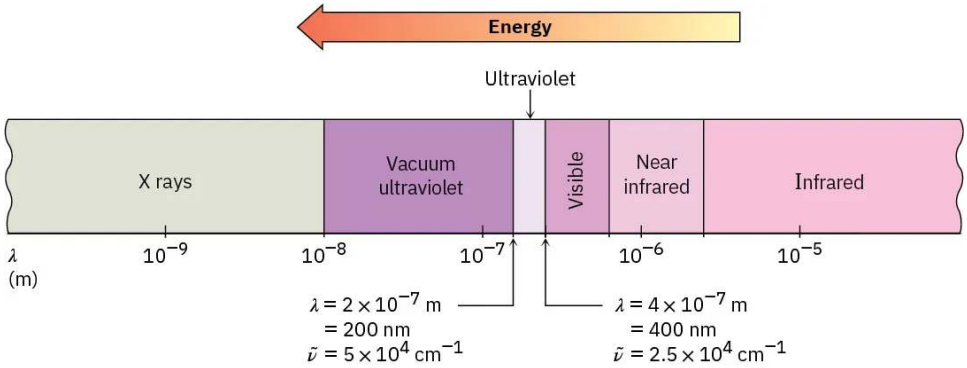


Figure 3.8.1: The ultraviolet (UV) and neighboring regions of the electromagnetic spectrum.

We saw in Section 12.5 that when an organic molecule is irradiated with electromagnetic energy, the radiation either passes through the sample or is absorbed, depending on its energy. With IR irradiation, the energy absorbed corresponds to the amount needed to increase molecular vibrations. With UV radiation, the energy absorbed corresponds to the amount needed to promote an electron from a lower-energy orbital to a higher-energy one in a conjugated molecule. The conjugated diene 1,3-butadiene, for instance, has four π molecular orbitals. The two lower-energy, bonding MOs are occupied in the ground state, and the two higher-energy, antibonding MOs are unoccupied.

On irradiation with ultraviolet light ($h\upsilon$), 1,3-butadiene absorbs energy and a π electron is promoted from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO). Because the electron is promoted from a bonding π molecular orbital to an antibonding π^* molecular orbital, we call this a $\pi \rightarrow \pi^*$ excitation (read as "pi to pi star"). The energy gap between the HOMO and the LUMO of 1,3-butadiene is such that UV light of 217 nm wavelength is required to effect the $\pi \rightarrow \pi^*$ electronic transition (Figure 3.8.2).

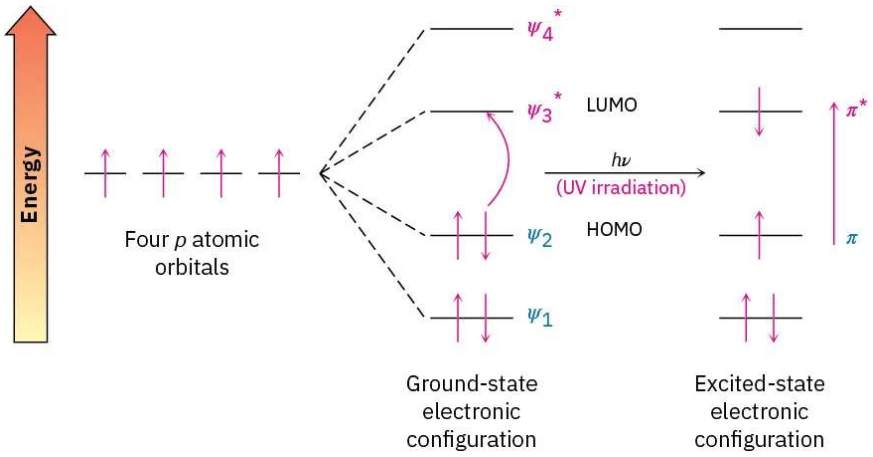


Figure 3.8.2: Ultraviolet excitation of 1,3-butadiene results in the promotion of an electron from ψ_2, the highest occupied molecular orbital (HOMO), to ψ_3*, the lowest unoccupied molecular orbital (LUMO).

An ultraviolet spectrum is recorded by irradiating a sample with UV light of continuously changing wavelength. When the wavelength corresponds to the energy level required to excite an electron to a higher level, energy is absorbed. This absorption is detected and displayed on a chart that plots wavelength versus *absorbance (A)*, defined as

$$A = \log \frac{I_0}{I}$$

where I_0 is the intensity of the incident light and I is the intensity of the light transmitted through the sample.

Note that UV spectra differ from IR spectra in how they are presented. For historical reasons, IR spectra are usually displayed so that the baseline corresponding to zero absorption runs across the top of the chart and a valley indicates an absorption, whereas UV spectra are displayed with the baseline at the bottom of the chart so that a peak indicates an absorption (Figure 3.8.3).

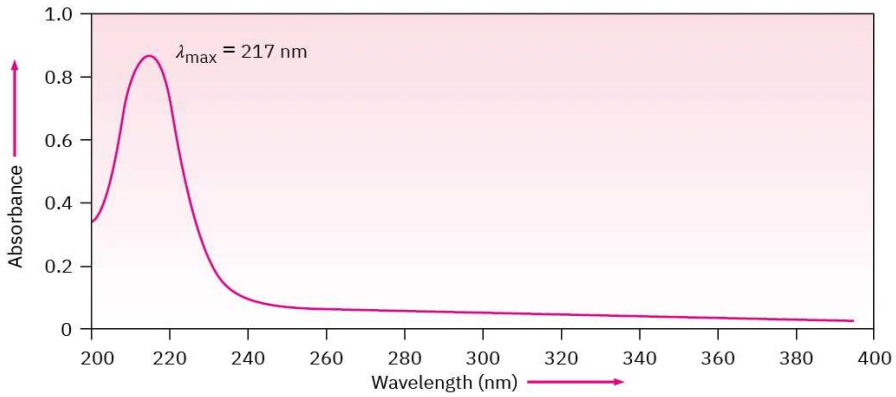


Figure 3.8.3: The ultraviolet spectrum of 1,3-butadiene, λ_{max} = 217 nm.

The amount of UV light absorbed is expressed as the sample's **molar absorptivity** (ϵ), defined by the equation

$$\varepsilon = \frac{A}{c \times l}$$

where A is Absorbance, c is the concentration (in mol/L), and l is the sample pathlength (in cm).

Molar absorptivity is a physical constant, characteristic of the particular substance being observed and thus characteristic of the particular π electron system in the molecule. Typical values for conjugated dienes are in the range ε = 10,000 to 25,000. The units for molar absorptivity, L/(mol · cm), are usually dropped.

A particularly important use of this equation comes from rearranging it to the form

$$c = \frac{A}{\varepsilon \times l}.$$

This formulation lets us measure the concentration of a sample in solution when A, ε, and l are known. As an example, β-carotene, the pigment responsible for the orange color of carrots, has ε = 138,000 L/(mol · cm). If a sample of β-carotene is placed in a cell with a pathlength of 1.0 cm and the UV absorbance reads 0.37, then the concentration of β-carotene in the sample is

$$c = \frac{A}{\varepsilon l} = \frac{0.37}{\left(1.38 \times 10^5 \frac{\text{L}}{\text{mol} \cdot \text{cm}}\right)(1.00\ \text{cm})} = 2.7 \times 10^{-6}\ \text{mol/L} \tag{3.8.1}$$

Unlike IR and NMR spectra, which show many absorptions for a given molecule, UV spectra are usually quite simple—often only a single peak. The peak is usually broad, and we identify its position by noting the wavelength at the top of the peak—λ_{max}, read as "lambda max."

? Exercise 3.8.1

Calculate the energy range of electromagnetic radiation in the UV region of the spectrum from 200 to 400 nm (see Section 12.6). How does this value compare with the values calculated previously for IR and NMR spectroscopy?

Answer

300–600 kJ/mol; UV energy is greater than IR or NMR energy.

? Exercise 3.8.2

If pure vitamin A has λ_{max} = 325 (ε = 50,100), what is the vitamin A concentration in a sample whose absorbance at 325 nm is A = 0.735 in a cell with a pathlength of 1.00 cm?

Answer

1.46×10^{-5} M.

This page titled 3.8: Ultraviolet Spectroscopy is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **14.7: Ultraviolet Spectroscopy** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

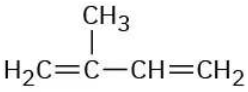
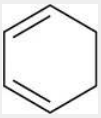
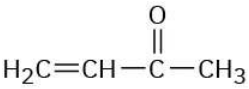
3.9: Interpreting Ultraviolet Spectra- The Effect of Conjugation

The wavelength necessary to effect the $\pi \rightarrow \pi^*$ transition in a conjugated molecule depends on the energy gap between HOMO and LUMO, which in turn depends on the nature of the conjugated system. Thus, by measuring the UV spectrum of an unknown, we can derive structural information about the nature of any conjugated π electron system present in a molecule.

One of the most important factors affecting the wavelength of UV absorption by a molecule is the extent of conjugation. Molecular orbital calculations show that the energy difference between HOMO and LUMO decreases as the extent of conjugation increases. Thus, 1,3-butadiene absorbs at λ_{max} = 217 nm, 1,3,5-hexatriene absorbs at λ_{max} = 258 nm, and 1,3,5,7-octatetraene absorbs at λ_{max} = 290 nm. (Remember: longer wavelength means lower energy.)

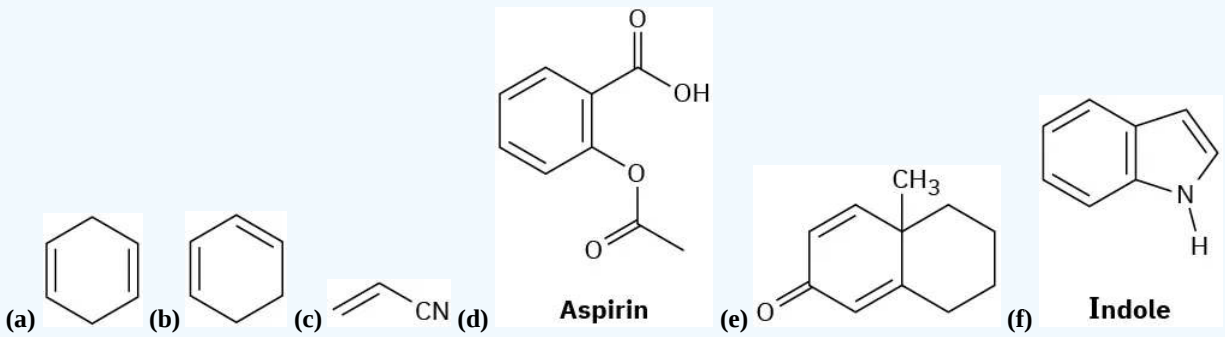
Other kinds of conjugated systems, such as conjugated enones and aromatic rings, also have characteristic UV absorptions that are useful in structure determination. The UV absorption maxima of some representative conjugated molecules are given in Table 3.9.1.

Table 3.9.1: Ultraviolet Absorptions of Some Conjugated Molecules

Name	Structure	λ_{max} (nm)
2-Methyl-1,3-butadiene		220
1,3-Cyclohexadiene		256
1,3,5-Hexatriene	$H_2C{=}CH{-}CH{=}CH{-}CH{=}CH_2$	258
1,3,5,7-Octatetraene	$H_2C{=}CH{-}CH{=}CH{-}CH{=}CH{-}CH{=}CH_2$	290
3-Buten-2-one		219
Benzene		203

Exercise 3.9.1

Which of the following compounds would you expect to show ultraviolet absorptions in the 200 to 400 nm range?



Answer

All except **(a)** have UV absorptions.

This page titled 3.9: Interpreting Ultraviolet Spectra- The Effect of Conjugation is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **14.8: Interpreting Ultraviolet Spectra- The Effect of Conjugation** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

3.10: Conjugation, Color, and the Chemistry of Vision

Why are some organic compounds colored while others are not? β-Carotene, the pigment in carrots, is yellow-orange, for instance, while cholesterol is colorless. The answer involves both the chemical structures of colored molecules and the way we perceive light.

The visible region of the electromagnetic spectrum is adjacent to the ultraviolet region, extending from approximately 400 to 800 nm. Colored compounds have such elaborate systems of conjugation that their "UV" absorptions extend into the visible region. β-Carotene, for instance, has 11 double bonds in conjugation, and its absorption occurs at λ_{max} = 455 nm (Figure 3.10.1).

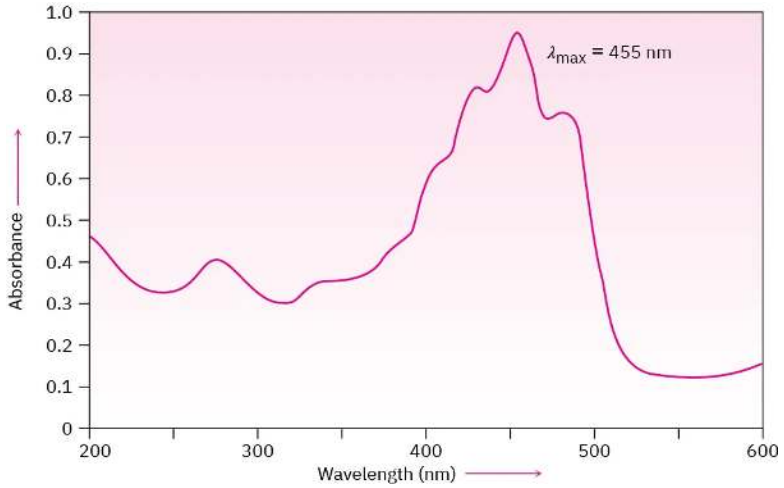
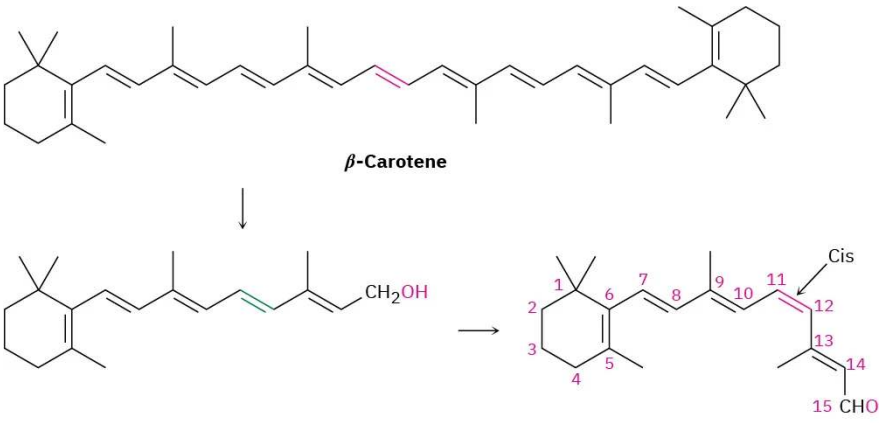


Figure 3.10.1: Ultraviolet spectrum of β-carotene, a conjugated molecule with 11 double bonds. The absorption occurs in the visible region.

"White" light from the sun or from a lamp consists of all wavelengths in the visible region. When white light strikes β-carotene, the wavelengths from 400 to 500 nm (blue) are absorbed while all other wavelengths are transmitted and can reach our eyes. We therefore see the white light with the blue removed, which we perceive as a yellow-orange color for β-carotene.

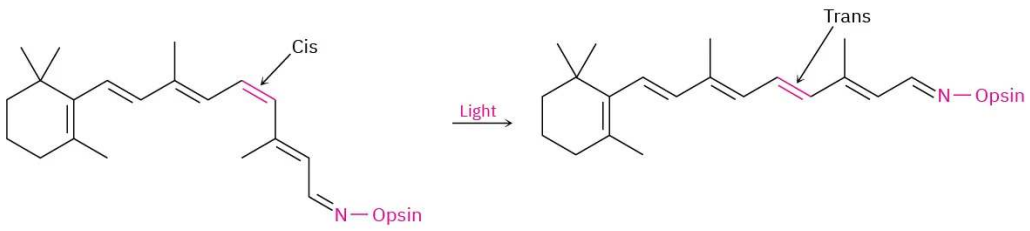
Conjugation is crucial not only for the colors we see in organic molecules but also for the light-sensitive molecules on which our visual system is based. The key substance for vision is dietary β-carotene, which is converted to vitamin A by enzymes in the liver, oxidized to an aldehyde called 11-*trans*-retinal, and then isomerized by a change in geometry of the C11–C12 double bond to produce 11-*cis*-retinal.



Vitamin A **11-*cis*-Retinal**

There are two main types of light-sensitive receptor cells in the retina of the human eye: *rod* cells and *cone* cells. The 3 million or so rod cells are primarily responsible for seeing dim light and shades of gray, whereas the 100 million cone cells are responsible for seeing bright light and colors. In the rod cells of the eye, 11-*cis*-retinal is converted into rhodopsin, a light-sensitive substance formed from the protein opsin and 11-*cis*-retinal. When light strikes the rod cells, isomerization of the C11–C12 double bond

occurs and *trans*-rhodopsin, called metarhodopsin II, is produced. In the absence of light, this cis–trans isomerization takes approximately 1100 years, but in the presence of light, it occurs within 2×10^{-13} seconds! Isomerization of rhodopsin is accompanied by a change in molecular geometry, which in turn causes a nerve impulse to be sent through the optic nerve to the brain, where it is perceived as vision.



Rhodopsin **Metarhodopsin II**

Metarhodopsin II is then recycled back into rhodopsin by a multistep sequence involving cleavage to all-*trans*-retinal and cis–trans isomerization back to 11-*cis*-retinal.

This page titled 3.10: Conjugation, Color, and the Chemistry of Vision is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **14.9: Conjugation, Color, and the Chemistry of Vision** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

3.11: Chemistry Matters—Photolithography

Fifty years ago, someone interested in owning a computer would have paid approximately $150,000 for 16 megabytes of random-access memory that would have occupied a volume the size of a small desk. Today, anyone can buy 60 times as much computer memory for $10 and fit the small chip into their shirt pocket. The difference between then and now is due to improvements in **photolithography**, the process by which integrated-circuit chips are made.

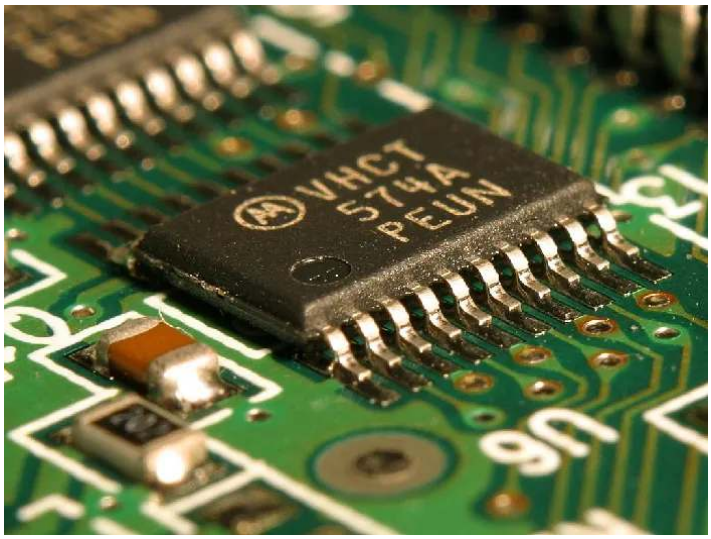


Figure 3.11.1: Manufacturing the ultrathin circuitry on this computer chip depends on the organic chemical reactions of special polymers. (credit: “Integrated circuit on microchip” by Jon Sullivan/Wikimedia Commons, Public Domain)

Photolithography begins by coating a layer of SiO_2 onto a silicon wafer and further coating with a thin (0.5–1.0 μm) film of a light-sensitive organic polymer called a *resist.* A *mask* is then used to cover those parts of the chip that will become a circuit, and the wafer is irradiated with UV light. The nonmasked sections of the polymer undergo a chemical change when irradiated, which makes them more soluble than the masked, unirradiated sections. On washing the irradiated chip with solvent, solubilized polymer is selectively removed from the irradiated areas, exposing the SiO_2 underneath. This SiO_2 is then chemically etched away by reaction with hydrofluoric acid, leaving behind a pattern of polymer-coated SiO_2. Further washing removes the remaining polymer, leaving a positive image of the mask in the form of exposed ridges of SiO_2 (Figure 13.11.2). Additional cycles of coating, masking, and etching then produce the completed chips.

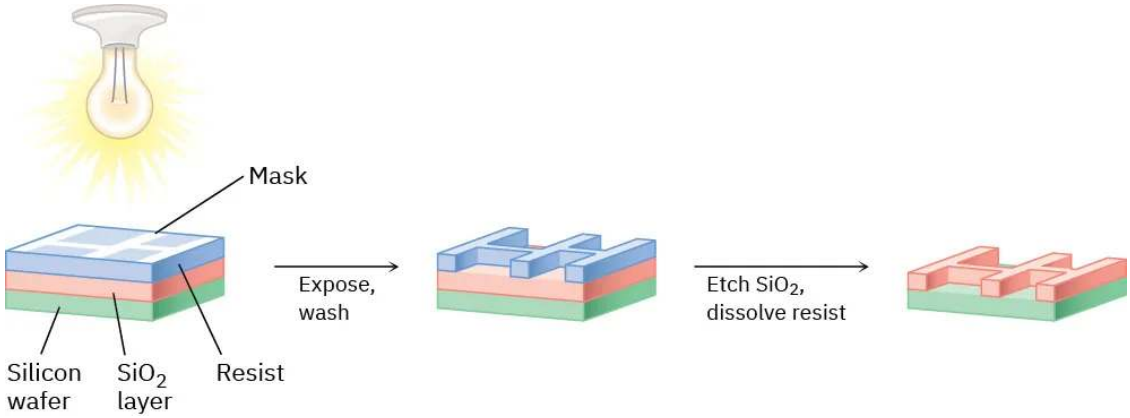
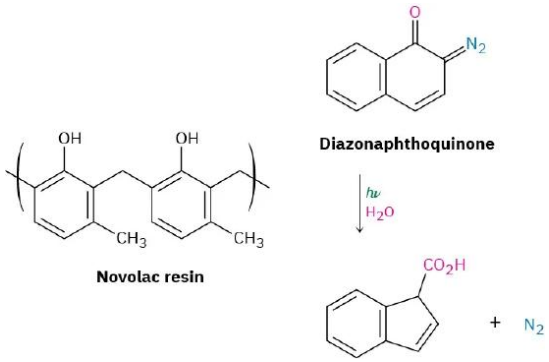


Figure 3.11.2: Outline of the photolithography process for producing integrated circuit chips.

The polymer resist currently used in chip manufacturing is based on the two-component *diazoquinone–novolac system.* Novolac resin is a soft, relatively low-molecular-weight polymer made from methylphenol and formaldehyde, while the diazoquinone is a bicyclic (two-ring) molecule containing a diazo group =N=N) adjacent to a ketone carbonyl (C=O). The diazoquinone–novolac mix is relatively insoluble when fresh, but on exposure to ultraviolet light and water vapor, the diazoquinone component undergoes reaction to yield N_2 and a carboxylic acid, which can be washed away with dilute base. Novolac–diazoquinone technology is

capable of producing features as small as 0.5 μm (5×10^{-7} m), but further improvements in miniaturization are still being developed.



This page titled 3.11: Chemistry Matters—Photolithography is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **14.10: Chemistry Matters—Photolithography** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

3.12: Key Terms

- 1,2-addition
- 1,4-addition
- conjugated
- Diels–Alder cycloaddition reaction
- dienophile
- endo
- exo
- highest occupied molecular orbital (HOMO)
- kinetic control
- lowest unoccupied molecular orbital (LUMO)
- molar absorptivity (ε)
- *s*-cis conformation
- stereospecific
- thermodynamic control
- ultraviolet (UV) spectroscopy

This page titled 3.12: Key Terms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **14.11: Key Terms** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

3.13: Summary

The unsaturated compounds we've looked at previously have had only one double bond, but many compounds have numerous sites of unsaturation, which gives them some distinctive properties. Many such compounds are common in nature, including pigments and hormones.

A **conjugated** diene or other compound is one that contains alternating double and single bonds. One characteristic of conjugated dienes is that they are more stable than their nonconjugated counterparts. This stability can be explained by a molecular orbital description in which four *p* atomic orbitals combine to form four π molecular orbitals. Only the two bonding orbitals are occupied; the two antibonding orbitals are unoccupied. A π bonding interaction in the lowest-energy MO introduces some partial double-bond character between carbons 2 and 3, thereby strengthening the C2–C3 bond and stabilizing the molecule.

Conjugated dienes undergo several reactions not observed for nonconjugated dienes. One is the 1,4-addition of electrophiles. When a conjugated diene is treated with an electrophile such as HCl, **1,2-** and **1,4-addition** products are formed. Both result from the same resonance-stabilized allylic carbocation intermediate and are produced in varying amounts depending on the reaction conditions. The 1,2 adduct is usually formed faster and is said to be the product of **kinetic control**. The 1,4 adduct is usually more stable and is said to be the product of **thermodynamic control**.

Another reaction unique to conjugated dienes is **Diels–Alder cycloaddition**. Conjugated dienes react with electron-poor alkenes (**dienophiles**) in a single step through a cyclic transition state to yield a cyclohexene product. The reaction is stereospecific, meaning that only a single product stereoisomer is formed, and can occur only if the diene is able to adopt an *s*-cis conformation.

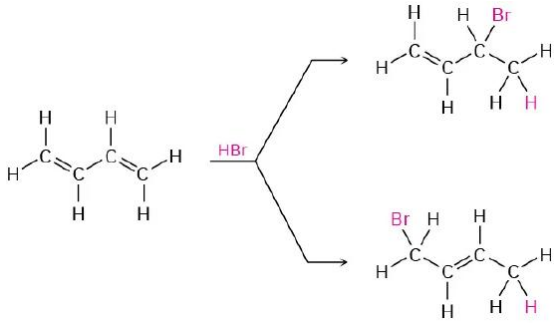
Ultraviolet (UV) spectroscopy is a method of structure determination applicable specifically to conjugated π-electron systems. When a conjugated molecule is irradiated with ultraviolet light, energy absorption occurs and a π electron is promoted from the **highest occupied molecular orbital (HOMO)** to the **lowest unoccupied molecular orbital (LUMO)**. For 1,3-butadiene, radiation of λ_{max} = 217 nm is required. The greater the extent of conjugation, the less the energy needed and the longer the wavelength of radiation required.

This page titled 3.13: Summary is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

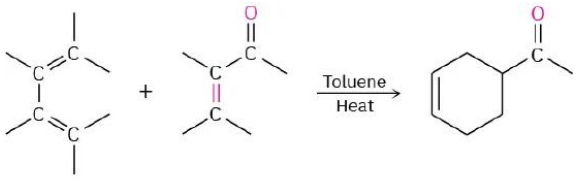
- **14.12: Summary** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

3.14: Summary of Reactions

1. Electrophilic addition reactions (Section 14.2 and Section 14.3)



- Diels–Alder cycloaddition reaction (Section 14.4 and Section 14.5)



A diene **A dienophile** **A cyclohexene**

This page titled 3.14: Summary of Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

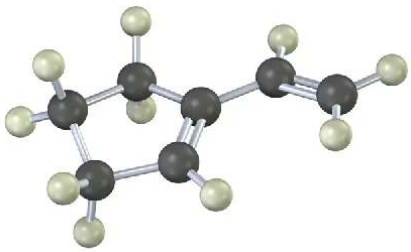
- **14.13: Summary of Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

3.15: Additional Problems

14 • Additional Problems

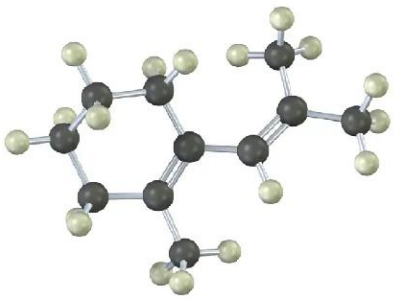
Visualizing Chemistry

PROBLEM 14-16 Show the structures of all possible adducts of the following diene with 1 equivalent of HCl:

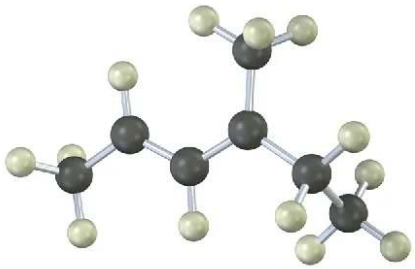


PROBLEM 14-17 Show the product of the Diels–Alder reaction of the following diene with 3-buten-2-one, $H_2C{=}CHCOCH_3$. Make sure you show the full stereochemistry of the reaction product.

PROBLEM 14-18 The following diene does not undergo Diels–Alder reactions. Explain.

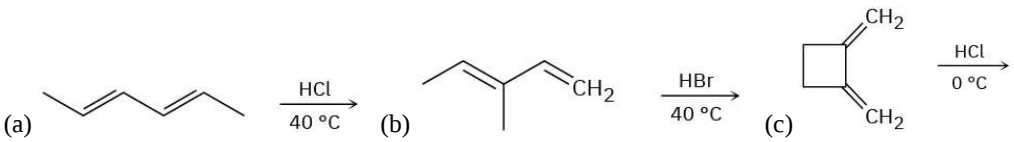


PROBLEM 14-19 The following model is that of an allylic carbocation intermediate formed by protonation of a conjugated diene with HBr. Show the structure of the diene and the structures of the final reaction products.

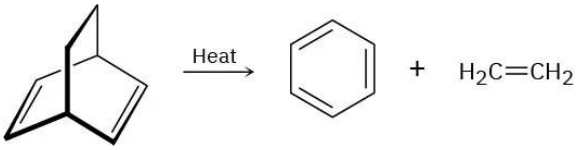


Mechanism Problems

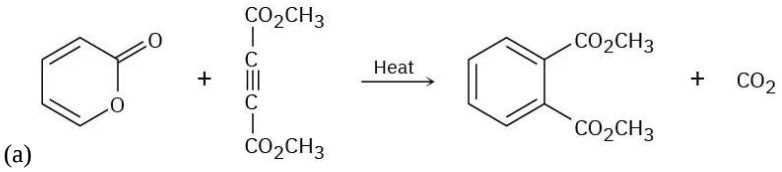
PROBLEM 14-20 Predict the major product(s) from the addition of 1 equivalent of HX and show the mechanism for each of the following reactions.

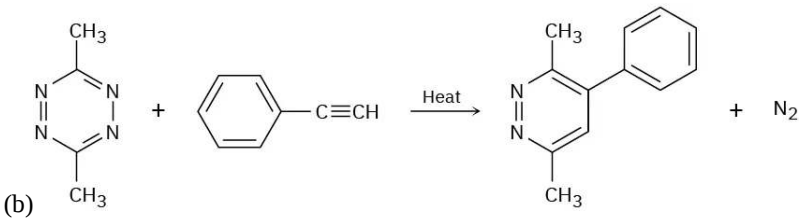


PROBLEM 14-21 We've seen that the Diels–Alder cycloaddition reaction is a one-step, pericyclic process that occurs through a cyclic transition state. Propose a mechanism for the following reaction:

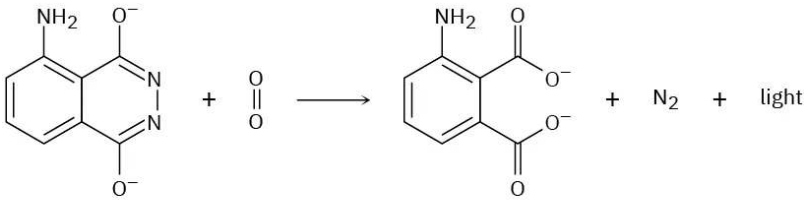


PROBLEM 14-22 In light of your answer to Problem 21 propose mechanisms for the following reactions.



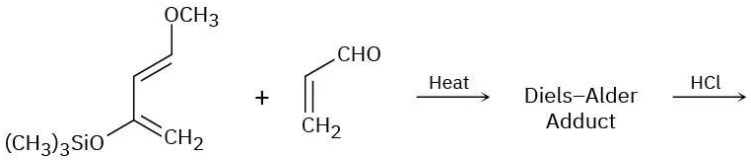


PROBLEM 14-23 Luminol, which is used by forensic scientists to find blood, fluoresces as a result of Diels–Alder-like process. The dianion of luminol reacts with O_2 to form an unstable peroxide intermediate that then loses nitrogen to form a dicarboxylate and emit light. The process is similar to that in Problems 21 and 22. Propose a mechanism for this process.

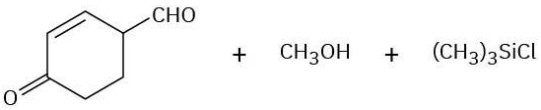


Luminol dianion

PROBLEM 14-24 A useful diene in the synthesis of many naturally occurring substances is known as Danishefsky's diene. It's useful because after the Diels–Alder reaction it can be converted into a product that can't be accessed by a typical Diels–Alder reaction. Show the Diels–Alder adduct and propose a mechanism that accounts for the final products.



Danishefsky's Diene



Conjugated Dienes

PROBLEM 14-25 Name the following compounds:

(a) $CH_3CH{=}\overset{\displaystyle CH_3}{\overset{|}{C}}CH{=}CHCH_3$ (b) $H_2C{=}CHCH{=}CHCH{=}CHCH_3$

(c) $CH_3CH{=}C{=}CHCH{=}CHCH_3$ (d) $CH_3CH{=}\overset{\displaystyle CH_2CH_2CH_3}{\overset{|}{C}}CH{=}CH_2$

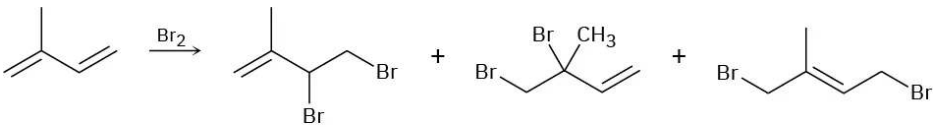
PROBLEM 14-26 Draw and name the six possible diene isomers of formula C_5H_8. Which of the six are conjugated dienes?

PROBLEM 14-27 What product(s) would you expect to obtain from the reaction of 1,3-cyclohexadiene with each of the following?

(a) 1 mol Br_2 in CH_2Cl_2 **(b)** O_3 followed by Zn **(c)** 1 mol HCl in ether **(d)** 1 mol DCl in ether

(e) 3-Buten-2-one ($H_2C{=}CHCOCH_3$) **(f)** Excess OsO_4, followed by $NaHSO_3$

PROBLEM 14-28 Electrophilic addition of Br_2 to isoprene (2-methyl-1,3-butadiene) yields the following product mixture:

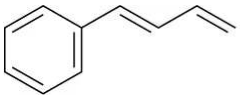


(3%) **(21%)** **(76%)**

Of the 1,2-addition products, explain why 3,4-dibromo-3-methyl-1-butene (21%) predominates over 3,4-dibromo-2-methyl-1-butene (3%).

PROBLEM 14-29 Propose a structure for a conjugated diene that gives the same product from both 1,2 and 1,4-addition of HBr.

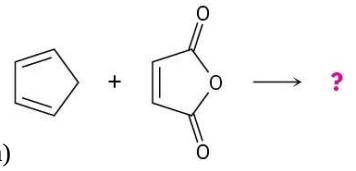
PROBLEM 14-30 Draw the possible products resulting from addition of 1 equivalent of HCl to 1-phenyl-1,3-butadiene. Which would you expect to predominate, and why?



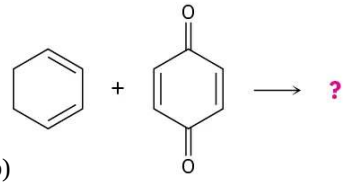
1-Phenyl-1,3-butadiene

Diels–Alder Reactions

PROBLEM 14-31 Predict the products of the following Diels–Alder reactions:

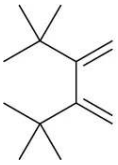


(a)



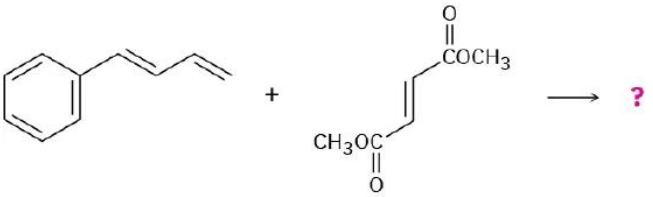
(b)

PROBLEM 14-32 2,3-Di-*tert*-butyl-1,3-butadiene does not undergo Diels–Alder reactions. Explain.



2,3-Di-*tert*-butyl-1,3-butadiene

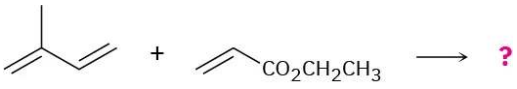
PROBLEM 14-33 Show the structure, including stereochemistry, of the product from the following Diels–Alder reaction:



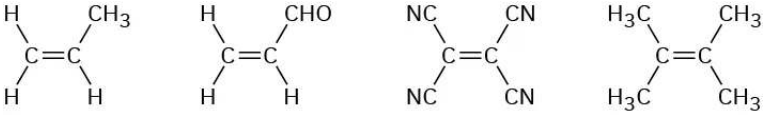
PROBLEM 14-34 How can you account for the fact that *cis*-1,3-pentadiene is much less reactive than *trans*-1,3-pentadiene in the Diels–Alder reaction?

PROBLEM 14-35 Would you expect a conjugated diyne such as 1,3-butadiyne to undergo Diels–Alder reaction with a dienophile? Explain.

PROBLEM 14-36 Reaction of isoprene (2-methyl-1,3-butadiene) with ethyl propenoate gives a mixture of two Diels–Alder adducts. Show the structure of both, and explain why a mixture is formed.

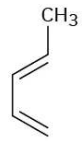


PROBLEM 14-37 Rank the following dienophiles in order of their expected reactivity in the Diels–Alder reaction.

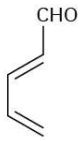


PROBLEM 14-38 1,3-Cyclopentadiene is very reactive in Diels–Alder cycloaddition reactions, but 1,3-cyclohexadiene is less reactive and 1,3-cycloheptadiene is nearly inert. Explain. (Molecular models are helpful.)

PROBLEM 14-39 1,3-Pentadiene is much more reactive in Diels–Alder reactions than 2,4-pentadienal. Why might this be?



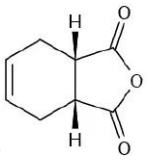
1,3-Pentadiene



2,4-Pentadienal

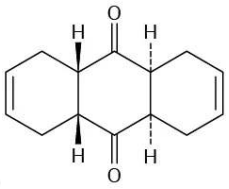
PROBLEM 14-40 How could you use Diels–Alder reactions to prepare the following products? Show the starting diene and dienophile in each case.

(a)

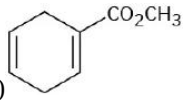


(b)

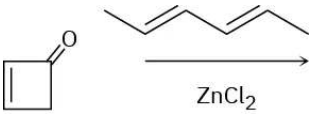
(c)



(d)



PROBLEM 14-41 Show the product of the following reaction.



Diene Polymers

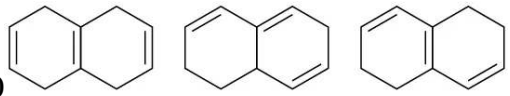
PROBLEM 14-42 Tires whose sidewalls are made of natural rubber tend to crack and weather rapidly in areas around cities where high levels of ozone and other industrial pollutants are found. Explain.

PROBLEM 14-43 1,3-Cyclopentadiene polymerizes slowly at room temperature to yield a polymer that has no double bonds except on the ends. On heating, the polymer breaks down to regenerate 1,3-cyclopentadiene. Propose a structure for the product.

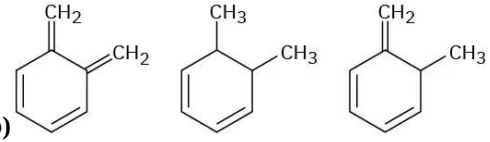
UV Spectroscopy

PROBLEM 14-44 Arrange the molecules in each of the following sets according to where you would expect to find their wavelength of maximum absorption in UV spectroscopy, from shortest to longest wavelength.

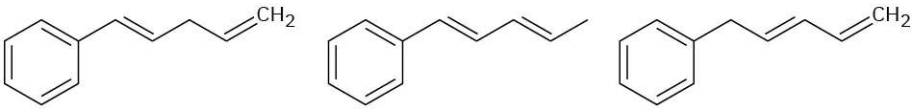
(a)



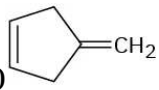
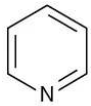
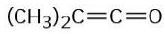
(b)



https://chem.libretexts.org/@go/page/564173

(c) 

Problem 14-45 Which of the following compounds would you expect to have a $\pi \rightarrow \pi^*$ UV absorption in the 200 to 400 nm range?

(a)  (b)  **Pyridine** (c)  **A ketene**

Problem 14-46 Would you expect allene, $H_2C{=}C{=}CH_2$, to show a UV absorption in the 200 to 400 nm range? Explain.

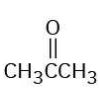
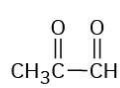
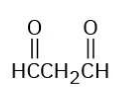
Problem 14-47 The following ultraviolet absorption maxima have been measured:

Molecule	ultraviolet absorption maxima
1,3-Butadiene	217 nm
2-Methyl-1,3-butadiene	220 nm
1,3-Pentadiene	223 nm
2,3-Dimethyl-1,3-butadiene	226 nm
2,4-Hexadiene	227 nm
2,4-Dimethyl-1,3-pentadiene	232 nm
2,5-Dimethyl-2,4-hexadiene	240 nm

What conclusion can you draw about the effect of alkyl substitution on UV absorption maxima? Approximately what effect does each added alkyl group have?

Problem 14-48 1,3,5-Hexatriene has λ_{max} = 258 nm. In light of your answer to Problem 14-47, approximately where would you expect 2,3-dimethyl-1,3,5-hexatriene to absorb?

Problem 14-49 β-Ocimene is a pleasant-smelling hydrocarbon found in the leaves of certain herbs. It has the molecular formula $C_{10}H_{16}$ and a UV absorption maximum at 232 nm. On hydrogenation with a palladium catalyst, 2,6-dimethyloctane is obtained. Ozonolysis of β-ocimene, followed by treatment with zinc and acetic acid, produces the following four fragments:

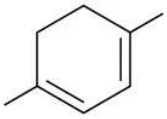
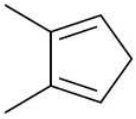
  

Acetone **Formaldehyde** **Pyruvaldehyde** **Malonaldehyde**

- (a) How many double bonds does β-ocimene have?
- (b) Is β-ocimene conjugated or nonconjugated?
- (c) Propose a structure for β-ocimene.
- (d) Write the reactions, showing starting material and products.

General Problems

Problem 14-50 Draw the resonance forms that result when the following dienes are protonated. If the resonance forms differ in energy, identify the most stable one.

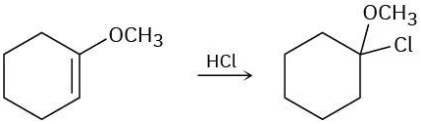
(a) (b)  (c) 

Problem 14-51 Answer the following questions for 1,3,5-cycloheptatriene.

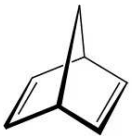
- (a) How many *p* atomic orbitals are in the conjugated system?
- (b) How many molecular orbitals describe the conjugated system?
- (c) How many molecular orbitals are bonding molecular orbitals?
- (d) How many molecular orbitals are anti-bonding molecular orbitals?
- (e) Which molecular orbitals are filled with electrons?
- (f) If this molecule were to absorb a photon of UV light an electron would move between which two molecular orbitals (be specific)?

Problem 14-52 Treatment of 3,4-dibromohexane with strong base leads to loss of 2 equivalents of HBr and formation of a product with formula C_6H_{10}. Three products are possible. Name each of the three, and tell how you would use ^1H and ^{13}C NMR spectroscopy to help identify them. How would you use UV spectroscopy?

Problem 14-53 Addition of HCl to 1-methoxycyclohexene yields 1-chloro-1-methoxycyclohexane as a sole product. Use resonance structures to explain why none of the other regioisomer is formed.



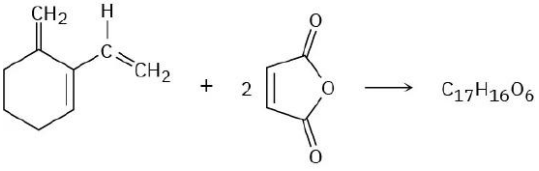
Problem 14-54 Aldrin, a chlorinated insecticide now banned from use in most countries since 1990, can be made by Diels–Alder reaction of hexachloro-1,3-cyclopentadiene with norbornadiene. What is the structure of aldrin?



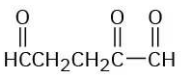
Norbornadiene

Problem 14-55 Norbornadiene (Problem 54) can be prepared by reaction of chloroethylene with 1,3-cyclopentadiene, followed by treatment of the product with sodium ethoxide. Write the overall scheme, and identify the two kinds of reactions.

Problem 14-56 The triene shown here reacts with 2 equivalents of maleic anhydride to yield a product with the formula $C_{17}H_{16}O_6$. Predict a structure for the product.



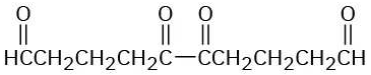
Problem 14-57 Myrcene, $C_{10}H_{16}$, is found in oil of bay leaves and is isomeric with *β*-ocimene (Problem 49). It has an ultraviolet absorption at 226 nm and can be hydrogenated to yield 2,6-dimethyloctane. On ozonolysis followed by zinc/acetic acid treatment, myrcene yields formaldehyde, acetone, and 2-oxopentanedial:



2-Oxopentanedial

Propose a structure for myrcene, and write the reactions, showing starting material and products.

Problem 14-58 Hydrocarbon **A**, $C_{10}H_{14}$, has a UV absorption at λ_{max} = 236 nm and gives hydrocarbon **B**, $C_{10}H_{18}$, on hydrogenation. Ozonolysis of **A**, followed by zinc/acetic acid treatment, yields the following diketo dialdehyde:



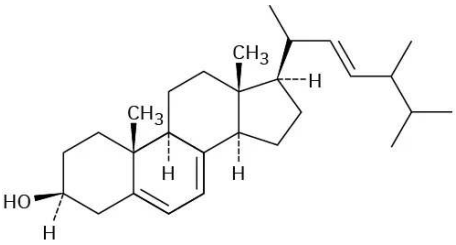
An illustration shows the structure of diketo dialdehyde. It shows two carbonyl groups single bonded to each other. Each carbonyl group is bonded to a chain of three methylene groups and then to an aldehyde group.

- (a) Propose two possible structures for **A**.
- (b) Hydrocarbon **A** reacts with maleic anhydride to yield a Diels–Alder adduct. Which of your structures for **A** is correct?
- (c) Write the reactions, showing the starting material and products.

Problem 14-59 Adiponitrile, a starting material used in the manufacture of nylon, can be prepared in three steps from 1,3-butadiene. How would you carry out this synthesis?

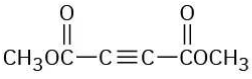
Adiponitrile

Problem 14-60 Ergosterol, a precursor of vitamin D, has λ_{max} = 282 nm and molar absorptivity ϵ = 11,900. What is the concentration of ergosterol in a solution whose absorbance A = 0.065 with a sample pathlength l = 1.00 cm?



Ergosterol ($C_{28}H_{44}O$)

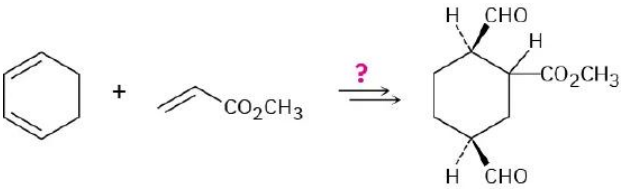
Problem 14-61 Dimethyl butynedioate undergoes a Diels–Alder reaction with (2*E*,4*E*)-2,4-hexadiene. Show the structure and stereochemistry of the product.



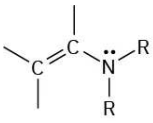
Dimethyl butynedioate

Problem 14-62 Dimethyl butynedioate also undergoes a Diels–Alder reaction with (2*E*,4*Z*)-2,4-hexadiene, but the stereochemistry of the product is different from that of the (2*E*,4*E*) isomer (Problem 14-61). Explain.

Problem 14-63 How would you carry out the following synthesis (more than one step is required)? What stereochemical relationship between the $-CO_2CH_3$ group attached to the cyclohexane ring and the –CHO groups would your synthesis produce?



Problem 14-64 The double bond of an *enamine* (alk*ene* + *amine*) is much more nucleophilic than a typical alkene double bond. Assuming that the nitrogen atom in an enamine is sp^2-hybridized, draw an orbital picture of an enamine, and explain why the double bond is electron-rich.



An enamine

Problem 14-65 Benzene has an ultraviolet absorption at λ_{max} = 204 nm, and para-toluidine has λ_{max} = 235 nm. How do you account for this difference?

Benzene
(λ_{max} = 204 nm)

***p*-Toluidine**
(λ_{max} = 235 nm)

This page titled 3.15: Additional Problems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **14.14: Additional Problems** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

CHAPTER OVERVIEW

4: Benzene and Aromaticity

Learning Objectives

After you have completed Chapter 15, you should be able to

1. fulfillall of the detailed objectives listed under each individual section.
2. use the information presented in this chapter, along with material from earlier chapters, to solve problems, particularly road-map problems and those requiring an understanding of spectroscopy.
3. explain the concept of aromaticity and the stability of aromatic compounds.
4. define, and use in context, the key terms introduced.

In Chapter 3, we identified an aromatic compound as being a compound which contains a benzene ring (or phenyl group). It is now time to define aromaticity in a more sophisticated manner. In this chapter, we discuss the stability of benzene and other aromatic compounds, explaining it in terms of resonance and molecular orbital theory. You will study the nomenclature of aromatic compounds and the Hückel (4*n* + 2) rule for predicting aromaticity. The chapter concludes with a brief summary of the spectroscopic properties of arenes.

4.1: Why This Chapter?
4.2: Naming Aromatic Compounds
4.3: Structure and Stability of Benzene
4.4: Aromaticity and the Hückel 4n + 2 Rule
4.5: Aromatic Ions
4.6: Aromatic Heterocycles - Pyridine and Pyrrole
4.7: Polycyclic Aromatic Compounds
4.8: Spectroscopy of Aromatic Compounds
4.9: Chemistry Matters—Aspirin, NSAIDs, and COX-2 Inhibitors
4.10: Key Terms
4.11: Summary
4.12: Additional Problems

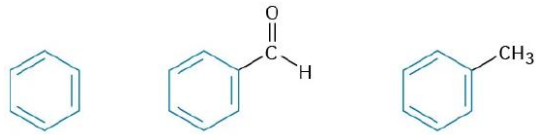
This page titled 4: Benzene and Aromaticity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

4.1: Why This Chapter?

The reactivity of substituted aromatic compounds, more than that of any other class of substances, is intimately tied to their exact structure. As a result, aromatic compounds provide an extraordinarily sensitive probe for studying the relationship between structure and reactivity. We'll examine this relationship here and in the following chapter, and we'll find that the lessons learned are applicable to all other organic compounds, including important substances such as the nucleic acids that control our genetic makeup.

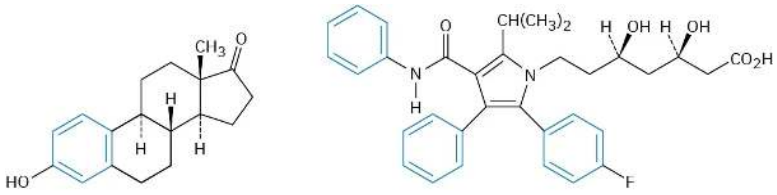
Figure 4.1.1: A fennel plant is an aromatic herb used in cooking. A phenyl group—pronounced exactly the same way—is the characteristic structural unit of "aromatic" organic compounds. (credit: "Fennel" by Ruth Hartnup/Flickr, CC BY 2.0)

In the early days of organic chemistry, the word *aromatic* was used to describe such fragrant substances as benzaldehyde (from cherries, peaches, and almonds), toluene (from Tolu balsam), and benzene (from coal distillate). It was soon realized, however, that substances grouped as aromatic differed from most other organic compounds in their chemical behavior.



Benzene **Benzaldehyde** **Toluene**

Today, the association of aromaticity with fragrance has long been lost, and we now use the word aromatic to refer to the class of compounds that contain six-membered rings with three alternating double bonds. Many naturally occurring compounds are aromatic in part, including steroids such as estrone and well-known pharmaceuticals such as the cholesterol-lowering drug atorvastatin, marketed as Lipitor. Benzene itself causes a depressed white blood cell count (leukopenia) on prolonged exposure and should not be used as a laboratory solvent.



Estrone **Atorvastatin (Lipitor)**

This page titled 4.1: Why This Chapter? is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **15.0: Why This Chapter?** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

4.2: Naming Aromatic Compounds

Simple aromatic hydrocarbons come from two main sources: coal and petroleum. Coal is an enormously complex mixture consisting primarily of large arrays of benzene-like rings joined together. Thermal breakdown of coal occurs when heated to 1000 °C in the absence of air, and a mixture of volatile products called *coal tar* boils off. Fractional distillation of coal tar yields benzene, toluene, xylene (dimethylbenzene), naphthalene, and a host of other aromatic compounds (Figure 4.2.1).

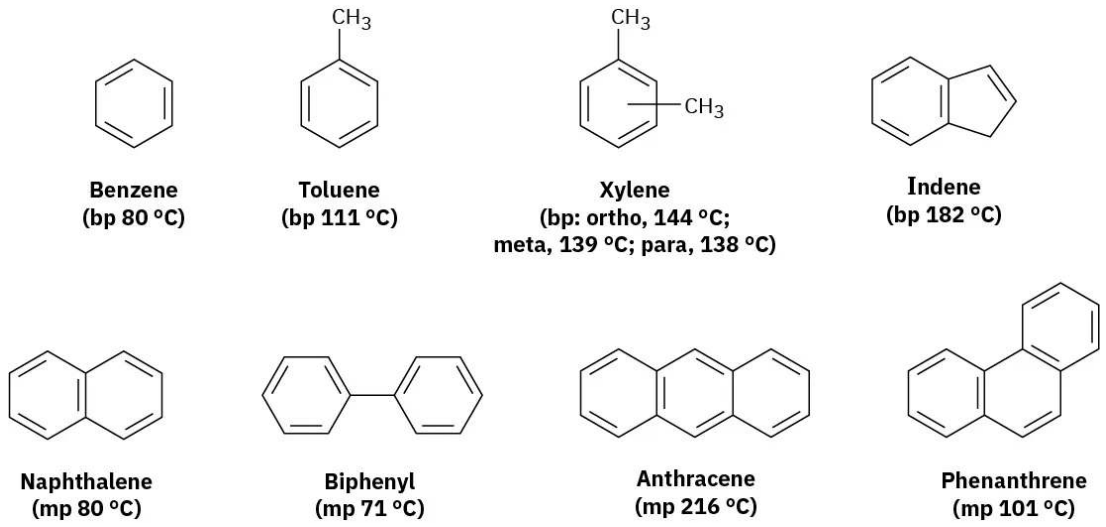
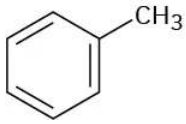
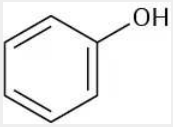
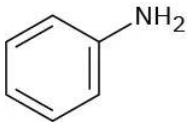
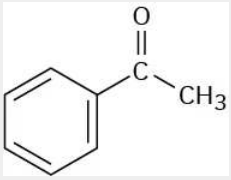
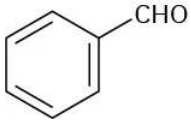
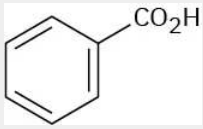
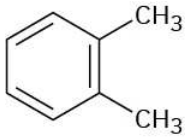
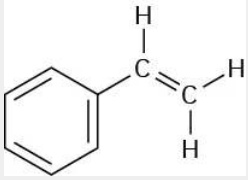


Figure 4.2.1: Some aromatic hydrocarbons found in coal tar.

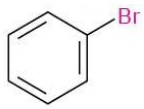
Unlike coal, petroleum contains few aromatic compounds and consists largely of alkanes (see Chapter 3 *Chemistry Matters*). During petroleum refining, however, aromatic molecules are formed when alkanes are passed over a catalyst at about 500 °C under high pressure.

Aromatic substances, more than any other class of organic compounds, have acquired a large number of nonsystematic names. IUPAC rules discourage the use of most such names but do allow some of the more widely used ones to be retained (Figure 4.2.1). Thus, methylbenzene is known commonly as *toluene;* hydroxybenzene as *phenol;* aminobenzene as *aniline;* and so on.

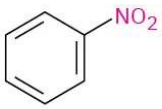
Figure 4.2.1 Common Names of Some Aromatic Compounds

Structure	Name
	Toluene (bp 111 °C)
	Phenol (mp 43 °C)
	Aniline (bp 184 °C)
	Acetophenone (mp 21 °C)
	Benzaldehyde (bp 178 °C)
	Benzoic acid (mp 122 °C)
	*ortho*-Xylene (bp 144 °C)
	Styrene (bp 145 °C)

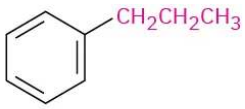
Monosubstituted benzenes are named systematically in the same manner as other hydrocarbons, with *-benzene* as the parent name. Thus, C_6H_5Br is bromobenzene, $C_6H_5NO_2$ is nitrobenzene, and $C_6H_5CH_2CH_2CH_3$ is propylbenzene.



Bromobenzene



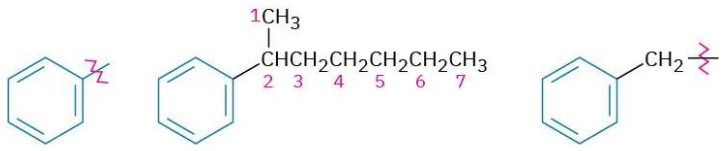
Nitrobenzene



Propylbenzene

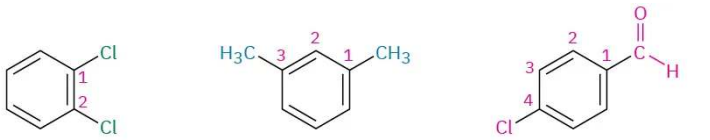
Alkyl-substituted benzenes are sometimes referred to as arenes and are named in different ways depending on the size of the alkyl group. If the alkyl substituent is smaller than the ring (six or fewer carbons), the arene is referred to as an alkyl-substituted benzene. If the alkyl substituent is larger than the ring (seven or more carbons), the compound is referred to as a phenyl-substituted alkane.

The name phenyl, pronounced **fen**-nil and sometimes abbreviated as Ph or Φ (Greek *phi*), is used for the $–C_6H_5$ unit when the benzene ring is considered a substituent. The word is derived from the Greek *pheno* ("I bear light"), commemorating the discovery of benzene by Michael Faraday in 1825 from the oily residue left by the illuminating gas used in London street lamps. In addition, the name benzyl is used for the $C_6H_5CH_2–$ group.



A phenyl group **2-Phenylheptane** **A benzyl group**

Disubstituted benzenes are named using the prefixes ortho (*o*), meta (*m*), or para (*p*). An ortho-disubstituted benzene has its two substituents in a 1,2 relationship on the ring, a meta-disubstituted benzene has its two substituents in a 1,3 relationship, and a para-disubstituted benzene has its substituents in a 1,4 relationship.

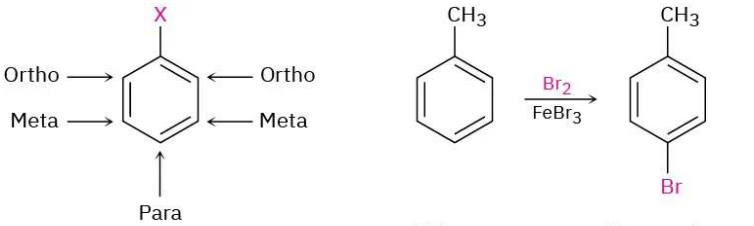


***ortho*-Dichlorobenzene**
1,2 disubstituted

***meta*-Dimethylbenzene**
(*meta*-xylene)
1,3 disubstituted

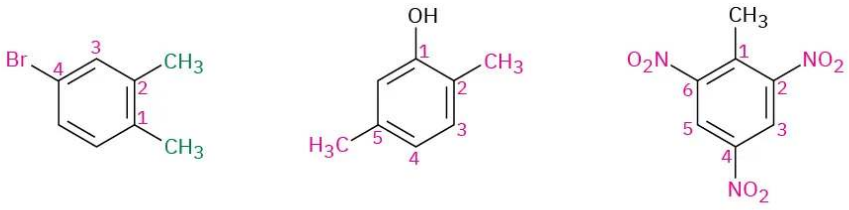
***para*-Chlorobenzaldehyde**
1,4 disubstituted

The ortho, meta, para system of nomenclature is also useful when discussing reactions. For example, we might describe the reaction of bromine with toluene by saying, "Reaction occurs at the para position," meaning at the position para to the methyl group already present on the ring.



Toluene ***p*-Bromotoluene**

As with cycloalkanes (Section 4.1), benzenes with more than two substituents are named by choosing a point of attachment as carbon 1 and numbering the substituents on the ring so that the second substituent has as low a number as possible. If ambiguity still exists, number so that the third or fourth substituent has as low a number as possible, until a point of difference is found. The substituents are listed alphabetically when writing the name.

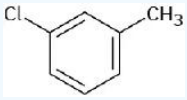


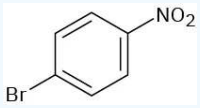
4-Bromo-1,2-dimethylbenzene **2,5-Dimethylphenol** **2,4,6-Trinitrotoluene (TNT)**

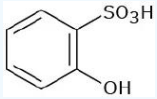
Note in the second and third examples shown that *-phenol* and *-toluene* are used as the parent names rather than *-benzene*. Any of the monosubstituted aromatic compounds shown in Figure 4.2.1 can serve as a parent name, with the principal substituent (–OH in phenol or $–CH_3$ in toluene) attached to C1 on the ring.

Exercise 4.2.1

Tell whether the following compounds are ortho-, meta-, or para-disubstituted:

a. 

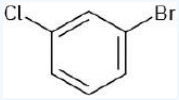
b. 

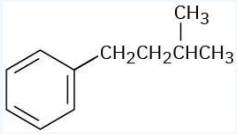
c. 

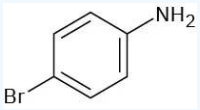
Answer

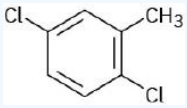
a. Meta
b. Para
c. Ortho

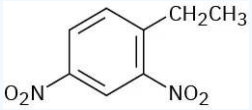
Exercise 4.2.2

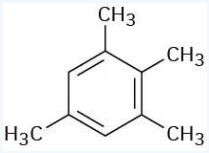
a. 

b. 

c. 

d. 

e. 

f. 

Answer

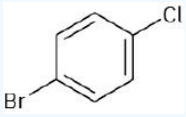
a. m-Bromochlorobenzene
b. (3-Methylbutyl)benzene
c. p-Bromoaniline
d. 2,5-Dichlorotoluene
e. 1-Ethyl-2,4-dinitrobenzene
f. 1,2,3,5-Tetramethylbenzene

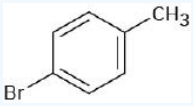
Exercise 4.2.3

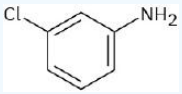
Draw structures corresponding to the following IUPAC names:

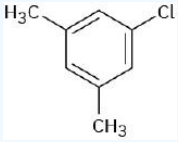
a. p-Bromochlorobenzene
b. p-Bromotoluene
c. m-Chloroaniline
d. 1-Chloro-3,5-dimethylbenzene

Answer

a. 

b. 

c. 

d. 

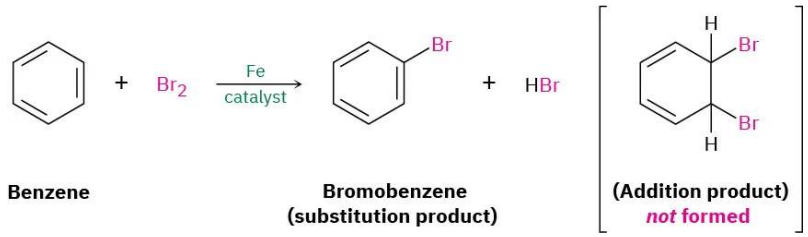
1.

This page titled 4.2: Naming Aromatic Compounds is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **15.1: Naming Aromatic Compounds** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

4.3: Structure and Stability of Benzene

Benzene (C_6H_6) has six fewer hydrogens than the six-carbon cycloalkane cyclohexane (C_6H_{12}) and is clearly unsaturated, usually being represented as a six-membered ring with alternating double and single bonds. Yet it has been known since the mid-1800s that benzene is much less reactive than typical alkenes and fails to undergo typical alkene addition reactions. Cyclohexene, for instance, reacts rapidly with Br_2 and gives the addition product 1,2-dibromocyclohexane, but benzene reacts slowly with Br_2 and gives the substitution product C_6H_5Br rather than the addition product.



We can get a quantitative idea of benzene's stability by measuring heats of hydrogenation (Section 7.6). Cyclohexene, an isolated alkene, has $\Delta H^\circ_{\text{hydrog}}$=–118kJ/ (–28.2 kcal/mol), and 1,3-cyclohexadiene, a conjugated diene, has $\Delta H^\circ_{\text{hydrog}}$ =–230kJ/ (–55.0 kcal/mol). As noted in Section 14.1, this value for 1,3-cyclohexadiene is a bit less than twice that for cyclohexene because conjugated dienes are more stable than isolated dienes.

Carrying the process one step further, we might expect $\Delta H^\circ_{\text{hydrog}}$ for "cyclohexatriene" (benzene) to be a bit less than 3 × 118 = 354 kJ/mol, or three times the cyclohexene value. The actual value, however, is –206 kJ/mol, some 148 kJ/mol (35.4 kcal/mol) less than expected. Because of this difference in actual and expected energy released during hydrogenation, benzene must have 148 kJ/mol less energy to begin with. In other words, benzene is more stable than expected by 148 kJ/mol (Figure 15.3).

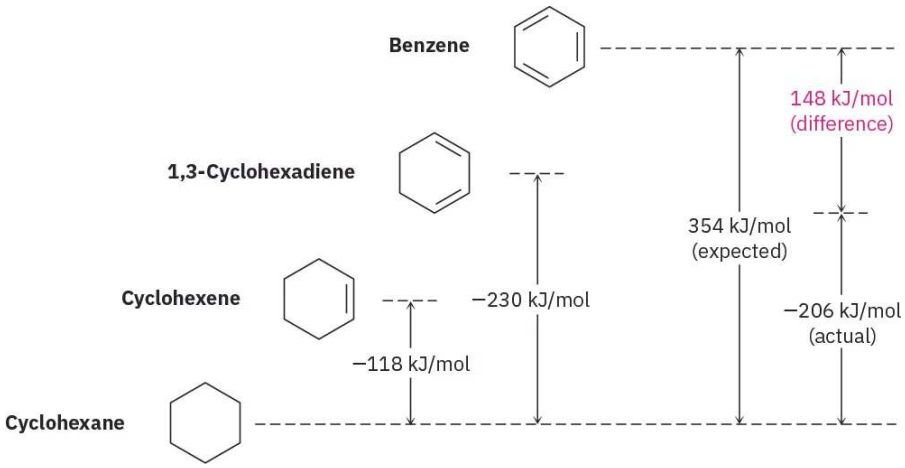
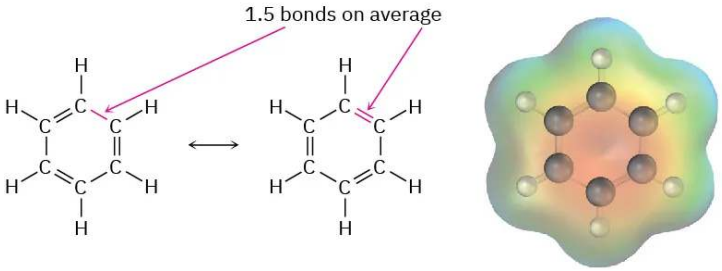


Figure 4.3.1: A comparison of the heats of hydrogenation for cyclohexene, 1,3-cyclohexadiene, and benzene. Benzene is 148 kJ/mol (35.4 kcal/mol) more stable than might be expected for "cyclohexatriene."

Further evidence for the unusual nature of benzene is that all its carbon–carbon bonds have the same length—139 pm, which is intermediate between typical single (154 pm) and double (134 pm) bonds. In addition, an electrostatic potential map shows that the electron density in all six C–C bonds is identical. Thus, benzene is a planar molecule with the shape of a regular hexagon. All C–C–C bond angles are 120°, all six carbon atoms are sp^2-hybridized, and each carbon has a *p* orbital perpendicular to the plane of the six-membered ring.



Because all six carbon atoms and all six *p* orbitals in benzene are equivalent, it's impossible to define three localized π bonds in which a given *p* orbital overlaps only one neighboring *p* orbital. Rather, each *p* orbital overlaps equally well with both neighboring *p* orbitals, leading to a picture of benzene in which all six π electrons are free to move about the entire ring (Figure 4.3.2b). In resonance terms (Section 2.4 and Section 2.5), benzene is a hybrid of two equivalent forms. Neither form is correct by itself; the true structure of benzene is somewhere in between the two resonance forms but is impossible to draw with our usual conventions. Because of this resonance, benzene is more stable and less reactive than a typical alkene.

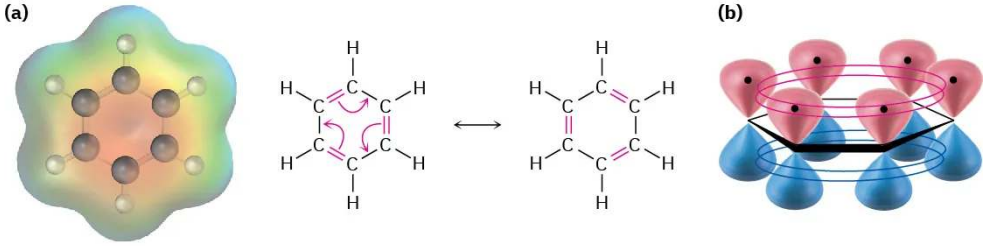
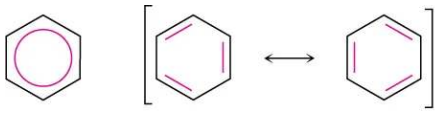


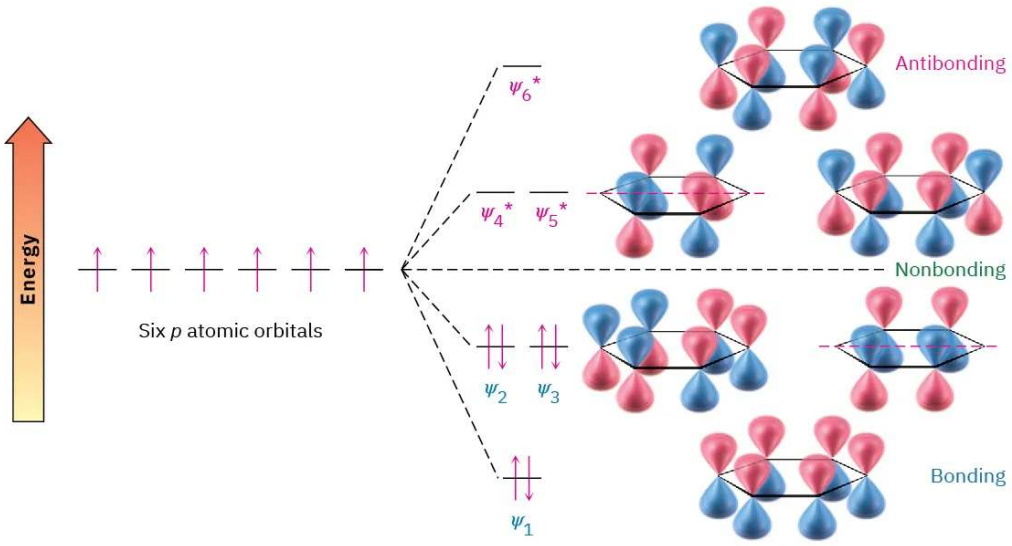
Figure 4.3.2: (a) An electrostatic potential map of benzene and (b) an orbital picture. Each of the six carbon atoms has a *p* orbital that can overlap equally well with neighboring *p* orbitals on both sides. As a result, all C–C bonds are equivalent and benzene must be represented as a hybrid of two resonance forms.

Chemists sometimes represent the two benzene resonance forms by using a circle to indicate the equivalence of the carbon–carbon bonds, but this representation has to be used carefully because it doesn't indicate the number of π electrons in the ring. (How many electrons does a circle represent?) In this book, benzene and other aromatic compounds will be represented by single line-bond structures. We'll be able to keep count of π electrons this way but must be aware of the limitations of the drawings.



Alternative representations of benzene. The "circle" representation must be used carefully since it doesn't indicate the number of *p* electrons in the ring.

Having just seen a resonance description of benzene, let's now look at the alternative molecular orbital description. We can construct π molecular orbitals for benzene just as we did for 1,3-butadiene in Section 14.1. If six *p* atomic orbitals combine in a cyclic manner, six benzene molecular orbitals result, as shown in Figure 4.3.3. The three low-energy molecular orbitals, denoted ψ_1, ψ_2, and ψ_3, are bonding combinations, and the three high-energy orbitals are antibonding.



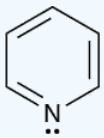
Six benzene molecular orbitals

Figure 4.3.3: The six benzene π molecular orbitals. The bonding orbitals ψ_2 and ψ_3 have the same energy and are said to be degenerate, as are the antibonding orbitals ψ_4* and ψ_5*. The orbitals ψ_3 and ψ_4* have no π electron density on two carbons because of a node passing through these atoms.

Note that the two bonding orbitals ψ_2 and ψ_3 have the same energy, as do the two antibonding orbitals ψ_4* and ψ_5*. Such orbitals with the same energy are said to be degenerate. Note also that the two orbitals ψ_3 and ψ_4* have nodes passing through ring carbon atoms, thereby leaving no π electron density on these carbons. The six *p* electrons of benzene occupy the three bonding molecular orbitals and are delocalized over the entire conjugated system, leading to the observed 150 kJ/mol stabilization of benzene.

? Exercise 4.3.1

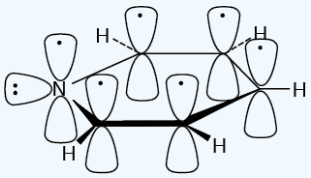
Pyridine is a flat, hexagonal molecule with bond angles of 120°. It undergoes substitution rather than addition and generally behaves like benzene. Draw a picture of the π orbitals of pyridine to explain its properties. Check your answer by looking ahead to Section 15.5.



Pyridine

Answer

Pyridine has an aromatic sextet of electrons.



Pyridine

This page titled 4.3: Structure and Stability of Benzene is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **15.2: Structure and Stability of Benzene** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

4.4: Aromaticity and the Hückel 4n + 2 Rule

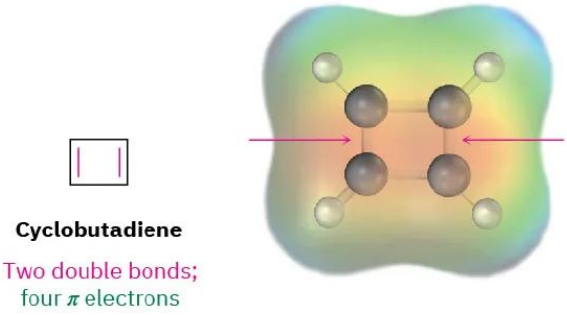
Let's list what we've said thus far about benzene and, by extension, about other benzene-like aromatic molecules.

- Benzene is cyclic and conjugated.
- Benzene is unusually stable, having a heat of hydrogenation 150 kJ/mol less negative than we might expect for a conjugated cyclic triene.
- Benzene is planar and has the shape of a regular hexagon. All bond angles are 120°, all carbon atoms are sp^2-hybridized, and all carbon–carbon bond lengths are 139 pm.
- Benzene undergoes substitution reactions that retain the cyclic conjugation rather than electrophilic addition reactions that would destroy it.
- Benzene can be described as a resonance hybrid whose structure is intermediate between two line-bond structures.

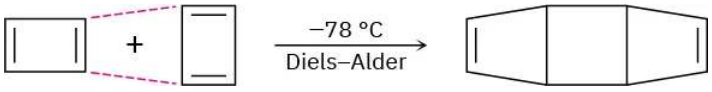
This list might seem to be a good description of benzene and other aromatic molecules, but it isn't enough. Something else, called the Hückel $4n + 2$ rule, is needed to complete a description of aromaticity. According to a theory devised in 1931 by the German physicist Erich Hückel, a molecule is aromatic only if it has a planar, monocyclic system of conjugation and contains a total of $4n + 2$ π *electrons*, where n is an integer (n = 0, 1, 2, 3,). In other words, only molecules with 2, 6, 10, 14, 18, π electrons can be aromatic. Molecules with $4n$ π electrons (4, 8, 12, 16,) can't be aromatic, even though they may be cyclic, planar, and apparently conjugated. In fact, planar, conjugated molecules with $4n$ π electrons are said to be antiaromatic because delocalization of their π electrons would lead to their destabilization.

Let's look at several examples to see how the Hückel $4n + 2$ rule works.

- **Cyclobutadiene** has four π electrons and is antiaromatic. As indicated by the electrostatic potential map, the π electrons are localized in two double bonds rather than delocalized around the ring.

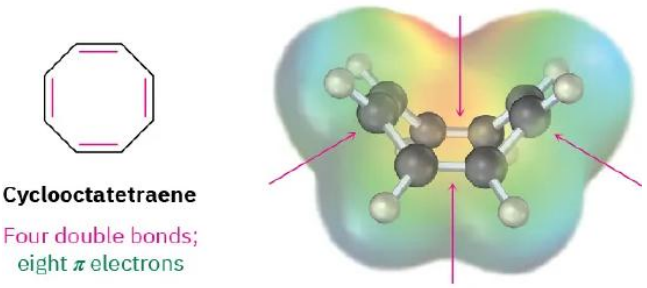


Cyclobutadiene is highly reactive and shows none of the properties associated with aromaticity. In fact, it was not even prepared until 1965, when Rowland Pettit at the University of Texas was able to make it at low temperature. Even at –78 °C, however, cyclobutadiene is so reactive that it dimerizes by a Diels–Alder reaction. One molecule behaves as a diene and the other as a dienophile.



- **Benzene** has six π electrons ($4n + 2 = 6$ when $n = 1$) and is aromatic.

- **Cyclooctatetraene** has eight π electrons, but when it was first prepared in 1911 by the German chemist Richard Willstätter, it was found not to be particularly stable. In fact, its π electrons are localized into four double bonds rather than delocalized around the ring, and the molecule is tub-shaped rather than planar. It has no cyclic conjugation because neighboring p orbitals don't have the necessary parallel alignment for overlap, and it resembles an open-chain polyene in its reactivity.



X-ray studies show that the C–C single bonds in cyclooctatetraene are 147 pm long and the double bonds are 134 pm long. In addition, the ^{1}H NMR spectrum shows a single sharp resonance line at 5.78 δ, a value characteristic of an alkene rather than an aromatic molecule.

What's so special about $4n + 2$ π electrons? Why do 2, 6, 10, 14 π electrons lead to aromatic stability, while other numbers of electrons do not? The answer comes from molecular orbital theory. When the energy levels of molecular orbitals for cyclic conjugated molecules are calculated, it turns out that there is always a single lowest-lying MO, above which the MOs come in degenerate pairs. Thus, when electrons fill the various molecular orbitals, it takes two electrons, or one pair, to fill the lowest-lying orbital and four electrons, or two pairs, to fill each of n succeeding energy levels—a total of $4n + 2$. Any other number would leave an energy level partially filled.

The six π molecular orbitals of benzene were shown previously, and their relative energies are shown again in Figure 4.4.1. The lowest-energy MO, ψ_1, occurs singly and contains two electrons. The next two lowest-energy orbitals, ψ_2 and ψ_3, are degenerate, and it therefore takes four electrons to fill both. The result is a stable six-π-electron aromatic molecule with filled bonding orbitals.

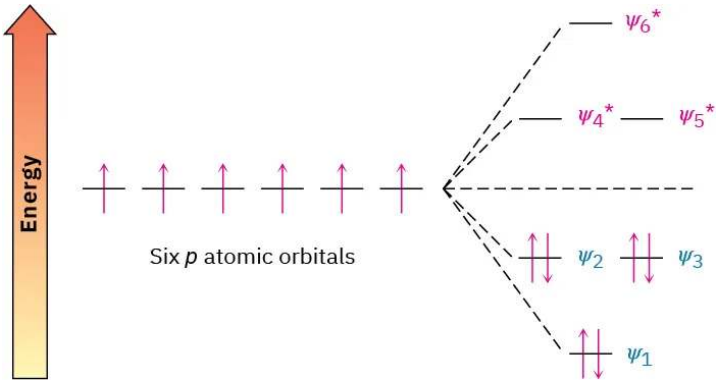
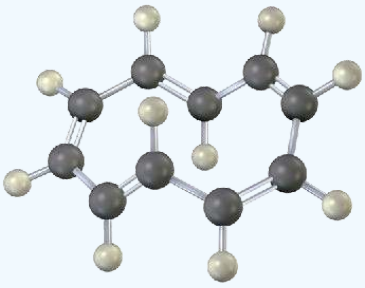


Figure 4.4.1: Energy levels of the six benzene π molecular orbitals. There is a single, lowest-energy orbital, above which the orbitals come in degenerate pairs.

? Exercise 4.4.1

To be aromatic, a molecule must have $4n + 2$ π electrons and must have a planar, monocyclic system of conjugation. Cyclodecapentaene fulfills one of these criteria but not the other and has resisted all attempts at synthesis. Explain.



Answer

Cyclodecapentaene is not flat because of steric interactions.

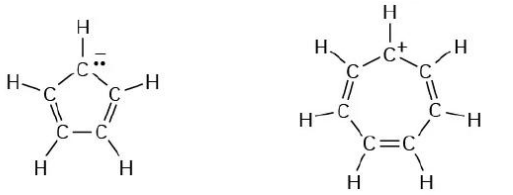
https://chem.libretexts.org/@go/page/564178

This page titled 4.4: Aromaticity and the Hückel 4n + 2 Rule is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **15.3: Aromaticity and the Hückel 4n + 2 Rule** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

4.5: Aromatic Ions

According to the Hückel criteria for aromaticity, a molecule must be cyclic, conjugated (nearly planar with a *p* orbital on each atom), and have $4n + 2$ π electrons. Nothing in this definition says that the number of π electrons must be the same as the number of atoms in the ring or that the substance must be neutral. In fact, the numbers can differ and the substance can be an ion. Thus, both the cyclopentadienyl anion and the cycloheptatrienyl cation are aromatic even though both are ions and neither contains a six-membered ring.



Cyclopentadienyl anion **Cycloheptatrienyl cation**

Six π electrons; aromatic ions

To understand why the cyclopentadienyl anion and the cycloheptatrienyl cation are aromatic, imagine starting from the related neutral hydrocarbons, 1,3-cyclopentadiene and 1,3,5-cycloheptatriene, and removing one hydrogen from the saturated CH_2 carbon in each. If that carbon then rehybridizes from sp^3 to sp^2, the resultant products would be fully conjugated, with a *p* orbital on every carbon. There are three ways in which the hydrogen might be removed.

- The hydrogen can be removed with *both* electrons ($H{:}^-$) from the C–H bond, leaving a carbocation as product.
- The hydrogen can be removed with *one* electron ($H\cdot$) from the C–H bond, leaving a carbon radical as product.
- The hydrogen can be removed with *no* electrons (H^+) from the C–H bond, leaving a carbanion as product.

All the potential products formed by removing a hydrogen from 1,3-cyclopentadiene and from 1,3,5-cycloheptatriene can be drawn with numerous resonance structures, but Hückel's rule predicts that only the six-π-electron cyclopentadienyl anion and cycloheptatrienyl cation can be aromatic. The other products are predicted by the $4n + 2$ rule to be unstable and antiaromatic (Figure 4.5.1).

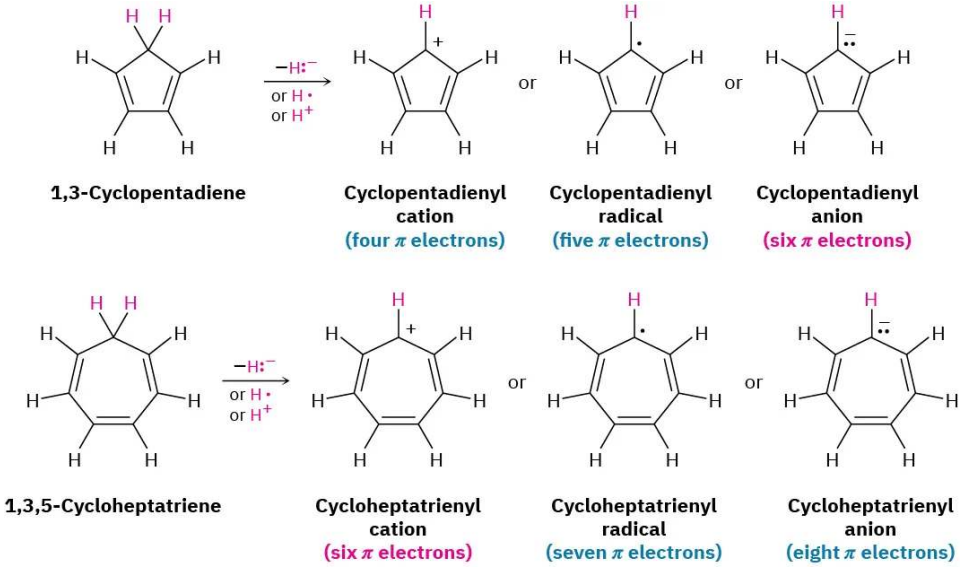


Figure 4.5.1: The aromatic six-π-electron cyclopentadienyl anion and the six-π-electron cycloheptatrienyl cation. The anion can be formed by removing a hydrogen ion (H^+) from the CH_2 group of 1,3-cyclopentadiene. The cation can be generated by removing a hydride ion ($H{:}^-$) from the CH_2 group of 1,3,5-cycloheptatriene.

In practice, both the four-π-electron cyclopentadienyl cation and the five-π-electron cyclopentadienyl radical are highly reactive and difficult to prepare. Neither shows any sign of the stability expected for an aromatic system. The six-π-electron cyclopentadienyl anion, by contrast, is easily prepared and remarkably stable (Figure 4.5.2*a*). In fact, the anion is so stable and

easily formed that 1,3-cyclopentadiene is one of the most acidic hydrocarbons known, with pK_a = 16, a value comparable to that of water!

In the same way, the seven-π-electron cycloheptatrienyl radical and eight-π-electron anion are reactive and difficult to prepare, while the six-π-electron cycloheptatrienyl cation is extraordinarily stable (Figure 4.5.2*b*). In fact, the cycloheptatrienyl cation was first prepared more than a century ago by reaction of 1,3,5-cycloheptatriene with Br_2, although its structure was not recognized at the time.

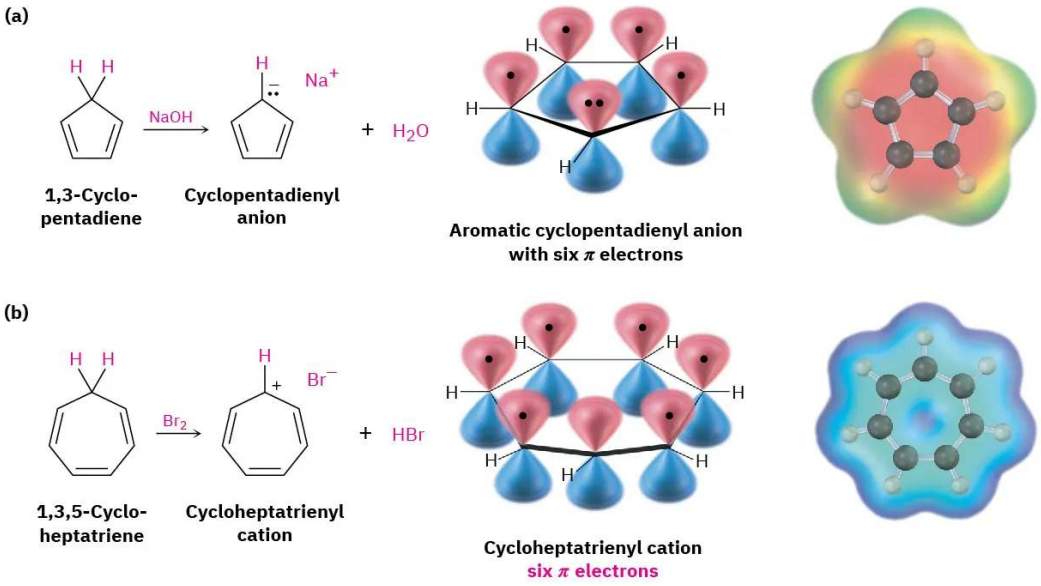


Figure 4.5.2: (a) The aromatic cyclopentadienyl anion, showing cyclic conjugation and six π electrons in five *p* orbitals, and (b) the aromatic cycloheptatrienyl cation, showing cyclic conjugation and six π electrons in seven *p* orbitals. Electrostatic potential maps indicate that both ions are symmetrical, with the charge equally shared among all atoms in each ring.

? Exercise 4.5.1

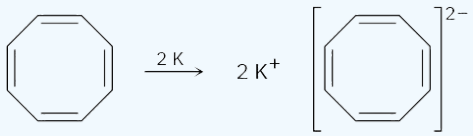
Draw the five resonance structures of the cyclopentadienyl anion. Are all carbon–carbon bonds equivalent? How many absorption lines would you expect to see in the ^{1}H NMR and ^{13}C NMR spectra of the anion?

Answer

All C–C bonds are equivalent; one resonance line in both ^{1}H and ^{13}C NMR spectra.

? Exercise 4.5.2

Cyclooctatetraene readily reacts with potassium metal to form the stable cyclooctatetraene dianion, $C_8H_8^{2-}$. Why do you suppose this reaction occurs so easily? What geometry do you expect for the cyclooctatetraene dianion?



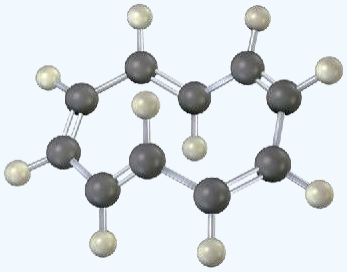
Answer

The cyclooctatetraenyl dianion is aromatic (ten π electrons) and flat.

Example 4.5.3

The relative energy levels of the five π molecular orbitals of the cyclopentadienyl system are similar to those in benzene. That is, there is a single lowest-energy MO, above which the orbitals come in degenerate pairs. Draw a diagram and tell which of the five orbitals are occupied in the cation, radical, and anion.

Answer



This page titled 4.5: Aromatic Ions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **15.4: Aromatic Ions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

4.6: Aromatic Heterocycles - Pyridine and Pyrrole

Look back once again at the definition of aromaticity in Section 15.3: a cyclic, conjugated molecule containing $4n + 2$ π electrons. Nothing in this definition says that the atoms in the ring must be *carbon*. In fact, *heterocyclic* compounds can also be aromatic. A heterocycle is a cyclic compound that contains atoms of more than one element in its ring, usually carbon along with nitrogen, oxygen, or sulfur. Pyridine and pyrimidine, for example, are six-membered heterocycles with carbon and nitrogen in their rings (Figure 4.6.1).

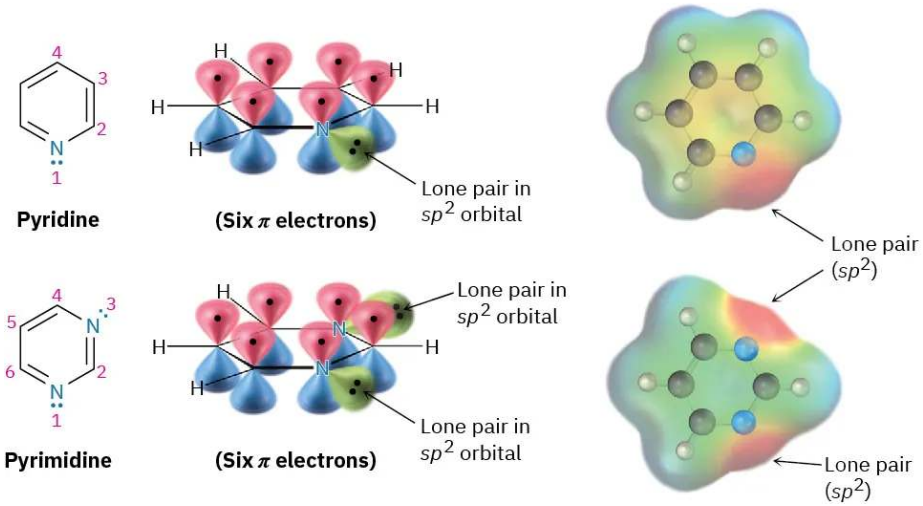


Figure 4.6.1: Pyridine and pyrimidine are nitrogen-containing aromatic heterocycles with π electron arrangements like that of benzene. Both have a lone pair of electrons on nitrogen in an sp^2 orbital in the plane of the ring.

Pyridine is much like benzene in its π electron structure. Each of the five sp^2-hybridized carbons has a *p* orbital perpendicular to the plane of the ring, and each *p* orbital contains one π electron. The nitrogen atom is also sp^2-hybridized and has one electron in a *p* orbital, bringing the total to six π electrons. The nitrogen lone-pair electrons (red in an electrostatic potential map) are in a sp^2 orbital in the plane of the ring and are not part of the aromatic π system. Pyrimidine, also shown in Figure 4.6.1), is a benzene analog that has two nitrogen atoms in a six-membered, unsaturated ring. Both nitrogens are sp^2-hybridized, and each contributes one electron to the aromatic π system.

Pyrrole (spelled with two *r*'s and one *l*) and imidazole are *five*-membered heterocycles, yet both have *six* π electrons and are aromatic. In pyrrole, each of the four sp^2-hybridized carbons contributes one π electron and the sp^2-hybridized nitrogen atom contributes the two from its lone pair, which occupies a *p* orbital (Figure 4.6.2). Imidazole, also shown in (Figure 4.6.2, is an analog of pyrrole that has two nitrogen atoms in a five-membered, unsaturated ring. Both nitrogens are sp^2-hybridized, but one is in a double bond and contributes only one electron to the aromatic π system whereas the other is not in a double bond and contributes two from its lone pair.

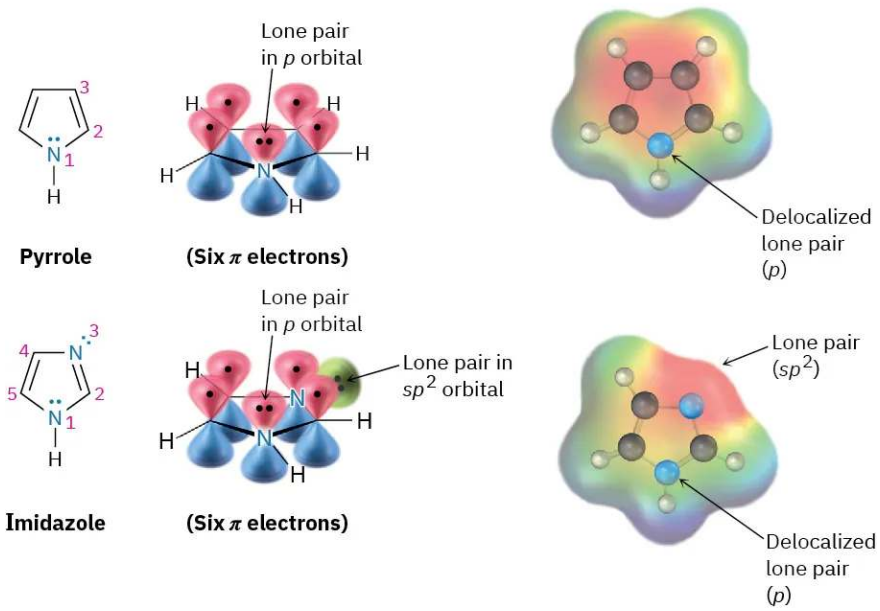
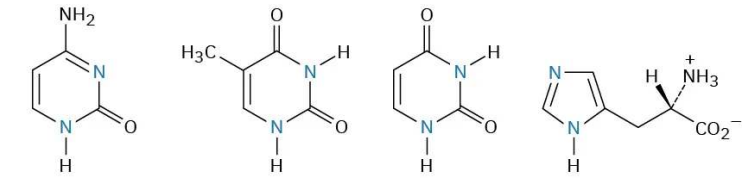


Figure 4.6.2: Pyrrole and imidazole are five-membered, nitrogen-containing heterocycles but have six-π-electron arrangements like that of the cyclopentadienyl anion. Both have a lone pair of electrons on nitrogen in a *p* orbital perpendicular to the ring.

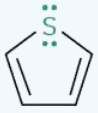
Note that nitrogen atoms have different roles depending on the structure of the molecule. The nitrogen atoms in pyridine and pyrimidine are both in double bonds and contribute only one π electron to the aromatic sextet, just as a carbon atom in benzene does. The nitrogen atom in pyrrole, however, is not in a double bond and contributes two π electrons (its lone pair) to the aromatic sextet. In imidazole, both kinds of nitrogen are present in the same molecule—a double-bonded "pyridine-like" nitrogen that contributes one π electron and a "pyrrole-like" nitrogen that contributes two.

Pyrimidine and imidazole rings are particularly important in biological chemistry. Pyrimidine, for instance, is the parent ring system in cytosine, thymine, and uracil, three of the five heterocyclic amine bases found in nucleic acids. An aromatic imidazole ring is present in histidine, one of the 20 amino acids found in proteins.



Worked Example 4.6.1: Accounting for the Aromaticity of a Heterocycle

Thiophene, a sulfur-containing heterocycle, undergoes typical aromatic substitution reactions rather than addition reactions. Why is thiophene aromatic?



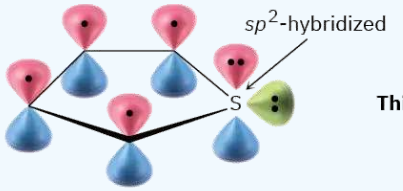
Thiophene

Strategy

Recall the requirements for aromaticity—a planar, cyclic, conjugated molecule with $4n + 2$ π electrons—and see how these requirements apply to thiophene.

Solution

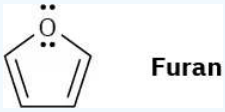
Thiophene is the sulfur analog of pyrrole. The sulfur atom is sp^2-hybridized and has a lone pair of electrons in a *p* orbital perpendicular to the plane of the ring. Sulfur also has a second lone pair of electrons in the ring plane.



Thiophene

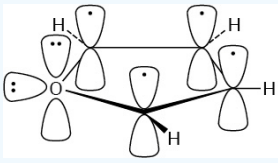
Exercise 4.6.1

Draw an orbital picture of furan to show how the molecule is aromatic.



Furan

Answer



Furan

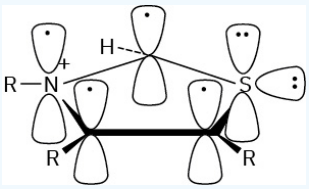
Exercise 4.6.2

Thiamin, or vitamin B_1, contains a positively charged five-membered nitrogen–sulfur heterocycle called a *thiazolium* ring. Explain why the thiazolium ring is aromatic.

Thiamin

Answer

The thiazolium ring has six π electrons.

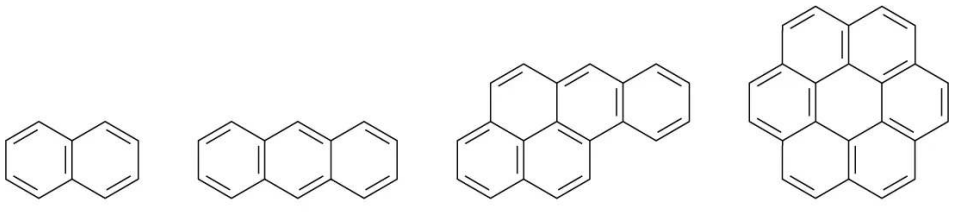


This page titled 4.6: Aromatic Heterocycles - Pyridine and Pyrrole is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

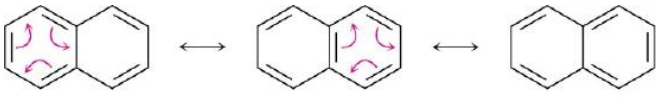
- **15.5: Aromatic Heterocycles - Pyridine and Pyrrole** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

4.7: Polycyclic Aromatic Compounds

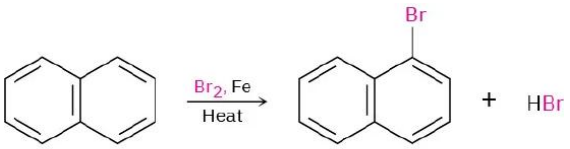
The Hückel rule is strictly applicable only to monocyclic compounds, but the general concept of aromaticity can be extended to include *polycyclic* aromatic compounds. Naphthalene, with two benzene-like rings fused together; anthracene, with three rings; benzo[a]pyrene, with five rings; and coronene, with six rings, are all well-known aromatic hydrocarbons. Benzo[a]pyrene is particularly interesting because it is one of the cancer-causing substances found in tobacco smoke.



All polycyclic aromatic hydrocarbons can be represented by a number of different resonance forms. Naphthalene, for instance, has three.



Naphthalene and other polycyclic aromatic hydrocarbons show many of the chemical properties associated with aromaticity. Thus, measurement of its heat of hydrogenation shows an aromatic stabilization energy of approximately 250 kJ/mol (60 kcal/mol). Furthermore, naphthalene reacts slowly with electrophiles such as Br_2 to give substitution products rather than double-bond addition products.



The aromaticity of naphthalene is explained by the orbital picture in Figure 4.7.1. Naphthalene has a cyclic, conjugated π electron system, with *p* orbital overlap both along the ten-carbon periphery of the molecule and across the central bond. Because ten π electrons is a Hückel number, there is π electron delocalization and consequent aromaticity in naphthalene.

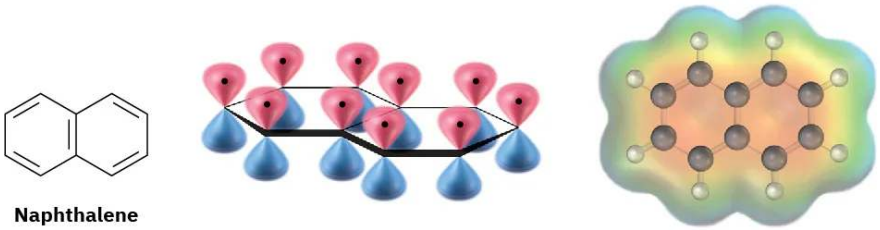
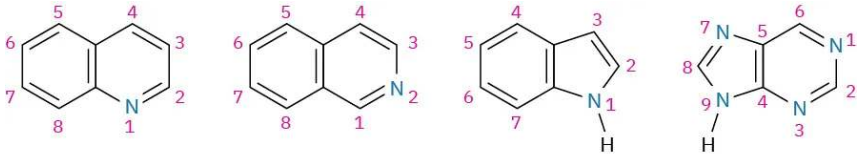


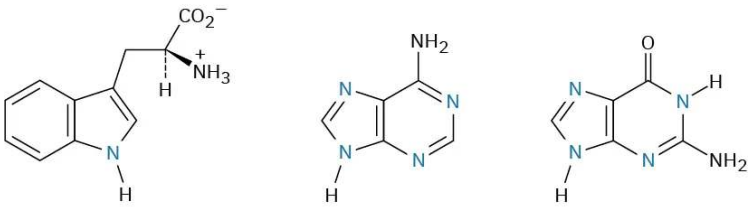
Figure 4.7.1: An orbital picture and electrostatic potential map of naphthalene, showing that the ten π electrons are fully delocalized throughout both rings.

Just as there are heterocyclic analogs of benzene, there are also many heterocyclic analogs of naphthalene. Among the most common are quinoline, isoquinoline, indole, and purine. Quinoline, isoquinoline, and purine all contain pyridine-like nitrogens that are part of a double bond and contribute one electron to the aromatic π system. Indole and purine both contain pyrrole-like nitrogens that contribute two π electrons.

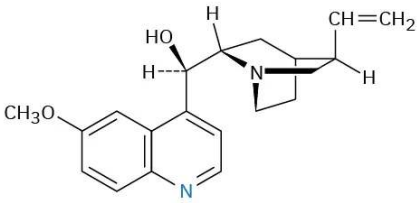


Quinoline **Isoquinoline** **Indole** **Purine**

Among the many biological molecules that contain polycyclic aromatic rings, the amino acid tryptophan contains an indole ring and the antimalarial drug quinine contains a quinoline ring. Adenine and guanine, two of the five heterocyclic amine bases found in nucleic acids, have rings based on purine.



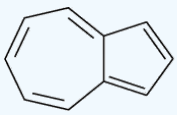
Tryptophan (an amino acid) **Adenine (in DNA and RNA)** **Guanine (in DNA and RNA)**



Quinine (an antimalarial agent)

Exercise 4.7.1

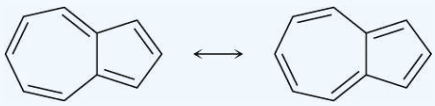
Azulene, a beautiful blue hydrocarbon, is an isomer of naphthalene. Is azulene aromatic? Draw a second resonance form of azulene in addition to that shown.



Azulene

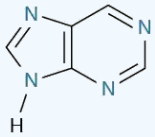
Answer

Yes, it's aromatic.



Exercise 4.7.2

How many electrons does each of the four nitrogen atoms in purine contribute to the aromatic π system?



Purine

Answer

The three nitrogens in double bonds each contribute one; the remaining nitrogen contributes two.

This page titled 4.7: Polycyclic Aromatic Compounds is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **15.6: Polycyclic Aromatic Compounds** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

4.8: Spectroscopy of Aromatic Compounds

Infrared Spectroscopy

As we saw in the brief introduction to infrared spectroscopy (Section 12.8), aromatic rings show a characteristic C–H stretching absorption at 3030 cm^{-1} and a series of peaks in the 1450 to 1600 cm^{-1} range of the infrared spectrum. The aromatic C–H band at 3030 cm^{-1} generally has low intensity and occurs just to the left of a typical saturated C–H band.

As many as four absorptions are sometimes observed in the 1450 to 1600 cm^{-1} region because of the complex molecular motions of the ring itself. Two bands, one at 1500 cm^{-1} and one at 1600 cm^{-1}, are usually the most intense. In addition, aromatic compounds show weak absorptions in the 1660 to 2000 cm^{-1} region and strong absorptions in the 690 to 900 cm^{-1} range due to C–H out-of-plane bending. The exact position of both sets of absorptions is diagnostic of the substitution pattern of the aromatic ring (Figure 12.24 in Section 12.8).

Monosubstituted:	690–710 cm^{-1}		**1,2,4-Trisubstituted:**	780–830 cm^{-1}
	730–770 cm^{-1}			870–900 cm^{-1}
***o*-Disubstituted:**	735–770 cm^{-1}		**1,2,3-Trisubstituted:**	670–720 cm^{-1}
***m*-Disubstituted:**	690–710 cm^{-1}			750–790 cm^{-1}
	810–850 cm^{-1}		**1,3,5-Trisubstituted:**	660–700 cm^{-1}
***p*-Disubstituted:**	810–840 cm^{-1}			830–900 cm^{-1}

The IR spectrum of toluene in Figure 4.8.1 shows these characteristic absorptions.

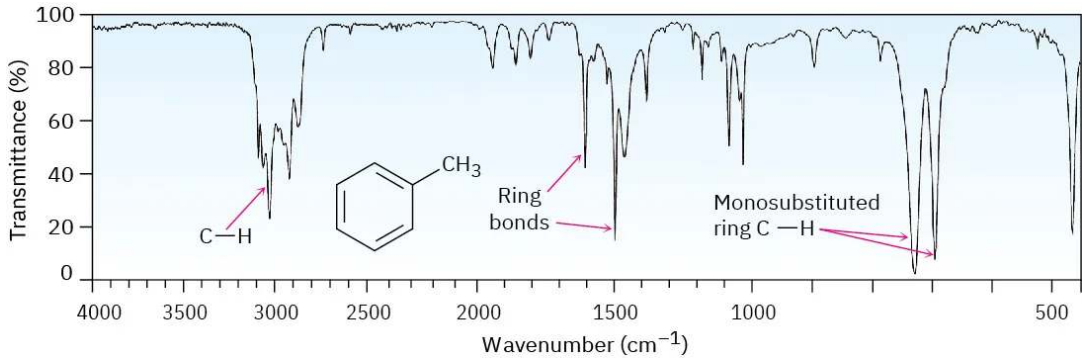


Figure 4.8.1: The infrared spectrum of toluene.

Ultraviolet Spectroscopy

Aromatic rings are detectable by ultraviolet spectroscopy because they contain a conjugated π electron system. In general, aromatic compounds show a series of bands, with a fairly intense absorption near 205 nm and a less intense absorption in the 255 to 275 nm range. The presence of these bands in the ultraviolet spectrum of a molecule is a sure indication of an aromatic ring. Figure 4.8.2 shows the ultraviolet spectrum of benzene.

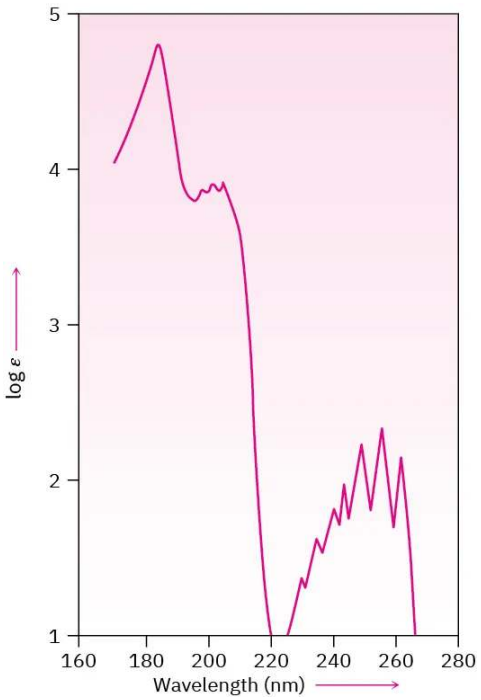


Figure 4.8.2: Ultraviolet spectrum of benzene. There are primary bands at 184 and 202 nm and secondary (fine-structure) bands at 255 nm.

Nuclear Magnetic Resonance Spectroscopy

Aromatic hydrogens are strongly deshielded by the ring and absorb between 6.5 and 8.0 δ. The spins of nonequivalent aromatic protons on substituted rings often couple with each other, giving rise to spin–spin splitting patterns that can identify the substitution of the ring.

Much of the difference in chemical shift between aromatic protons (6.5–8.0 δ) and vinylic protons (4.5–6.5 δ) is due to a property of aromatic rings called ring-current. When an aromatic ring is oriented perpendicular to a strong magnetic field, the electrons circulate around the ring, producing a small local magnetic field. This induced field opposes the applied field in the middle of the ring but reinforces the applied field outside the ring (Figure 4.8.3). Aromatic protons therefore experience an effective magnetic field greater than the applied field and come into resonance at a lower applied field.

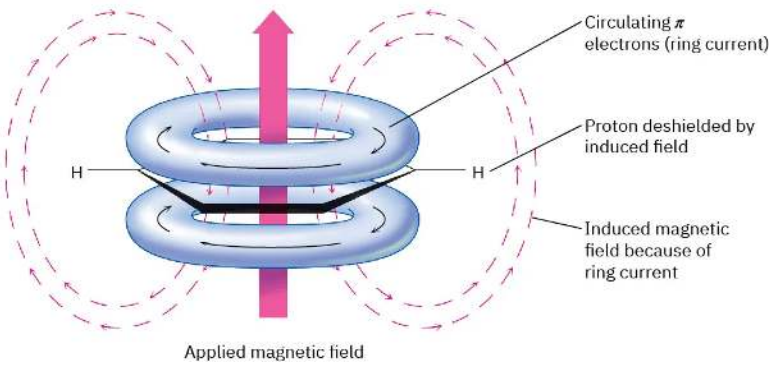
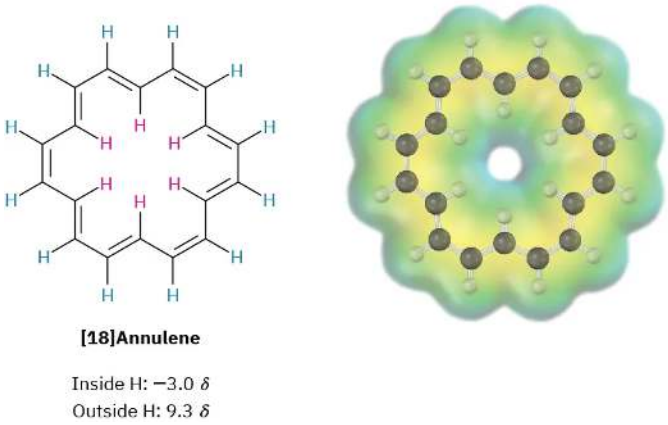


Figure 4.8.3: The origin of aromatic ring-current. Aromatic protons are deshielded by the induced magnetic field caused by delocalized π electrons circulating around the aromatic ring.

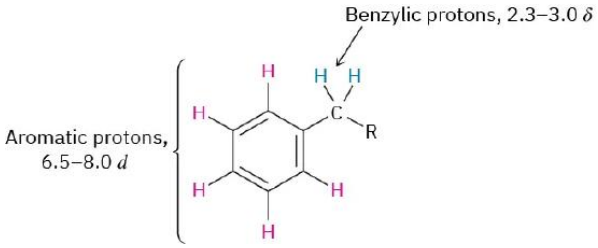
Note that the aromatic ring-current produces different effects inside and outside the ring. If a ring were large enough to have both "inside" and "outside" protons, the protons on the outside would be deshielded and absorb at a field lower than normal but those on the inside would be shielded and absorb at a field higher than normal. This prediction has been strikingly confirmed by studies on [18]annulene, an 18-π-electron cyclic conjugated polyene that contains a Hückel number of electrons ($4n + 2 = 18$ when $n = 4$). The six inside protons of [18]annulene are strongly shielded by the aromatic ring-current and absorb at –3.0 δ (that is, 3.0 ppm

upfield from TMS, off the normal chart), while the 12 outside protons are strongly deshielded and absorb in the typical aromatic region at 9.3 ppm downfield from TMS.



The presence of a ring-current is characteristic of all Hückel aromatic molecules and is a good test of aromaticity. For example, benzene, a six-π-electron aromatic molecule, absorbs at 7.37 δ because of its ring-current, but cyclooctatetraene, an eight-π-electron nonaromatic molecule, absorbs at 5.78 δ.

Hydrogens on carbon next to aromatic rings—*benzylic* hydrogens—also show distinctive absorptions in the NMR spectrum. Benzylic protons normally absorb downfield from other alkane protons in the region from 2.3 to 3.0 δ.



The ^{1}H NMR spectrum of *p*-bromotoluene, shown in Figure 4.8.4, displays many of the features just discussed. The aromatic protons appear as two doublets at 7.04 and 7.37 δ, and the benzylic methyl protons absorb as a sharp singlet at 2.26 δ. Integration of the spectrum shows the expected 2 : 2 : 3 ratio of peak areas.

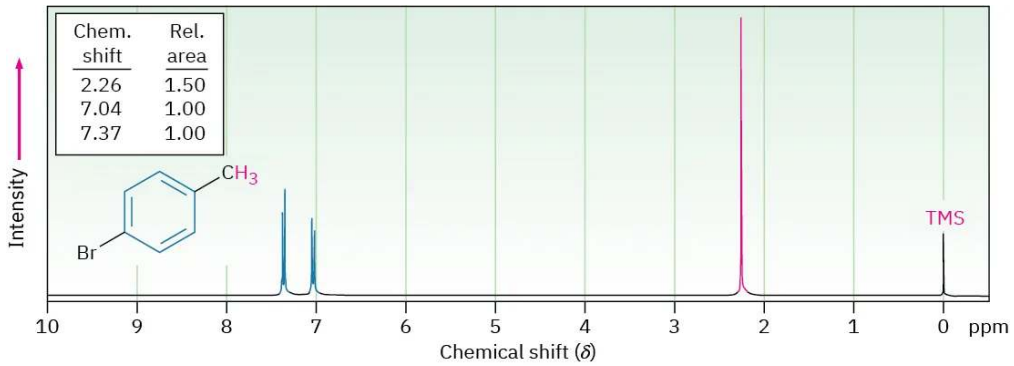


Figure 4.8.4: The ^{1}H NMR spectrum of *p*-bromotoluene.

The carbon atoms in an aromatic ring typically absorb in the range 110 to 140 δ in the ^{13}C NMR spectrum, as indicated by the examples in Figure 4.8.5. These resonances are easily distinguished from those of alkane carbons but occur in the same range as alkene carbons. Thus, the presence of ^{13}C absorptions at 110 to 140 δ does not by itself establish the presence of an aromatic ring. Supporting evidence from infrared, ultraviolet, or ^{1}H NMR spectra is needed.

Figure 4.8.5: Some ^{13}C NMR absorptions of aromatic compounds (δ units).

This page titled 4.8: Spectroscopy of Aromatic Compounds is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **15.7: Spectroscopy of Aromatic Compounds** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

4.9: Chemistry Matters—Aspirin, NSAIDs, and COX-2 Inhibitors

Whatever the cause—whether tennis elbow, a sprained ankle, or a wrenched knee—pain and inflammation seem to go together. They are, however, different in their origin, and powerful drugs are available for treating each separately. Codeine, for example, is a powerful *analgesic*, or pain reliever, used in the management of debilitating pain, while cortisone and related steroids are potent *anti-inflammatory* agents, used for treating arthritis and other crippling inflammations. For minor pains and inflammation, both problems are often treated together by using a common over-the-counter medication called an *NSAID*, or *nonsteroidal anti-inflammatory drug*.

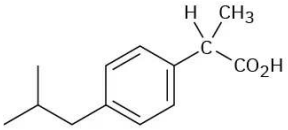
One of the most common NSAIDs is aspirin, or acetylsalicylic acid, whose use goes back to the late 1800s. It had been known from before the time of Hippocrates in 400 BC that fevers could be lowered by chewing the bark of willow trees. The active agent in willow bark was found in 1827 to be an aromatic compound called *salicin*, which could be converted by reaction with water into salicyl alcohol and then oxidized to give salicylic acid. Salicylic acid turned out to be even more effective than salicin for reducing fevers and to have analgesic and anti-inflammatory action as well. Unfortunately, it also turned out to be too corrosive to the walls of the stomach for everyday use. Conversion of the phenol –OH group into an acetate ester, however, yielded acetylsalicylic acid, which proved just as potent as salicylic acid but less corrosive to the stomach.

Figure 4.9.1: Many athletes rely on NSAIDs to help with pain and soreness. (credit: “Dillon Gee delivers a pitch” by Arturo Pardavila III/Wikimedia Commons, CC BY 2.0)

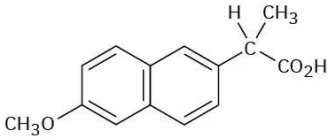
Salicyl alcohol **Salicylic acid** **Acetylsalicylic acid (aspirin)**

Although extraordinary in its effect, aspirin is also more dangerous than commonly believed. 15 g of aspirin would be fatal to a child of 9–10 years, and 10 g would be lethal for a 6-year-old, and aspirin can cause stomach bleeding and allergic reactions in long-term users. Even more serious is a condition called *Reye’s syndrome*, a potentially fatal reaction to aspirin sometimes seen in children recovering from the flu. As a result of these problems, numerous other NSAIDs have been developed in the last several decades, most notably ibuprofen and naproxen.

Like aspirin, both ibuprofen and naproxen are relatively simple aromatic compounds containing a side-chain carboxylic acid group. Ibuprofen, sold under the brand names Advil, Nuprin, Motrin, and others, has roughly the same potency as aspirin but is less prone to causing an upset stomach. Naproxen, sold under the names Aleve and Naprosyn, also has about the same potency as aspirin but remains active in the body six times longer.



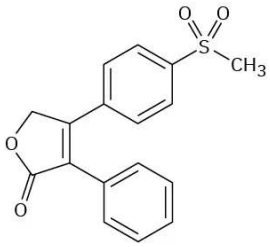
Ibuprofen
(Advil, Nuprin, Motrin)



Naproxen
(Aleve, Naprosyn)

Aspirin and other NSAIDs function by blocking the cyclooxygenase (COX) enzymes that carry out the body's synthesis of prostaglandins (Section 8.11 and Section 27.4). There are two forms of the enzyme: COX-1, which carries out the normal physiological production of prostaglandins, and COX-2, which mediates the body's response to arthritis and other inflammatory conditions. Unfortunately, both COX-1 and COX-2 enzymes are blocked by aspirin, ibuprofen, and other NSAIDs, thereby shutting down not only the response to inflammation but also various protective functions, including the control mechanism for production of acid in the stomach.

Medicinal chemists have therefore devised a number of drugs that act as selective inhibitors of only the COX-2 enzyme. Inflammation is thereby controlled without blocking protective functions. Originally heralded as a breakthrough in arthritis treatment, the first generation of COX-2 inhibitors, including rofecoxib, (marketed as Vioxx), celecoxib, (marketed as Celebrex), and Valdecoxib (marketed as Bextra), turned out to cause potentially serious heart problems, particularly in elderly or compromised patients. As a result, all three Cox-2 inhibitors were removed from the U.S. and other markets. Further studies, however, concluded that in proper doses the Cox-2 inhibitors were little different from other NSAIDs, and Vioxx returned to the market in 2017 for topical treatment of osteoarthritis.



Rofecoxib
(Vioxx)

This page titled 4.9: Chemistry Matters—Aspirin, NSAIDs, and COX-2 Inhibitors is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **15.8: Chemistry Matters—Aspirin, NSAIDs, and COX-2 Inhibitors** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

4.10: Key Terms

- antiaromatic
- arene
- aromatic
- benzyl group
- degenerate orbitals
- heterocycle
- Hückel $4n + 2$ rule
- meta (*m*)
- ortho (*o*)
- para (*p*)
- phenyl group
- ring-current

This page titled 4.10: Key Terms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **15.9: Key Terms** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

4.11: Summary

Aromatic rings are a common part of many biological structures and are particularly important in nucleic acid chemistry and in the chemistry of several amino acids. In this chapter, we've seen how and why aromatic compounds are different from such apparently related compounds as cycloalkenes.

The word **aromatic** is used for historical reasons to refer to the class of compounds related structurally to benzene. Aromatic compounds are systematically named according to IUPAC rules, but many common names are also used. Disubstituted benzenes are referred to as **ortho** (1,2 disubstituted), **meta** (1,3 disubstituted), or **para** (1,4 disubstituted) derivatives. The C_6H_5– unit itself is referred to as a **phenyl** group, and the $C_6H_5CH_2$– unit is a **benzyl** group.

Benzene is described by valence-bond theory as a resonance hybrid of two equivalent structures and is described by molecular orbital theory as a planar, cyclic, conjugated molecule with six π electrons. According to the **Hückel rule**, a molecule must have **4*n* + 2 π electrons**, where n = 0, 1, 2, 3, and so on, to be aromatic. Planar, cyclic, conjugated molecules with other numbers of π electrons are **antiaromatic**.

Other substances besides benzene-like compounds are also aromatic. The cyclopentadienyl anion and the cycloheptatrienyl cation, for instance, are aromatic ions. Pyridine and pyrimidine are six-membered, nitrogen-containing, aromatic **heterocycles**. Pyrrole and imidazole are five-membered, nitrogen-containing heterocycles. Naphthalene, quinoline, indole, and many others are polycyclic aromatic compounds.

Aromatic compounds have the following characteristics:

- Aromatic compounds are cyclic, planar, and conjugated.
- Aromatic compounds are unusually stable. Benzene, for instance, has a heat of hydrogenation 150 kJ/mol less than we might expect for a cyclic triene.
- Aromatic compounds react with electrophiles to give substitution products, in which cyclic conjugation is retained, rather than addition products, in which conjugation is destroyed.
- Aromatic compounds have $4n + 2$ π electrons, which are delocalized over the ring.

This page titled 4.11: Summary is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **15.10: Summary** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

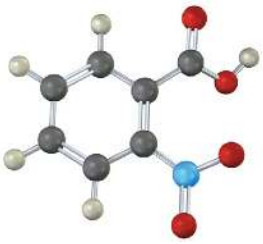
4.12: Additional Problems

15 • Additional Problems

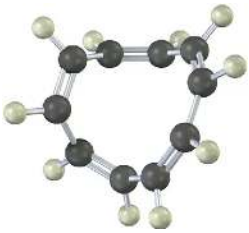
Visualizing Chemistry

PROBLEM 15-13 Give IUPAC names for the following substances (red = O, blue = N):

(a)

(b) 

PROBLEM 15-14 All-cis cyclodecapentaene is a stable molecule that shows a single absorption in its ^{1}H NMR spectrum at 5.67 δ. Tell whether it is aromatic, and explain its NMR spectrum.

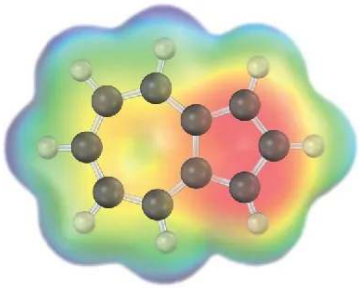


PROBLEM 15-15 1,6-Methanonaphthalene has an interesting ^{1}H NMR spectrum in which the eight hydrogens around the perimeter absorb at 6.9 to 7.3 δ, while the two CH_2 protons absorb at –0.5 δ. Tell whether it is aromatic, and explain its NMR spectrum.

1,6-Methanonaphthalene

PROBLEM 15-16 The following molecular model is that of a carbocation. Draw two resonance structures for the carbocation, indicating the positions of the double bonds.

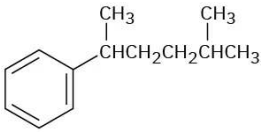
PROBLEM 15-17 Azulene, an isomer of naphthalene, has a remarkably large dipole moment for a hydrocarbon (μ = 1.0 D). Explain, using resonance structures.

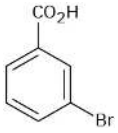


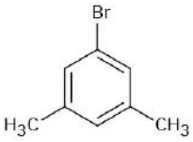
Azulene

Naming Aromatic Compounds

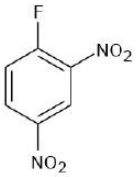
PROBLEM 15-18 Give IUPAC names for the following compounds:

(a) 

(b) 

(c) 

(d)

(e) 

(f)

PROBLEM 15-19 Draw structures corresponding to the following names:

(a) 3-Methyl-1,2-benzenediamine (b) 1,3,5-Benzenetriol (c) 3-Methyl-2-phenylhexane

(d) *o*-Aminobenzoic acid (e) *m*-Bromophenol (f) 2,4,6-Trinitrophenol (picric acid)

PROBLEM 15-20 Draw and name all possible isomers of the following:

(a) Dinitrobenzene (b) Bromodimethylbenzene (c) Trinitrophenol

PROBLEM 15-21 Draw and name all possible aromatic compounds with the formula C_7H_7Cl.

PROBLEM 15-22 Draw and name all possible aromatic compounds with the formula C_8H_9Br. (There are 14.)

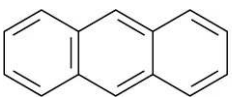
Structure of Aromatic Compounds

PROBLEM 15-23 Propose structures for aromatic hydrocarbons that meet the following descriptions:

- (a) C_9H_{12}; gives only one $C_9H_{11}Br$ product on substitution of a hydrogen on the aromatic ring with bromine
- (b) $C_{10}H_{14}$; gives only one $C_{10}H_{13}Cl$ product on substitution of a hydrogen on the aromatic ring with chlorine
- (c) C_8H_{10}; gives three C_8H_9Br products on substitution of a hydrogen on the aromatic ring with bromine
- (d) $C_{10}H_{14}$; gives two $C_{10}H_{13}Cl$ products on substitution of a hydrogen on the aromatic ring with chlorine

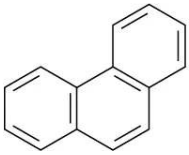
PROBLEM 15-24 Look at the three resonance structures of naphthalene shown in Section 15.6, and account for the fact that not all carbon–carbon bonds have the same length. The C1–C2 bond is 136 pm long, whereas the C2–C3 bond is 139 pm long.

PROBLEM 15-25 Anthracene has four resonance structures, one of which is shown. Draw the other three.



Anthracene

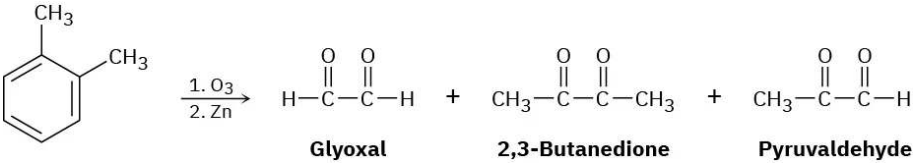
PROBLEM 15-26 Phenanthrene has five resonance structures, one of which is shown. Draw the other four.



Phenanthrene

PROBLEM 15-27 Look at the five resonance structures for phenanthrene (Problem 26), and predict which of its carbon–carbon bonds is shortest.

PROBLEM 15-28 In 1932, A. A. Levine and A. G. Cole studied the ozonolysis of *o*-xylene and isolated three products: glyoxal, 2,3-butanedione, and pyruvaldehyde:



Glyoxal **2,3-Butanedione** **Pyruvaldehyde**

In what ratio would you expect the three products to be formed if *o*-xylene is a resonance hybrid of two structures? The actual ratio found was 3 parts glyoxal, 1 part 2,3-butanedione, and 2 parts pyruvaldehyde. What conclusions can you draw about the structure of *o*-xylene?

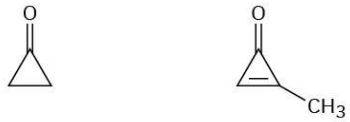
Aromaticity and Hückel's Rule

PROBLEM 15-29 3-Chlorocyclopropene, on treatment with $AgBF_4$, gives a precipitate of AgCl and a stable solution of a product that shows a single ^1H NMR absorption at 11.04 δ. What is a likely structure for the product, and what is its relation to Hückel's rule?

3-Chlorocyclopropene

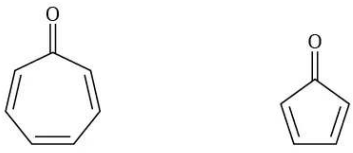
PROBLEM 15-30 Draw an energy diagram for the three molecular orbitals of the cyclopropenyl system (C_3H_3). How are these three molecular orbitals occupied in the cyclopropenyl anion, cation, and radical? Which of the three substances is aromatic according to Hückel's rule?

PROBLEM 15-31 Cyclopropanone is highly reactive because of its large amount of angle strain. Methylcyclopropenone, although even more strained than cyclopropanone, is nevertheless quite stable and can even be distilled. Explain, taking the polarity of the carbonyl group into account.



Cyclopropanone **Methylcyclopropenone**

PROBLEM 15-32 Cycloheptatrienone is stable, but cyclopentadienone is so reactive that it can't be isolated. Explain, taking the polarity of the carbonyl group into account.

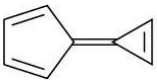


Cycloheptatrienone **Cyclopentadienone**

PROBLEM 15-33 Which would you expect to be most stable, cyclononatetraenyl radical, cation, or anion? (Cyclononatetraene has a ring of nine carbons and four double bonds.)

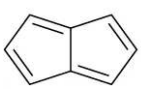
PROBLEM 15-34 How might you convert 1,3,5,7-cyclononatetraene to an aromatic substance?

PROBLEM 15-35 Calicene, like azulene (Problem 17), has an unusually large dipole moment for a hydrocarbon. Explain, using resonance structures.

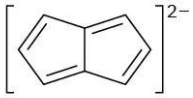


Calicene

PROBLEM 15-36 Pentalene is a most elusive molecule that has been isolated only at liquid-nitrogen temperature. The pentalene dianion, however, is well known and quite stable. Explain.



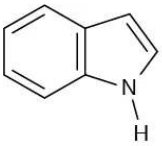
Pentalene



Pentalene dianion

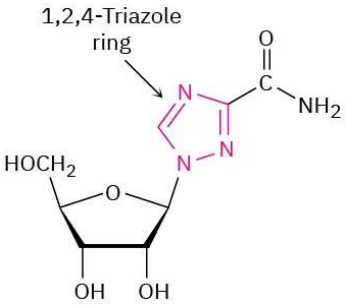
PROBLEM 15-37 Indole is an aromatic heterocycle that has a benzene ring fused to a pyrrole ring. Draw an orbital picture of indole.

- (a) How many π electrons does indole have?
- (b) What is the electronic relationship of indole to naphthalene?



Indole

PROBLEM 15-38 Ribavirin, an antiviral agent used against hepatitis C and viral pneumonia, contains a 1,2,4-triazole ring. Why is the ring aromatic?



Ribavirin

Spectroscopy

PROBLEM 15-39 Compound A, C_8H_{10}, yields three substitution products, C_8H_9Br, on reaction with Br_2. Propose two possible structures for A. The ^1H NMR spectrum of A shows a complex four-proton multiplet at 7.0 δ and a six-proton singlet at 2.30 δ. What is the structure of A?

PROBLEM 15-40 What is the structure of a hydrocarbon that has $M^+ = 120$ in its mass spectrum and has the following ^1H NMR spectrum?

7.25 δ (5 H, broad singlet); 2.90 δ (1 H, septet, J = 7 Hz); 1.22 δ (6 H, doublet, J = 7 Hz)

PROBLEM 15-41 Propose structures for compounds that fit the following descriptions:

(a) $C_{10}H_{14}$

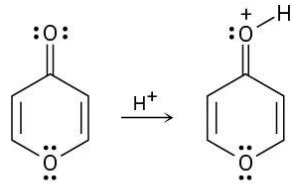
- ^1H NMR: 7.18 δ (4 H, broad singlet); 2.70 δ (4 H, quartet, J = 7 Hz); 1.20 δ (6 H, triplet, J = 7 Hz)
- IR absorption at 745 cm^{-1}

(b) $C_{10}H_{14}$

- ^{1}H NMR: 7.0 δ (4 H, broad singlet); 2.85 δ (1 H, septet, J = 8 Hz); 2.28 δ (3 H, singlet); 1.20 δ (6 H, doublet, J = 8 Hz)
- IR absorption at 825 cm^{-1}

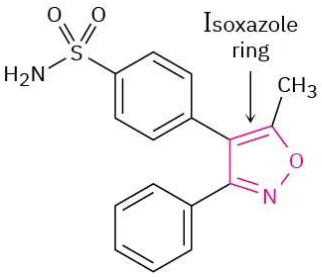
General Problems

PROBLEM 15-42 On reaction with acid, 4-pyrone is protonated on the carbonyl-group oxygen to give a stable cationic product. Using resonance structures and the Hückel 4n + 2 rule, explain why the protonated product is so stable.



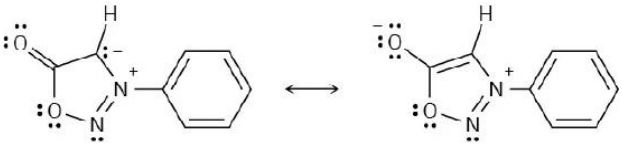
4-Pyrone

PROBLEM 15-43 Bextra, a COX-2 inhibitor once used in the treatment of arthritis, contains an isoxazole ring. Why is the ring aromatic?



Bextra

PROBLEM 15-44 *N*-Phenylsydnone, so-named because it was first studied at the University of Sydney, Australia, behaves like a typical aromatic molecule. Explain, using the Hückel 4n + 2 rule.



***N*-Phenylsydnone**

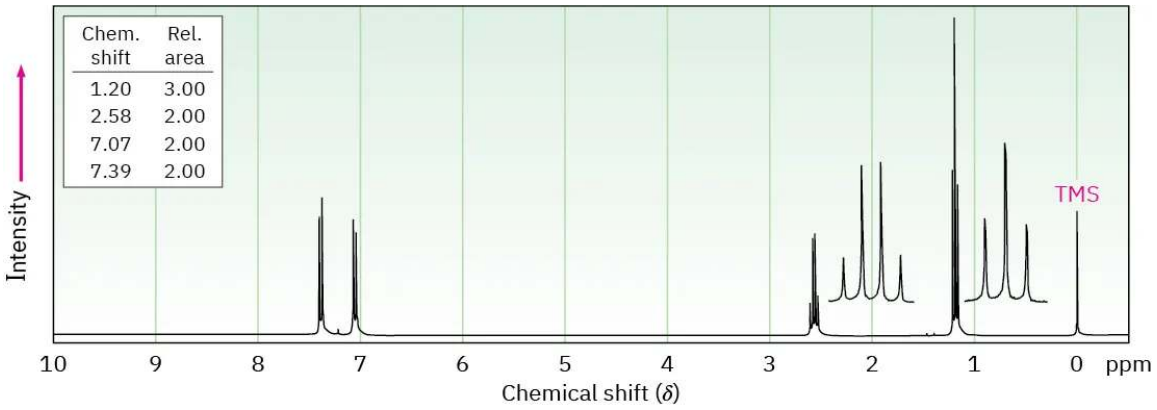
PROBLEM 15-45 Show the relative energy levels of the seven π molecular orbitals of the cycloheptatrienyl system. Tell which of the seven orbitals are filled in the cation, radical, and anion, and account for the aromaticity of the cycloheptatrienyl cation.

PROBLEM 15-46 1-Phenyl-2-butene has an ultraviolet absorption at λ_{max} = 208 nm (ε = 8000). On treatment with a small amount of strong acid, isomerization occurs and a new substance with λ_{max} = 250 nm (ε = 15,800) is formed. Propose a structure for this isomer, and suggest a mechanism for its formation.

PROBLEM 15-47 Propose structures for aromatic compounds that have the following <sup">1H NMR spectra:

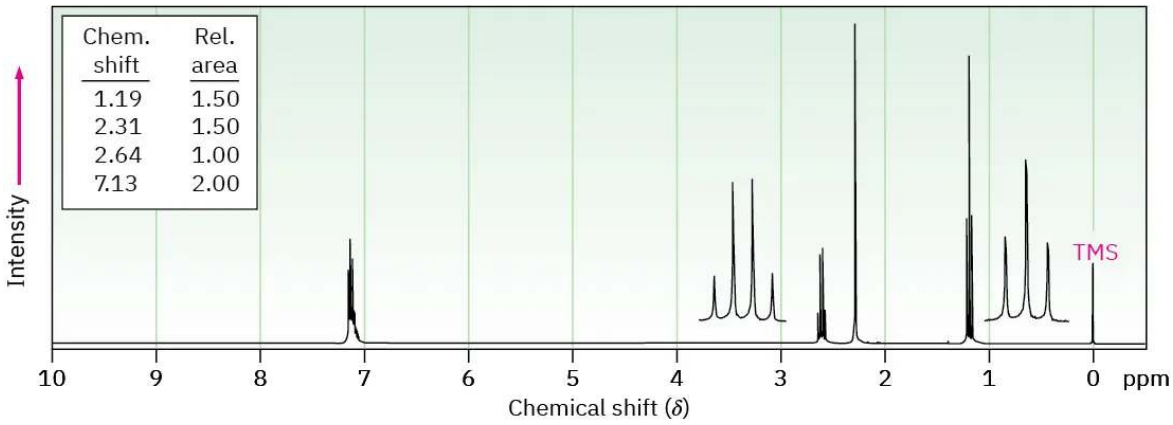
(a) C_8H_9Br

IR absorption at 820 cm^{-1}



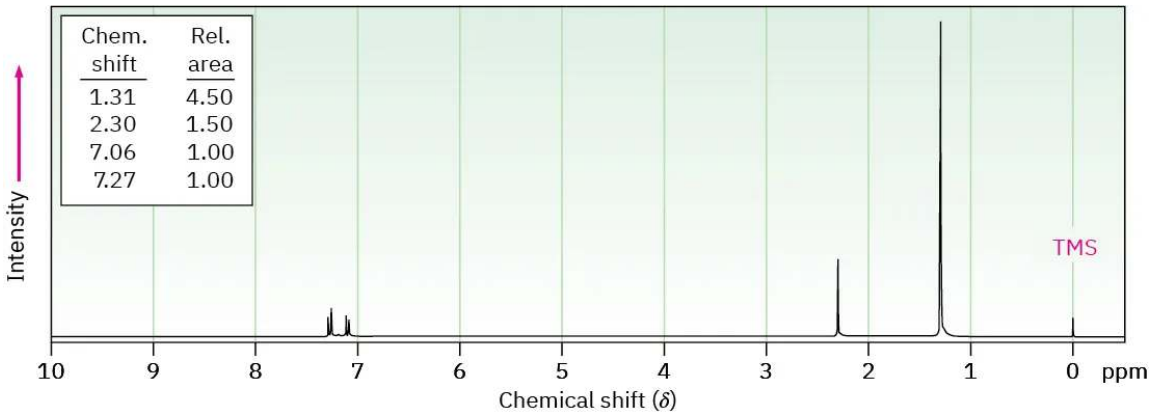
(b) C_9H_{12}

IR absorption at 750 cm^{-1}

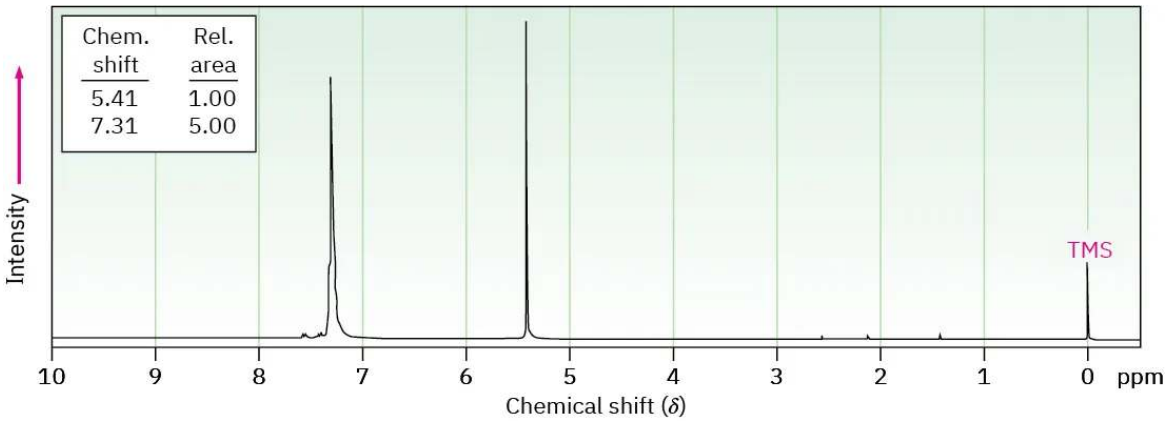


(c) $C_{11}H_{16}$

IR absorption at 820 cm^{-1}

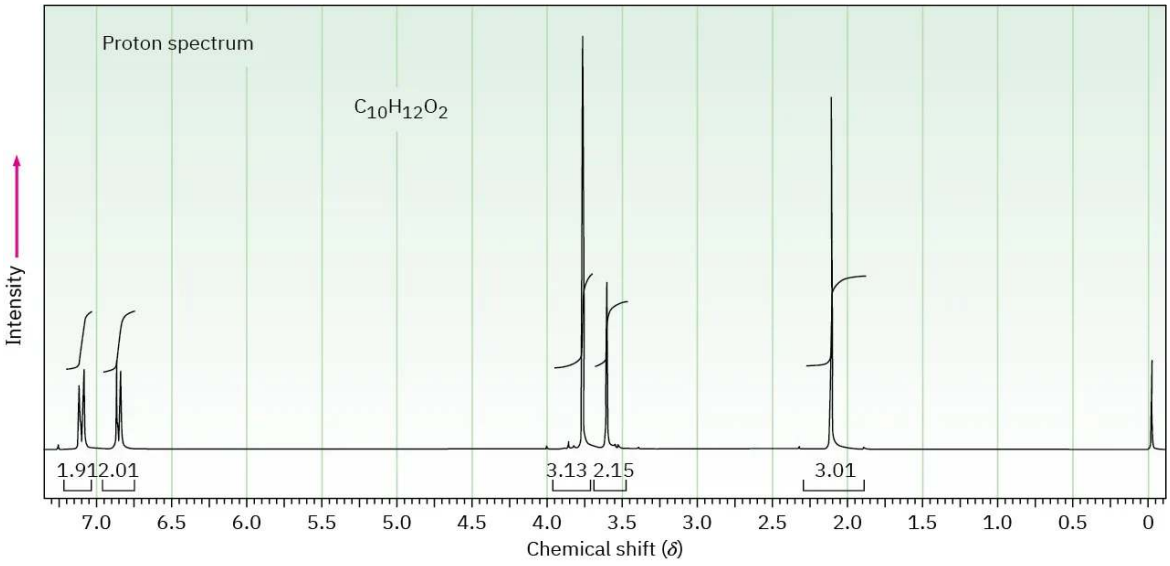


PROBLEM 15-48 Propose a structure for a molecule $C_{14}H_{12}$ that has the following ^1H NMR spectrum and has IR absorptions at 700, 740, and 890 cm^{-1}:



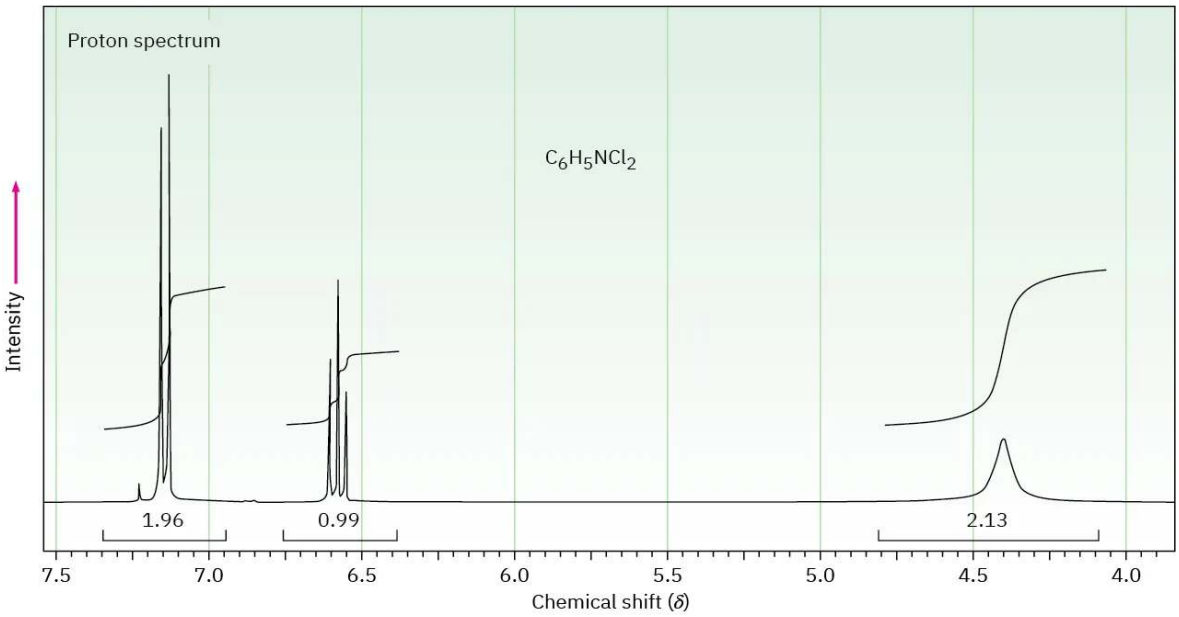
PROBLEM 15-49 The proton NMR spectrum for a compound with formula $C_{10}H_{12}O_2$ is shown. The infrared spectrum has a strong band at 1711 cm^{-1}. The normal carbon-13 NMR spectral results are tabulated along with the DEPT-135 and DEPT-90 information. Draw the structure of this compound.

Normal Carbon	DEPT-135	DEPT-90
29 ppm	Positive	No peak
50 ppm	Negative	No peak
55 ppm	Positive	No peak
114 ppm	Positive	Positive
126 ppm	No peak	No peak
130 ppm	Positive	Positive
159 ppm	No peak	No peak
207 ppm	No peak	No peak



PROBLEM 15-50 The proton NMR spectrum of a compound with formula $C_6H_5NCl_2$ is shown. The normal carbon-13 and DEPT experimental results are tabulated. The infrared spectrum shows peaks at 3432 and 3313 cm^{-1} and a series of medium-sized peaks between 1618 and 1466 cm^{-1}. Draw the structure of this compound.

Normal Carbon	DEPT-135	DEPT-90
118.0 ppm	Positive	Positive
119.5 ppm	No peak	No peak
128.0 ppm	Positive	Positive
140.0 ppm	No peak	No peak

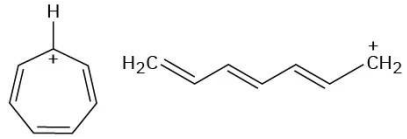


PROBLEM 15-51 Aromatic substitution reactions occur by addition of an electrophile such as Br^+ to an aromatic ring to yield an allylic carbocation intermediate, followed by loss of H^+. Show the structure of the intermediate formed by reaction of benzene with Br^+.

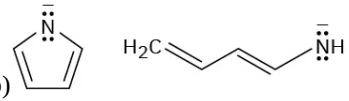
PROBLEM 15-52 The substitution reaction of toluene with Br_2 can, in principle, lead to the formation of three isomeric bromotoluene products. In practice, however, only *o*- and *p*-bromotoluene are formed in substantial amounts. The meta isomer is not formed. Draw the structures of the three possible carbocation intermediates (Problem 51), and explain why ortho and para products predominate over meta products.

PROBLEM 15-53 Look at the following aromatic anions and their linear counterparts, and draw all of the resonance forms for each. What patterns emerge?

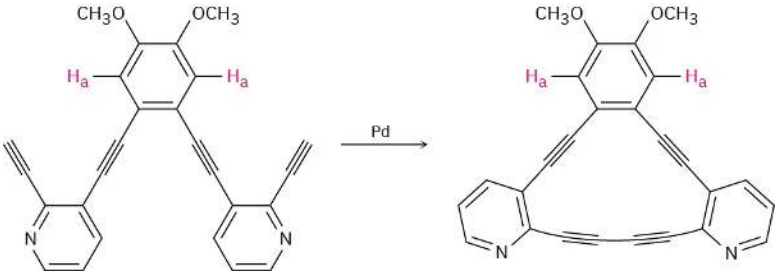
(a)



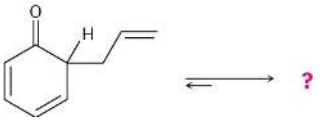
(b)



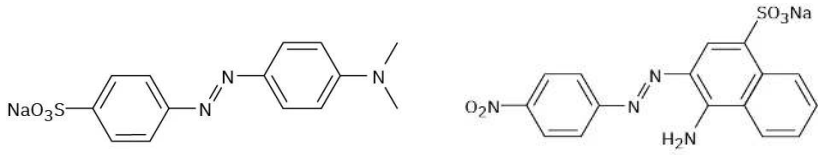
PROBLEM 15-54 After the following reaction, the chemical shift of H_a moves downfield from 6.98 ppm to 7.30 ppm. Explain.



PROBLEM 15-55 The following compound is the product initially formed in a Claisen rearrangement, which we'll see in Section 18.4. This product is not isolated, but tautomerizes to its enol form. Give the structure of the enol and provide an explanation as to why the enol tautomer is favored.



PROBLEM 15-56 Compounds called azo dyes are the major source of artificial color in textiles and food. Part of the reason for their intense coloring is the conjugation from an electron-donating group through the diazo bridge (−N=N−) to an electron-withdrawing group on the other side. For the following azo dyes, draw a resonance form that shows how the electron-donating group is related to the electron-withdrawing group on the other side of the diazo bridge. Used curved arrows to show how the electrons are reorganized.



This page titled 4.12: Additional Problems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **15.11: Additional Problems** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

CHAPTER OVERVIEW

5: Chemistry of Benzene - Electrophilic Aromatic Substitution

Learning Objectives

When you have completed Chapter 16, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. solve road-map problems that require an understanding of the chemistry discussed in this chapter and those that preceded it.
3. design multistep syntheses using the reactions discussed in this and the preceding chapters. In particular you should be prepared to show how an aromatic compound containing two or more substituents could be synthesized, taking care to introduce the substituents into the ring in the correct order.
4. define, and use in context, the key terms introduced.

In the preceding chapter, you studied the concept of aromaticity and spent considerable time on the theoretical aspects of the chemistry of aromatic compounds. In this chapter, you will begin to study the chemical reactions of aromatic compounds, focusing in particular on electrophilic aromatic substitution, and to a lesser extent on nucleophilic aromatic substitution. We will discuss, in detail, the mechanism of electrophilic substitution, paying particular attention to the factors that determine both the rate and position of substitution in those aromatic compounds which already have one or more substituents present in the aromatic ring. When we discuss nucleophilic aromatic substitution, you will see that it can be achieved by two different mechanisms, one of which involves the formation of an unusual looking intermediate, benzyne.

You will also see how alkyl and acyl groups can be introduced on to an aromatic ring; how, once introduced, alkyl groups can be converted to carboxyl groups; and how bromine can be introduced to the alkyl side chain of alkylbenzene. The latter reaction is particularly useful because the benzylic bromide so produced undergoes the reactions of a typical alkyl bromide, thus providing us with a synthetic route to a large variety of compounds.

5.1: Why This Chapter?
5.2: Electrophilic Aromatic Substitution Reactions - Bromination
5.3: Other Aromatic Substitutions
5.4: Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction
5.5: Substituent Effects in Electrophilic Substitutions
5.6: Trisubstituted Benzenes- Additivity of Effects
5.7: Nucleophilic Aromatic Substitution
5.8: Benzyne
5.9: Oxidation of Aromatic Compounds
5.10: Reduction of Aromatic Compounds
5.11: Synthesis of Polysubstituted Benzenes
5.12: Chemistry Matters—Combinatorial Chemistry
5.13: Key Terms
5.14: Summary
5.15: Summary of Reactions
5.16: Additional Problems

This page titled 5: Chemistry of Benzene - Electrophilic Aromatic Substitution is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

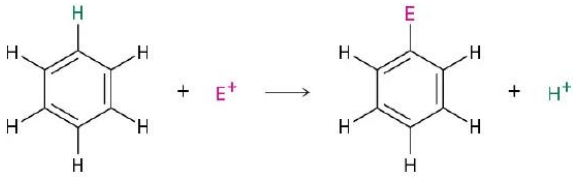
5.1: Why This Chapter?

This chapter continues the coverage of aromatic molecules begun in the preceding chapter, but we'll shift focus to concentrate on reactions, looking at the relationship between aromatic structure and reactivity. This relationship is critical in understanding how many biological molecules and pharmaceutical agents are synthesized and why they behave as they do.

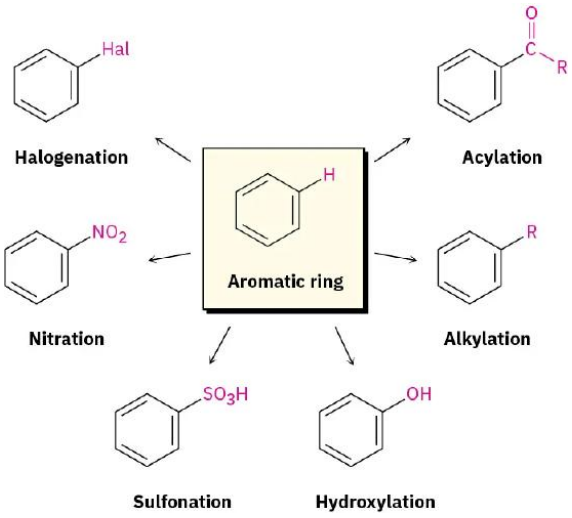
In the preceding chapter, we looked at aromaticity—the stability associated with benzene and related compounds that contain a cyclic conjugated system of $4n + 2$ π electrons. In this chapter, we'll look at some of the unique reactions that aromatic molecules undergo.

Figure 5.1.1: In the 19th and early-20th centuries, benzene was used as an aftershave lotion because of its pleasant smell and as a solvent to decaffeinate coffee beans. Neither is a good idea. (credit: modification of work "Ye Old Way" by Geo. H. Walker & Co./Library of Congress)

The most common reaction of aromatic compounds is electrophilic aromatic substitution, in which an electrophile (E^+) reacts with an aromatic ring and substitutes for one of the hydrogens. The reaction is characteristic of all aromatic rings, not just benzene and substituted benzenes. In fact, the ability of a compound to undergo electrophilic substitution is a good test of aromaticity.



Many different substituents can be introduced onto an aromatic ring through electrophilic substitution. To list some possibilities, an aromatic ring can be substituted by a halogen (–Cl, –Br, –I), a nitro group ($–NO_2$), a sulfonic acid group ($–SO_3H$), a hydroxyl group (–OH), an alkyl group (–R), or an acyl group (–COR). Starting from only a few simple materials, it's possible to prepare many thousands of substituted aromatic compounds.

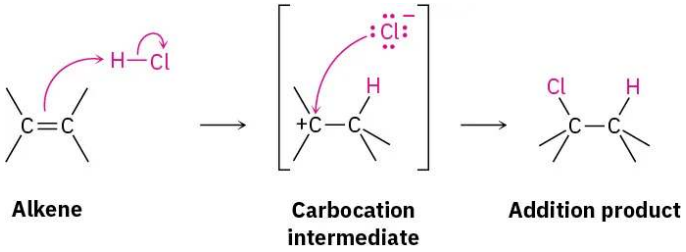


This page titled 5.1: Why This Chapter? is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

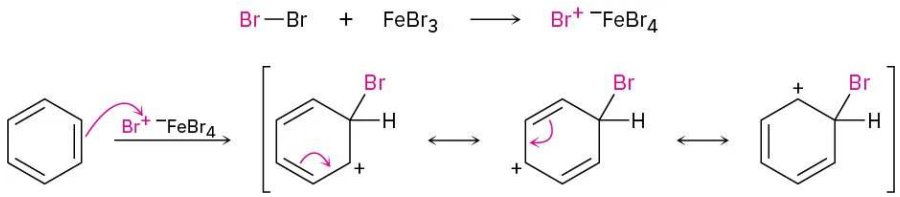
- **16.0: Why This Chapter?** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

5.2: Electrophilic Aromatic Substitution Reactions - Bromination

Before seeing how electrophilic aromatic substitutions occur, let's briefly recall what we said in the chapter on Alkenes: Structure and Reactivity about electrophilic alkene additions. When a reagent such as HCl adds to an alkene, the electrophilic hydrogen ion approaches the π electrons of the double bond and forms a bond to one carbon, leaving a positive charge at the other carbon. This carbocation intermediate then reacts with the nucleophilic Cl^- ion to yield the addition product.



An electrophilic aromatic substitution reaction begins in a similar way, but there are a number of differences. One difference is that aromatic rings are less reactive toward electrophiles than alkenes. For example, Br_2 in CH_2Cl_2 solution reacts instantly with most alkenes but does not react with benzene at room temperature. For bromination of benzene to take place, a catalyst such as $FeBr_3$ is needed. The catalyst makes the Br_2 molecule more electrophilic by polarizing it to give a $FeBr_4{}^-Br^+$ species that reacts as if it were Br^+. The polarized Br_2 molecule then reacts with the nucleophilic benzene ring to yield a nonaromatic carbocation intermediate that is doubly allylic (Section 11.5) and has three resonance forms.



Although more stable than a typical alkyl carbocation because of resonance, the intermediate in electrophilic aromatic substitution is nevertheless much less stable than the starting benzene ring itself, with its 150 kJ/mol (36 kcal/mol) of aromatic stability. Thus, the reaction of an electrophile with a benzene ring is endergonic, has a substantial activation energy, and is rather slow. Figure 5.2.1 shows an energy diagram comparing the reaction of an electrophile with an alkene and with benzene. The benzene reaction is slower (higher $\Delta G^{\ddagger}$) because the starting material is more stable.

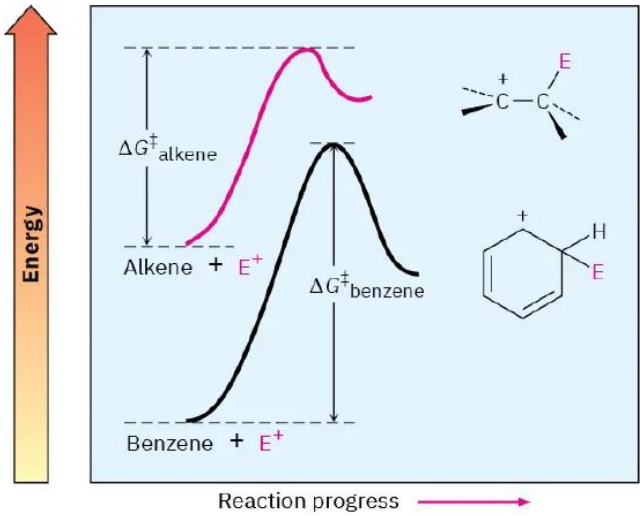


Figure 5.2.1: A comparison of the reactions of an electrophile (E^+) with an alkene and with benzene: $\Delta G\ddagger$alkene<$\Delta G\ddagger$. The benzene reaction is slower than the alkene reaction because of the stability of the aromatic ring.

Another difference between alkene addition and aromatic substitution occurs after the carbocation intermediate has formed. Instead of adding Br^- to give an addition product, the carbocation intermediate loses H^+ from the bromine-bearing carbon to give a

substitution product. Note that this loss of H^+ is similar to what occurs in the second step of an E1 reaction (Section 11.10). The net effect of reaction of Br_2 with benzene is the substitution of H^+ by Br^+ by the overall mechanism shown in Figure 5.2.2.

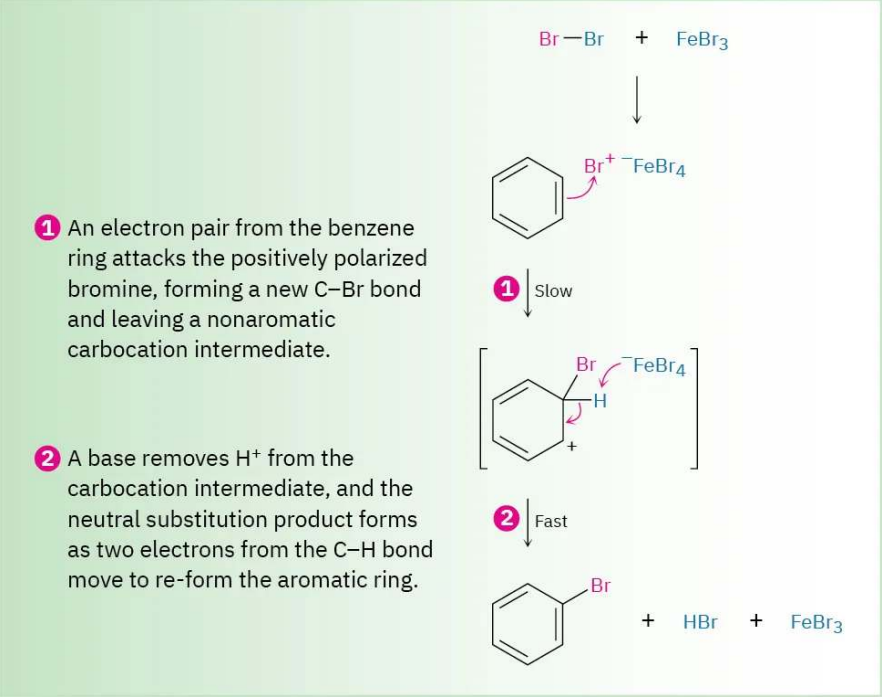


Figure 5.2.2: The mechanism for the electrophilic bromination of benzene. The reaction occurs in two steps and involves a resonance-stabilized carbocation intermediate.

Why does the reaction of Br_2 with benzene take a different course than its reaction with an alkene? The answer is straightforward. If addition occurred, the 150 kJ/mol stabilization energy of the aromatic ring would be lost and the overall reaction would be endergonic. When substitution occurs, though, the stability of the aromatic ring is retained and the reaction is exergonic. An energy diagram for the overall process is shown in Figure 5.2.3.

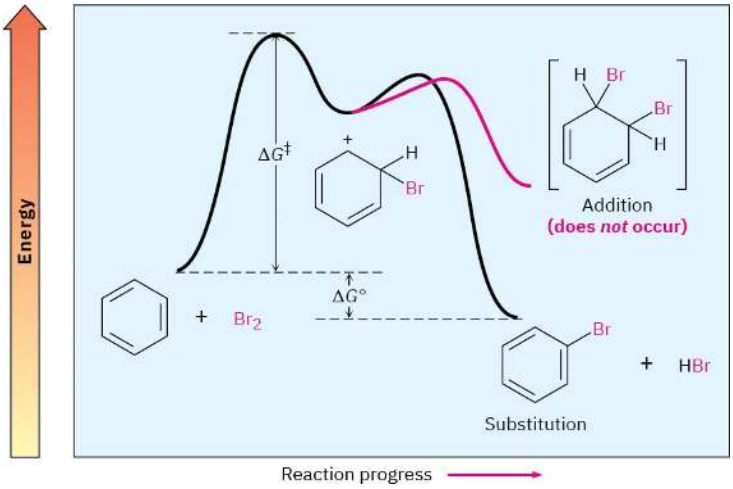


Figure 5.2.3: An energy diagram for the electrophilic bromination of benzene. Because the stability of the aromatic ring is retained, the overall process is exergonic.

? Exercise 5.2.1

Monobromination of toluene gives a mixture of three bromotoluene products. Draw and name them.

Answer

o-, *m*-, and *p*-Bromotoluene.

This page titled 5.2: Electrophilic Aromatic Substitution Reactions - Bromination is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

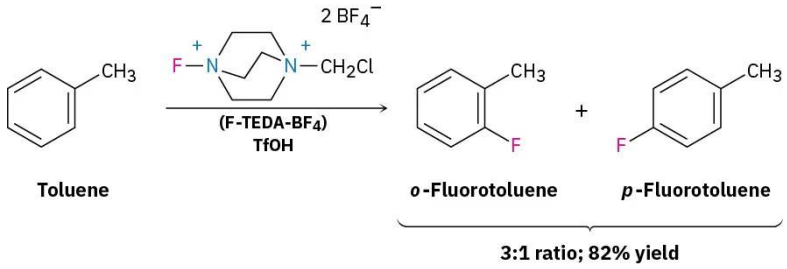
- **16.1: Electrophilic Aromatic Substitution Reactions - Bromination** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

5.3: Other Aromatic Substitutions

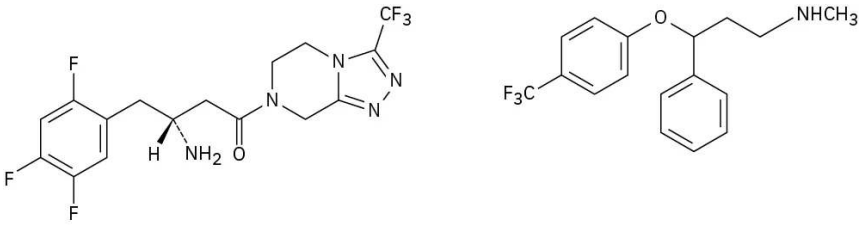
There are many other kinds of electrophilic aromatic substitutions besides bromination, and all occur by the same general mechanism. Let's look at some of these other reactions briefly.

Aromatic Halogenation

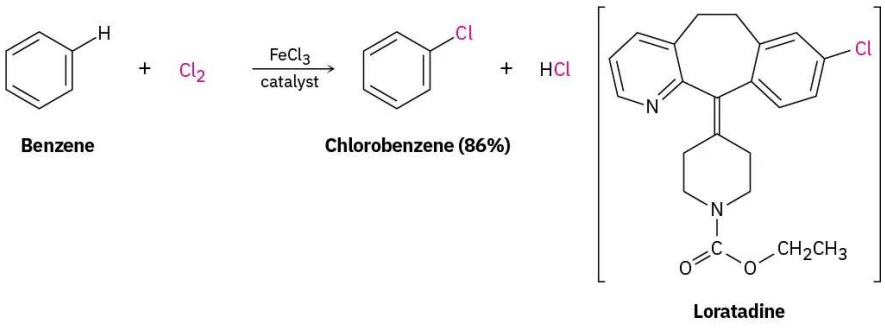
Chlorine and iodine can be introduced into aromatic rings by electrophilic substitution reactions just as bromine can, but fluorine is too reactive and only poor yields of monofluoroaromatic products are obtained by direct fluorination. Instead, other sources of "F^+" are used, in which a fluorine atom is bonded to a positively charged nitrogen. One of the most common such reagents goes by the acronym F-TEDA-BF_4 in the presence of trifluoromethanesulfonic acid (TfOH). (You don't need to know the full name of F-TEDA, which is sold under the name Selectfluor.)



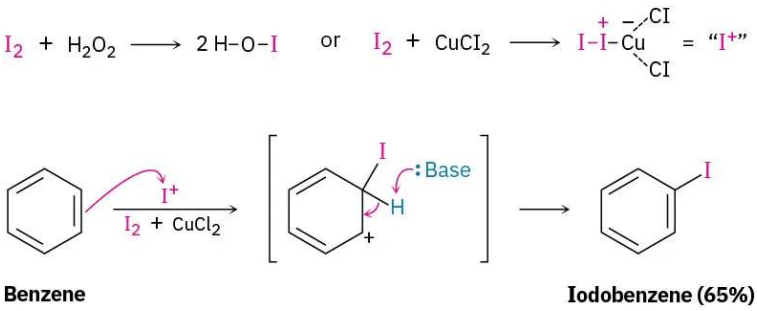
More than 20% of all pharmaceutical agents sold contain fluorine, including 30% of the top 100 drugs sold. Sitagliptin (Januvia), used to treat type 2 diabetes, fluoxetine (Prozac), an antidepressant, and atorvastatin (Lipitor), a statin used to lower cholesterol, are examples.



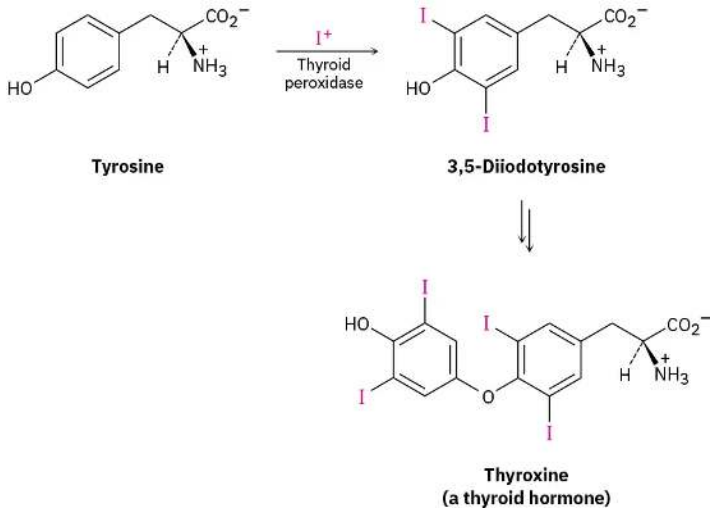
Aromatic rings react with Cl_2 in the presence of $FeCl_3$ catalyst to yield chlorobenzenes, just as they react with Br_2 and $FeBr_3$. This kind of reaction is used in the synthesis of numerous pharmaceutical agents, including the antiallergy medication loratadine, marketed as Claritin.



Iodine itself is unreactive toward aromatic rings, so an oxidizing agent such as hydrogen peroxide or a copper salt such as $CuCl_2$ must be added to the reaction. These substances accelerate the iodination reaction by oxidizing I_2 to a more powerful electrophilic species that reacts as if it were I^+. The aromatic ring then reacts with I^+ in the typical way, yielding a substitution product.



Electrophilic aromatic halogenations also occur in the biosynthesis of many naturally occurring molecules, particularly those produced by marine organisms. In humans, the best-known example occurs in the thyroid gland during the biosynthesis of thyroxine, a hormone involved in regulating growth and metabolism. The amino acid tyrosine is first iodinated by thyroid peroxidase, and two of the iodinated tyrosine molecules then couple. The electrophilic iodinating agent is an I^+ species, perhaps hypoiodous acid (HIO), that is formed from iodide ion by oxidation with H_2O_2.



Aromatic Nitration

Aromatic rings are nitrated by reaction with a mixture of concentrated nitric and sulfuric acids. The electrophile is the nitronium ion, NO_2^+, which is formed from HNO_3 by protonation and loss of water. The nitronium ion reacts with benzene to yield a carbocation intermediate, and loss of H^+ from this intermediate gives the neutral substitution product, nitrobenzene (Figure 5.3.1).

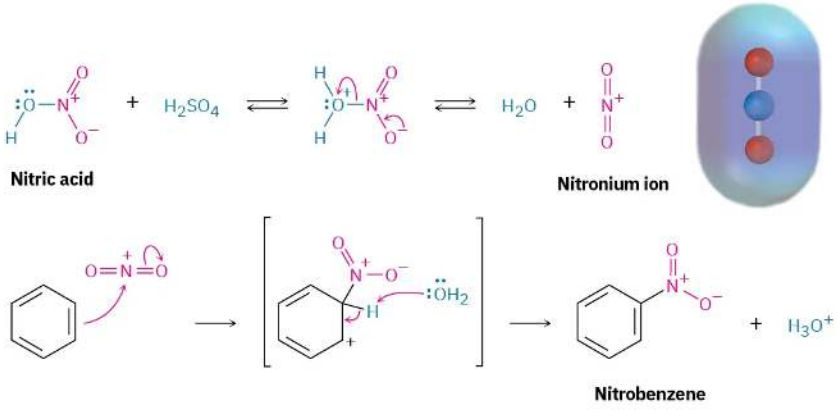
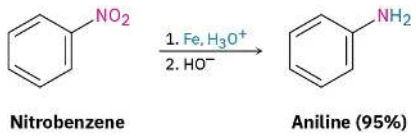


Figure 5.3.1: The mechanism for electrophilic nitration of an aromatic ring. An electrostatic potential map of the reactive electrophile NO_2^+ shows that the nitrogen atom is most positive.

Electrophilic nitration of an aromatic ring does not occur in nature but is particularly important in the laboratory because the nitro-substituted product can be reduced by reagents such as iron, tin, or $SnCl_2$ to yield the corresponding *arylamine*, $ArNH_2$. Attachment

of an amino group ($–NH_2$) to an aromatic ring by the two-step nitration/reduction sequence is a key part of the industrial synthesis of many dyes and pharmaceutical agents. We'll discuss this reduction and other reactions of aromatic nitrogen compounds in Chapter 24.



Aromatic Sulfonation

Aromatic rings can be sulfonated by reaction with so-called fuming sulfuric acid, a mixture of H_2SO_4 and SO_3. The reactive electrophile is either HSO_3^+ or neutral SO_3, depending on reaction conditions, and substitution occurs by the same two-step mechanism seen previously for bromination and nitration (Figure 5.3.2). Note, however, that the sulfonation reaction is readily reversible. It can occur either forward or backward, depending on the reaction conditions. Sulfonation is favored in strong acid, but desulfonation is favored in hot, dilute aqueous acid.

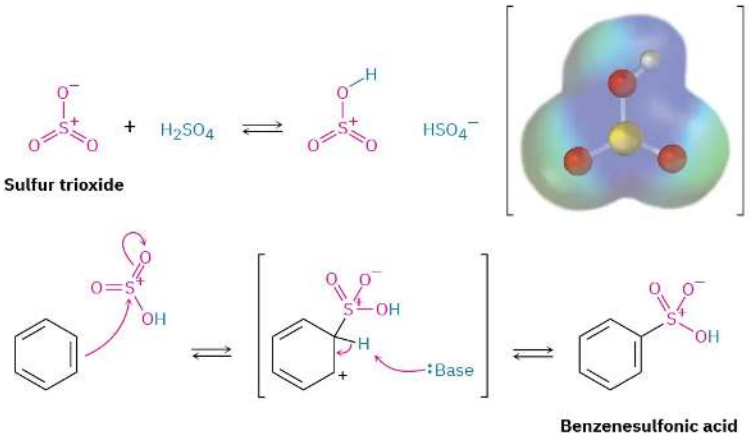
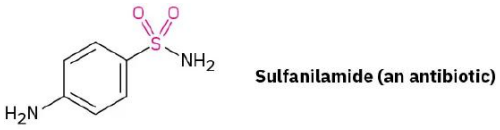


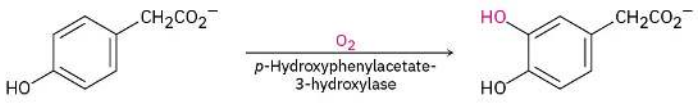
Figure 5.3.2: The mechanism for electrophilic sulfonation of an aromatic ring. An electrostatic potential map of the reactive electrophile $HOSO_2^+$ shows that sulfur and hydrogen are the most positive atoms.

Aromatic sulfonation does not occur naturally but is widely used in the preparation of dyes and pharmaceutical agents. For example, the sulfa drugs, such as sulfanilamide, were among the first clinically useful antibiotics. Although largely replaced today by more effective agents, sulfa drugs are still used in the treatment of meningitis and urinary tract infections. These drugs are prepared commercially by a process that involves aromatic sulfonation as its key step.



Aromatic Hydroxylation

Direct hydroxylation of an aromatic ring to yield a hydroxybenzene (a *phenol*) is difficult and rarely done in the laboratory but occurs much more frequently in biological pathways. An example is the hydroxylation of *p*-hydroxyphenylacetate to give 3,4-dihydroxyphenylacetate. The reaction is catalyzed by *p*-hydroxyphenylacetate-3-hydroxylase and requires molecular oxygen plus the coenzyme reduced flavin adenine dinucleotide, abbreviated $FADH_2$.



By analogy with other electrophilic aromatic substitutions, you might expect that an electrophilic oxygen species acting as an "OH+ equivalent" is needed for the hydroxylation reaction. That is just what happens, with the electrophilic oxygen arising by

protonation of FAD hydroperoxide, $RO{-}OH$ (Figure 5.3.3); that is, $RO{-}OH + H^+ \longrightarrow ROH + OH^+$. The FAD hydroperoxide itself is formed by reaction of FADH2 with O_2.

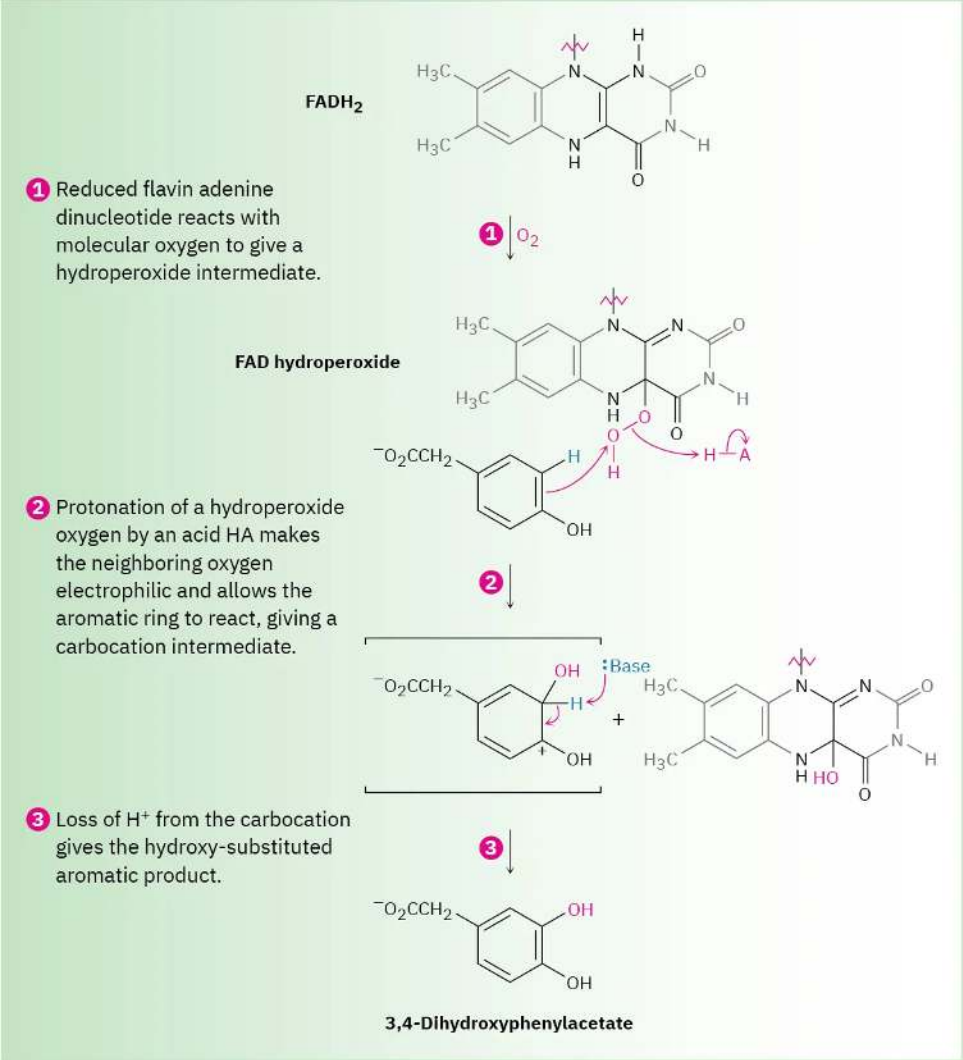
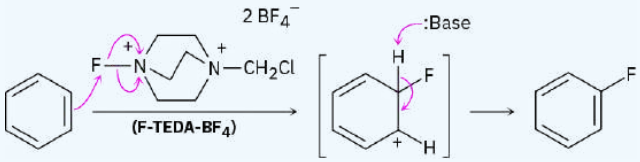


Figure 5.3.3: Mechanism for the electrophilic hydroxylation of p-hydroxyphenylacetate, by reaction with FAD hydroperoxide. The hydroxylating species is an "OH^+ equivalent" that arises by protonation of FAD hydroperoxide, RO–OH + H^+ → ROH + OH^+. The FAD hydroperoxide itself is formed by reaction of $FADH_2$ with O_2.

? Exercise 5.3.1

Propose a mechanism for the electrophilic fluorination of benzene with SelectFluor.

Answer



Exercise 5.3.2

How many products might be formed on chlorination of *o*-xylene (*o*-dimethylbenzene), *m*-xylene, and *p*-xylene?

Answer

o-xylene: 2; *p*-xylene: 1; *m*-xylene: 3

Exercise 5.3.3

When benzene is treated with D_2SO_4, deuterium slowly replaces all six hydrogens in the aromatic ring. Explain.

Answer

D^+ does electrophilic substitutions on the ring.

This page titled 5.3: Other Aromatic Substitutions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **16.2: Other Aromatic Substitutions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

5.4: Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction

Among the most useful electrophilic aromatic substitution reactions in the laboratory is alkylation—the introduction of an alkyl group onto the benzene ring. Called the Friedel–Crafts reaction after its founders in 1877, Charles Friedel and James Crafts, the reaction is carried out by treating an aromatic compound with an alkyl chloride, RCl, in the presence of $AlCl_3$ to generate a carbocation electrophile, R^+. Aluminum chloride catalyzes the reaction by helping the alkyl halide to generate a carbocation in much the same way that $FeBr_3$ catalyzes aromatic brominations by polarizing Br_2 (Section 16.1). Loss of H^+ then completes the reaction (Figure 5.4.1).

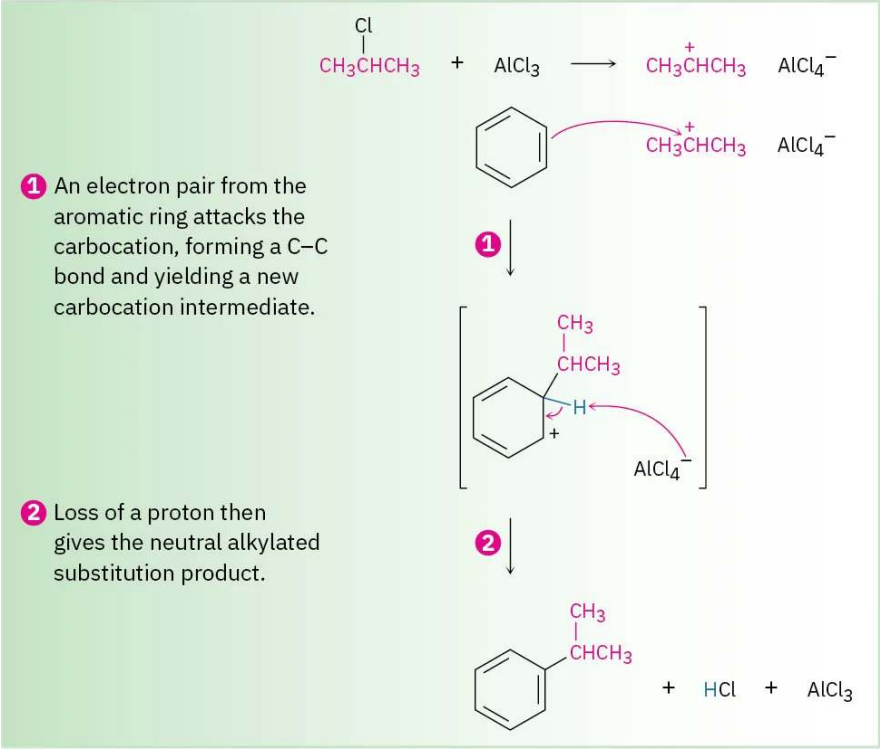
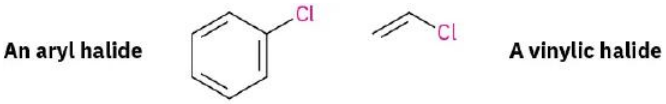


Figure 5.4.1: Mechanism for the Friedel–Crafts alkylation reaction of benzene with 2-chloropropane to yield isopropylbenzene (cumene). The electrophile is a carbocation, generated by $AlCl_3$-assisted dissociation of an alkyl halide.

Despite its utility, the Friedel–Crafts alkylation has several limitations. For one thing, only alkyl halides can be used. Aromatic (aryl) halides and vinylic halides don't react because aryl and vinylic carbocations are too high in energy to form under Friedel–Crafts conditions.



Another limitation is that Friedel–Crafts reactions don't succeed on aromatic rings that are substituted either by a strongly electron-withdrawing group such as carbonyl (C=O) or by a basic amino group that can be protonated. We'll see in the next section that the presence of a substituent group already on a ring can have a dramatic effect on that ring's reactivity to further electrophilic substitution. Rings that contain any of the substituents listed in Figure 5.4.2 do not undergo Friedel–Crafts alkylation.

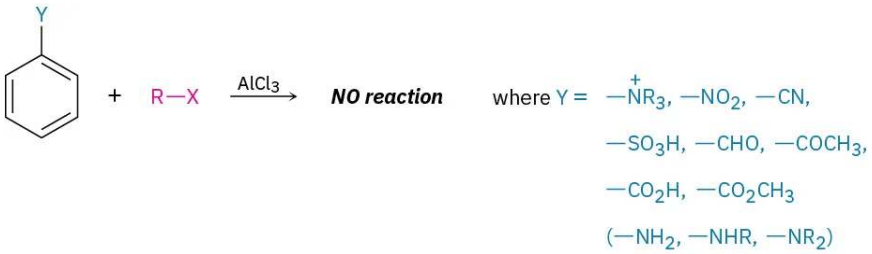
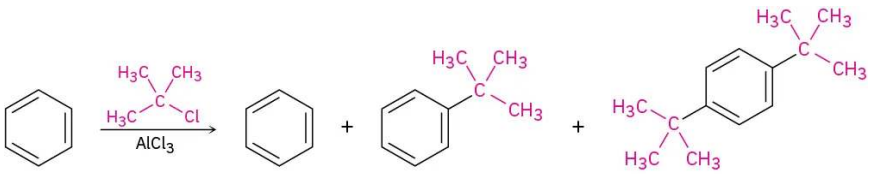


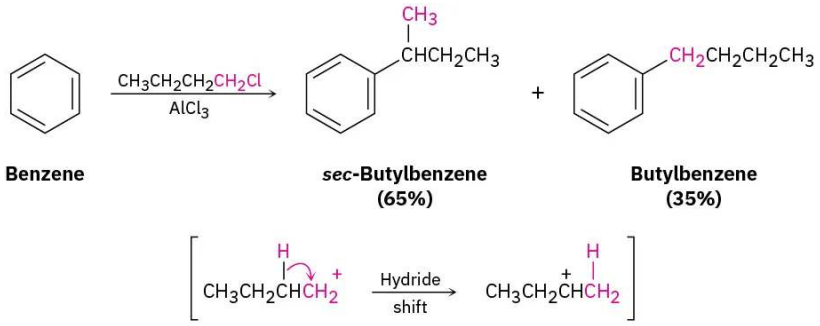
Figure 5.4.2: Limitations on the aromatic substrate in Friedel–Crafts reactions. No reaction occurs if the substrate has either an electron-withdrawing substituent or a basic amino group.

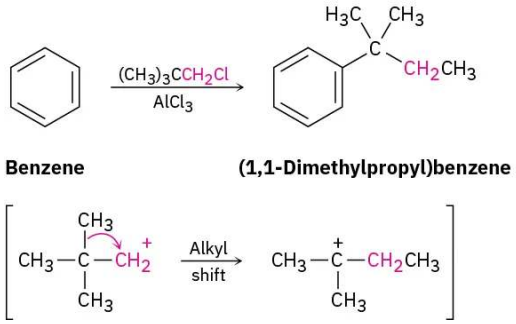
A third limitation to the Friedel–Crafts alkylation is that it's often difficult to stop the reaction after a single substitution. Once the first alkyl group is on the ring, a second substitution reaction is facilitated for reasons we'll discuss in the next section. Thus, we often observe *polyalkylation.* Reaction of benzene with 1 mol equivalent of 2-chloro-2-methylpropane, for example, yields *p*-di-*tert*-butylbenzene as the major product, along with small amounts of *tert*-butylbenzene and unreacted benzene. A high yield of mono-alkylation product is obtained only when a large excess of benzene is used.



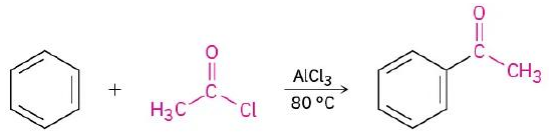
A final limitation to the Friedel–Crafts reaction is that a skeletal rearrangement of the alkyl carbocation electrophile sometimes occurs during reaction, particularly when a primary alkyl halide is used. Treatment of benzene with 1-chlorobutane at 0 °C, for instance, gives an approximately 2 : 1 ratio of rearranged (*sec*-butyl) to unrearranged (butyl) products.

The carbocation rearrangements that accompany Friedel–Crafts reactions are like those that accompany electrophilic additions to alkenes **(Section 7.11)** and occur either by hydride shift or alkyl shift. For example, the relatively unstable primary butyl carbocation produced by reaction of 1-chlorobutane with $AlCl_3$ rearranges to the more stable secondary butyl carbocation by the shift of a hydrogen atom and its electron pair (a hydride ion, $H{:}^-$) from C2 to C1. Similarly, alkylation of benzene with 1-chloro-2,2-dimethylpropane yields (1,1-dimethylpropyl)benzene. The initially formed primary carbocation rearranges to a tertiary carbocation by shift of a methyl group and its electron pair from C2 to C1.





Just as an aromatic ring is alkylated by reaction with an alkyl chloride, it is acylated by reaction with a carboxylic acid chloride, RCOCl, in the presence of $AlCl_3$. That is, an acyl group (–COR; pronounced **a**-sil) is substituted onto the aromatic ring. For example, reaction of benzene with acetyl chloride yields the ketone acetophenone.



The mechanism of Friedel–Crafts acylation is similar to that of Friedel–Crafts alkylation, and the same limitations on the aromatic substrate noted previously in Figure 5.4.2 for alkylation also apply to acylation. The reactive electrophile is a resonance-stabilized acyl cation, generated by reaction between the acyl chloride and $AlCl_3$ (Figure 5.4.3). As the resonance structures in the figure indicate, an acyl cation is stabilized by interaction of the vacant orbital on carbon with lone-pair electrons on the neighboring oxygen. Because of this stabilization, no carbocation rearrangement occurs during acylation.

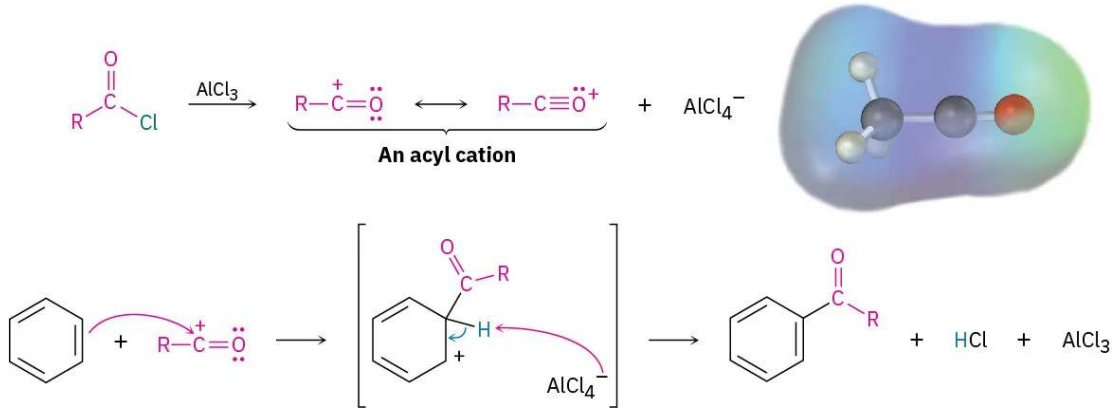
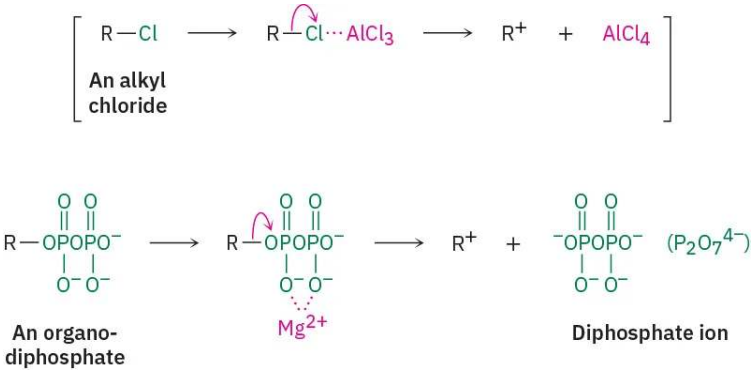


Figure 5.4.3: Mechanism of the Friedel–Crafts acylation reaction. The electrophile is a resonance-stabilized acyl cation, whose electrostatic potential map indicates that **carbon is the most positive atom.**

Unlike the multiple substitutions that often occur in Friedel–Crafts alkylations, acylations never occur more than once on a ring because the product acylbenzene is less reactive than the nonacylated starting material. We'll account for this reactivity difference in the next section.

Aromatic alkylations occur in numerous biological pathways, although there is of course no $AlCl_3$ present in living systems to catalyze the reaction. Instead, the carbocation electrophile is typically formed by dissociation of an organodiphosphate, as we saw in Section 11.6. The dissociation is usually assisted by complexation to a divalent metal cation such as Mg^{2+}, just as dissociation of an alkyl chloride is assisted by $AlCl_3$.



An example of a biological Friedel–Crafts reaction occurs during the biosynthesis of phylloquinone, or vitamin K_1, the human blood-clotting factor. Phylloquinone is formed by reaction of 1,4-dihydroxynaphthoic acid with phytyl diphosphate. Phytyl diphosphate first dissociates to a resonance-stabilized allylic carbocation, which then substitutes onto the aromatic ring in the typical way. Several further transformations lead to phylloquinone (Figure 5.4.4).

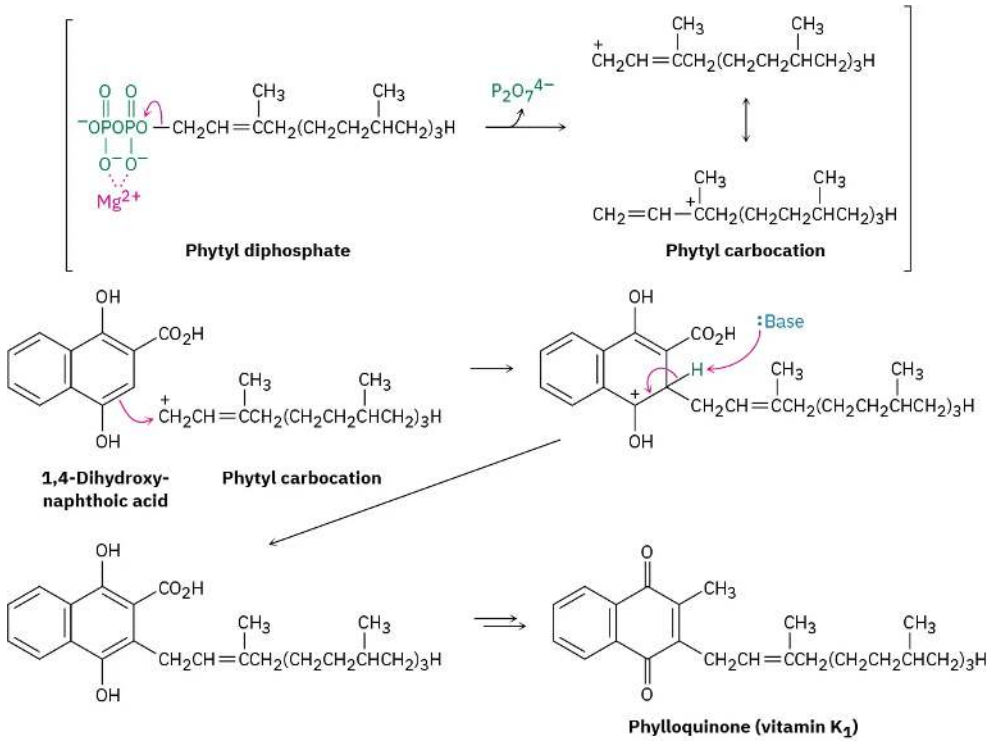


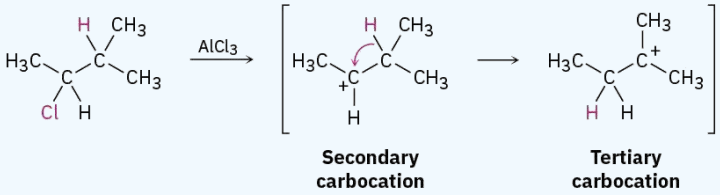
Figure 5.4.4: Biosynthesis of phylloquinone (vitamin K_1) from 1,4-dihydroxynaphthoic acid. The key step that joins the 20-carbon phytyl side chain to the aromatic ring is a Friedel–Crafts-like electrophilic substitution reaction with a diphosphate ion as the leaving group.

Worked Example 5.4.1: Predicting the Product of a Carbocation Rearrangement

The Friedel–Crafts reaction of benzene with 2-chloro-3-methylbutane in the presence of $AlCl_3$ occurs with a carbocation rearrangement. What is the structure of the product?

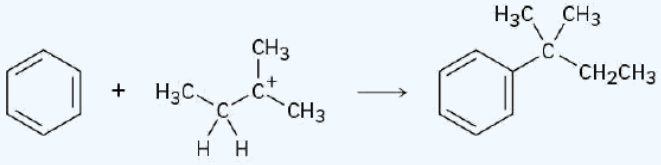
Strategy

A Friedel–Crafts reaction involves initial formation of a carbocation, which can rearrange by either a hydride shift or an alkyl shift to give a more stable carbocation. Draw the initial carbocation, assess its stability, and see if the shift of a hydride ion or an alkyl group from a neighboring carbon will result in increased stability. In the present instance, the initial carbocation is a secondary one that can rearrange to a more stable tertiary one by a hydride shift.



Use this more stable tertiary carbocation to complete the Friedel–Crafts reaction.

Solution



https://chem.libretexts.org/@go/page/564191

Exercise 5.4.1

Which of the following alkyl halides would you expect to undergo Friedel–Crafts reaction with rearrangement and which without? Explain.

a. CH_3CH_2Cl
b. $CH_3CH_2CH(Cl)CH_3$
c. $CH_3CH_2CH_2Cl$
d. $(CH_3)_3CCH_2Cl$
e. Chlorocyclohexane

Answer

No rearrangement: a, b, e.

Exercise 5.4.2

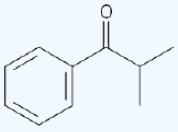
What is the major monosubstitution product from the Friedel–Crafts reaction of benzene with 1-chloro-2-methylpropane in the presence of $AlCl_3$?

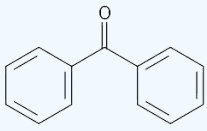
Answer

tert-Butylbenzene.

Exercise 5.4.3

Identify the carboxylic acid chloride that might be used in a Friedel–Crafts acylation reaction to prepare each of the following acylbenzenes:

a. 

b. 

Answer

a. $(CH_3)_2CHCOCl$
b. PhCOCl

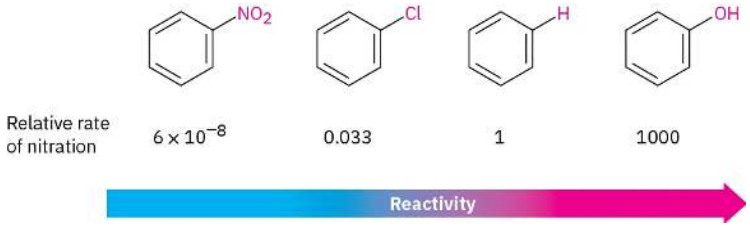
This page titled 5.4: Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **16.3: Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

5.5: Substituent Effects in Electrophilic Substitutions

Only one product can form when an electrophilic substitution occurs on benzene, but what would happen if we were to carry out a reaction on an aromatic ring that already has a substituent? The initial presence of a substituent on the ring has two effects.

- **Substituents affect the *reactivity* of the aromatic ring.** Some substituents activate the ring, making it more reactive than benzene, and some deactivate the ring, making it less reactive than benzene. In aromatic nitration, for instance, an –OH substituent makes the ring 1000 times more reactive than benzene, while an $–NO_2$ substituent makes the ring more than 10 million times less reactive.



- **Substituents affect the *orientation* of the reaction.** The three possible disubstituted products—ortho, meta, and para—are usually not formed in equal amounts. Instead, the nature of the substituent initially present on the benzene ring determines the position of the second substitution. An –OH group directs substitution toward the ortho and para positions, for instance, while a carbonyl group such as –CHO directs substitution primarily toward the meta position. Table 16.1 lists experimental results for the nitration of some substituted benzenes.

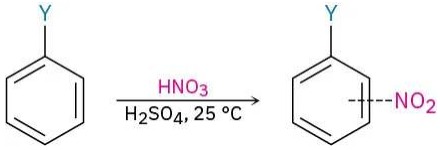


Table 16.1 Orientation of Nitration in Substituted Benzenes

	Product (%)		
	Ortho	Meta	Para
Meta-directing deactivators			
$-\overset{+}{N}(CH_3)_3$	2	87	11
$-NO_2$	7	91	2
$-CO_2H$	22	76	2
–CN	17	81	2
$-CO_2CH_3$	28	66	6
$-COCH_3$	26	72	2
–CHO	19	72	9
Ortho- and para-directing deactivators			
–F	13	1	86
–Cl	35	1	64
–Br	43	1	56
–I	45	1	54
Ortho- and para-directing activators			
$-CH_3$	63	3	34
–OH	50	0	50
$-NHCOCH_3$	19	2	79

Substituents can be classified into three groups, as shown in Figure 5.5.1: *ortho- and para-directing activators*, *ortho- and para-directing deactivators*, and *meta-directing deactivators*. There are no meta-directing activators. Notice how the directing effect of a group correlates with its reactivity. All meta-directing groups are strongly deactivating, and most ortho- and para-directing groups are activating. The halogens are unique in being ortho- and para-directing but weakly deactivating.

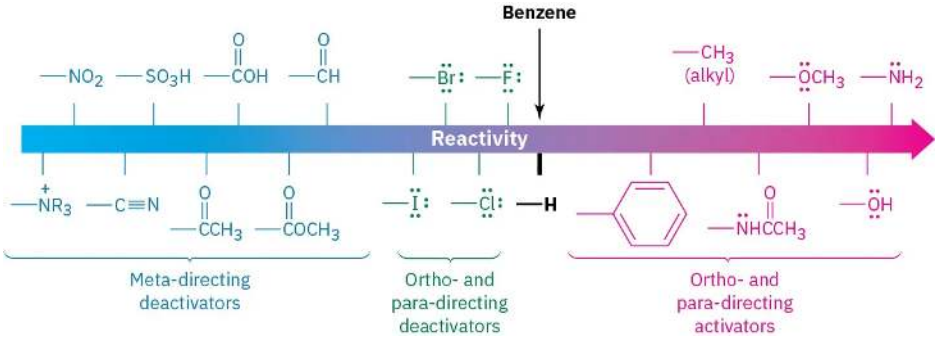


Figure 5.5.1: Classification of substituent effects in electrophilic aromatic substitution. All activating groups are ortho- and para-directing, and all deactivating groups other than halogen are meta-directing. Halogens are unique in being deactivating but ortho- and para-directing.

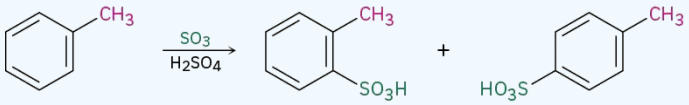
Worked Example 5.5.1: Predicting the Product of an Electrophilic Aromatic Substitution Reaction

Predict the major product of the sulfonation of toluene.

Strategy

Identify the substituent present on the ring, and decide whether it is ortho- and para-directing or meta-directing. According to Figure 5.5.1, an alkyl substituent is ortho- and para-directing, so sulfonation of toluene will primarily give a mixture of *o* -toluenesulfonic acid and *p* -toluenesulfonic acid.

Solution



Toluene **o-Toluenesulfonic acid** **p-Toluenesulfonic acid**

? Exercise 5.5.1

Rank the compounds in each of the following groups in order of their reactivity to electrophilic substitution:

a. Nitrobenzene, phenol, toluene, benzene
b. Phenol, benzene, chlorobenzene, benzoic acid
c. Benzene, bromobenzene, benzaldehyde, aniline

Answer

a. Phenol > Toluene > Benzene > Nitrobenzene
b. Phenol > Benzene > Chlorobenzene > Benzoic acid
c. Aniline > Benzene > Bromobenzene > Benzaldehyde

? Exercise 5.5.2

Predict the major products of the following reactions:

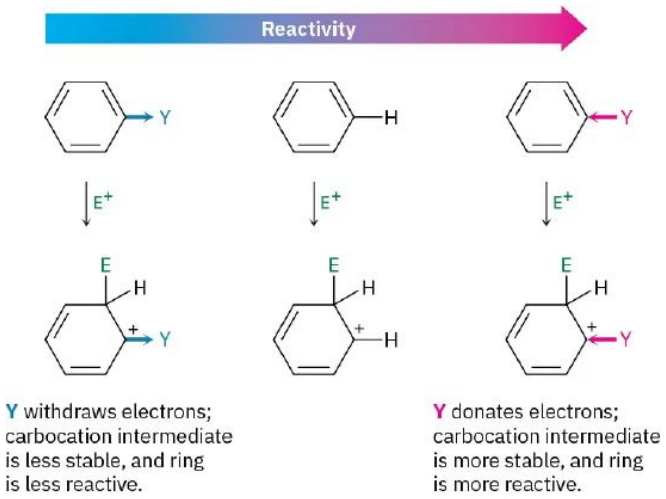
a. Nitration of bromobenzene
b. Bromination of nitrobenzene
c. Chlorination of phenol
d. Bromination of aniline

Answer

a. *o*- and *p*-Bromonitrobenzene
b. *m*-Bromonitrobenzene
c. *o*- and *p*-Chlorophenol
d. *o*- and *p*-Bromoaniline

Activating and Deactivating Effects

What makes a group either activating or deactivating? The common characteristic of all activating groups is that they donate electrons to the ring, thereby making the ring more electron-rich, stabilizing the carbocation intermediate, and lowering the activation energy for its formation. Conversely, the common characteristic of all deactivating groups is that they withdraw electrons from the ring, thereby making the ring more electron-poor, destabilizing the carbocation intermediate, and raising the activation energy for its formation.



Compare the electrostatic potential maps of benzaldehyde (deactivated), chlorobenzene (weakly deactivated), and phenol (activated) with that of benzene. As shown in Figure 5.5.2, the ring is more positive (yellow-green) when an electron-withdrawing group such as –CHO or –Cl is present and more negative (red) when an electron-donating group such as –OH is present.

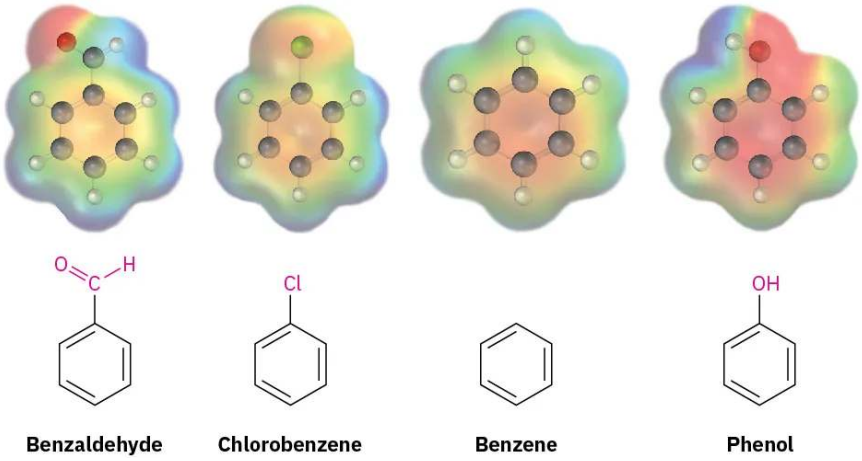
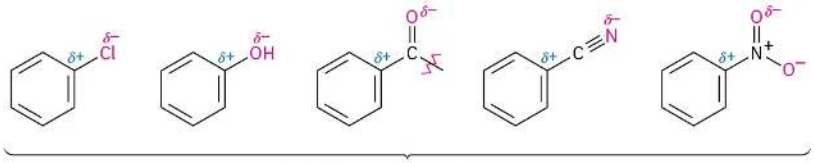
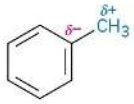


Figure 5.5.2: Electrostatic potential maps of benzene and several substituted benzenes show that an electron-withdrawing group (–CHO or –Cl) makes the ring more **electron-poor**, while an electron-donating group (–OH) makes the ring more **electron-rich**.

The withdrawal or donation of electrons by a substituent group is controlled by an interplay of *inductive effects* and *resonance effects*. As we saw in Section 2.1, an inductive effect is the withdrawal or donation of electrons through a σ bond due to electronegativity. Halogens, hydroxyl groups, carbonyl groups, cyano groups, and nitro groups inductively withdraw electrons through the σ bond linking the substituent to a benzene ring. This effect is most pronounced in halobenzenes and phenols, in which the electronegative atom is directly attached to the ring, but is also significant in carbonyl compounds, nitriles, and nitro compounds, in which the electronegative atom is farther removed. Alkyl groups, on the other hand, inductively donate electrons. This is the same hyperconjugative donating effect that causes alkyl substituents to stabilize alkenes (Section 7.6) and carbocations (Section 7.9).



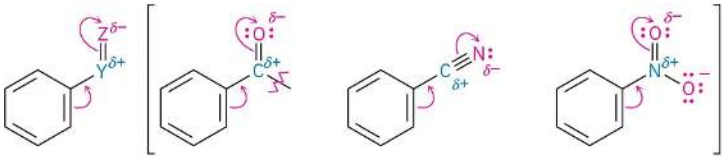
Inductive electron withdrawal



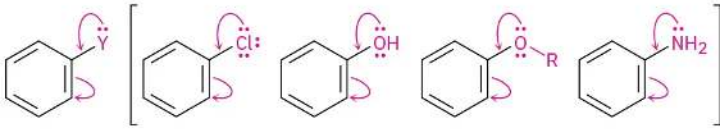
Inductive electron donation

A resonance effect is the withdrawal or donation of electrons through a π bond due to the overlap of a *p* orbital on the substituent with a *p* orbital on the aromatic ring. Carbonyl, cyano, and nitro substituents, for example, withdraw electrons from the aromatic ring by resonance. The π electrons flow from the ring to the substituent, leaving a positive charge in the ring. Note that substituents with an electron-withdrawing resonance effect have the general structure –Y=Z, where the Z atom is more electronegative than Y.

Conversely, halogen, hydroxyl, alkoxyl (–OR), and amino substituents donate electrons to the aromatic ring by resonance. Lone-pair electrons flow from the substituents to the ring, placing a negative charge on the ring. Substituents with an electron-donating resonance effect have the general structure –Ÿ, where the Y atom has a lone pair of electrons available for donation to the ring.



Resonance electron-withdrawing groups

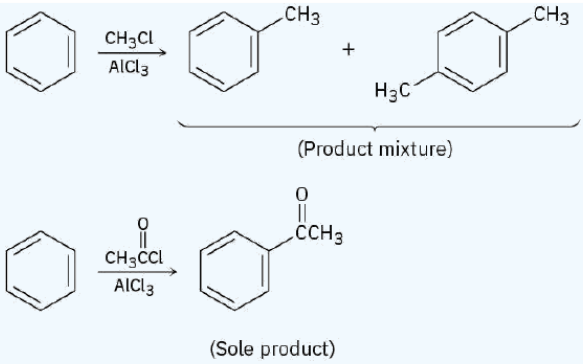


Resonance electron-donating groups

One further point: inductive effects and resonance effects don't necessarily act in the same direction. Halogen, hydroxyl, alkoxyl, and amino substituents, for instance, have electron-withdrawing inductive effects because of the electronegativity of the –X, –O, or –N atom bonded to the aromatic ring but have electron-donating resonance effects because of the lone-pair electrons on those –X, –O, or –N atoms. When the two effects act in opposite directions, the stronger effect dominates. Thus, hydroxyl, alkoxyl, and amino substituents are activators because their stronger electron-donating resonance effect outweighs their weaker electron-withdrawing inductive effect. Halogens, however, are deactivators because their stronger electron-withdrawing inductive effect outweighs their weaker electron-donating resonance effect.

? Exercise 5.5.3

Use Figure 5.5.1 to explain why Friedel–Crafts alkylations often give polysubstitution but Friedel–Crafts acylations do not.

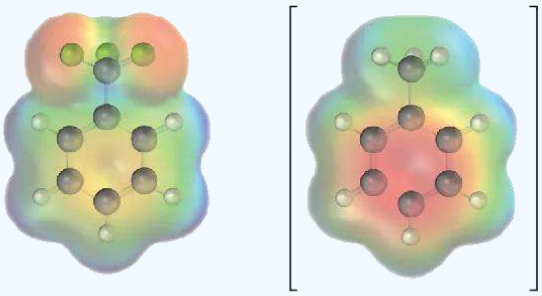


Answer

Alkylbenzenes are more reactive than benzene itself, but acylbenzenes are less reactive.

? Exercise 5.5.4

An electrostatic potential map of (trifluoromethyl)benzene, $C_6H_5CF_3$, is shown. Would you expect (trifluoromethyl)benzene to be more reactive or less reactive than toluene toward electrophilic substitution? Explain.



(Trifluoromethyl)benzene **Toluene**

Answer

Toluene is more reactive; the trifluoromethyl group is electron-withdrawing.

Ortho- and Para-Directing Activators: Alkyl Groups

Inductive and resonance effects account not only for reactivity but also for the orientation of electrophilic aromatic substitutions. Take alkyl groups, for instance, which have an electron-donating inductive effect and are ortho and para directors. The results of toluene nitration are shown in Figure 5.5.3.

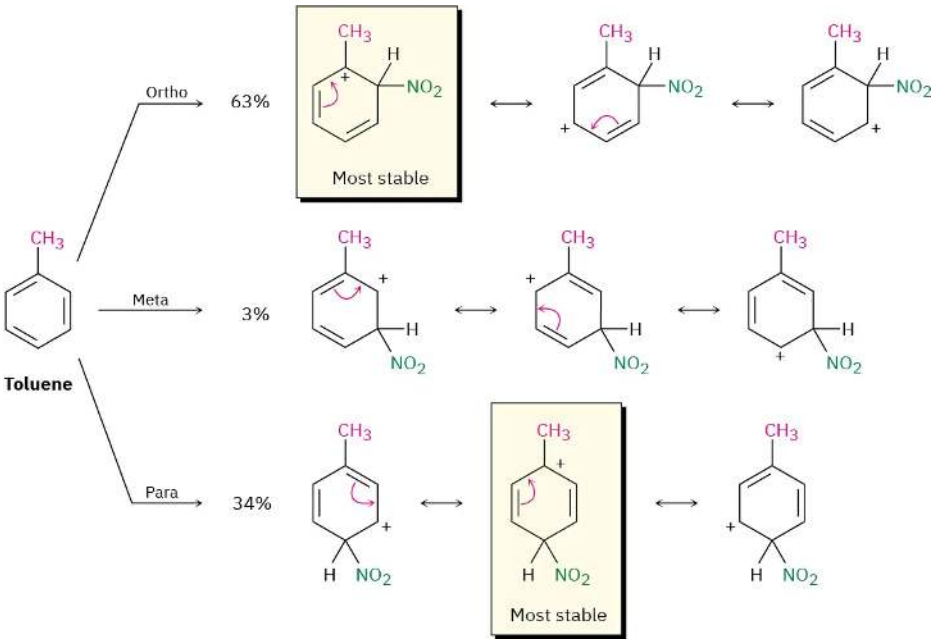


Figure 5.5.3: Carbocation intermediates in the nitration of toluene. Ortho and para intermediates are more stable than the meta intermediate because the positive charge is on a tertiary carbon rather than a secondary carbon.

Nitration of toluene might occur either ortho, meta, or para to the methyl group, giving the three carbocation intermediates shown in in Figure 5.5.3. Although all three intermediates are resonance-stabilized, the ortho and para intermediates are more stabilized than the meta intermediate. For both the ortho and para reactions, but not for the meta reaction, a resonance form places the positive charge directly on the methyl-substituted carbon, where it is in a tertiary position and can be stabilized by the electron-donating inductive effect of the methyl group. The ortho and para intermediates are thus lower in energy than the meta intermediate and form faster.

Ortho- and Para-Directing Activators: OH and NH_2

Hydroxyl, alkoxyl, and amino groups are also ortho–para activators, but for a different reason than for alkyl groups. As described earlier in this section, hydroxyl, alkoxyl, and amino groups have a strong, electron-donating resonance effect that outweighs a weaker electron-withdrawing inductive effect. When phenol is nitrated, for instance, reaction can occur either ortho, meta, or para to the –OH group, giving the carbocation intermediates shown in Figure 5.5.4. The ortho and para intermediates are more stable than the meta intermediate because they have more resonance forms, including one particularly favorable form that allows the positive charge to be stabilized by electron donation from the substituent oxygen atom. The intermediate from the meta reaction has no such stabilization.

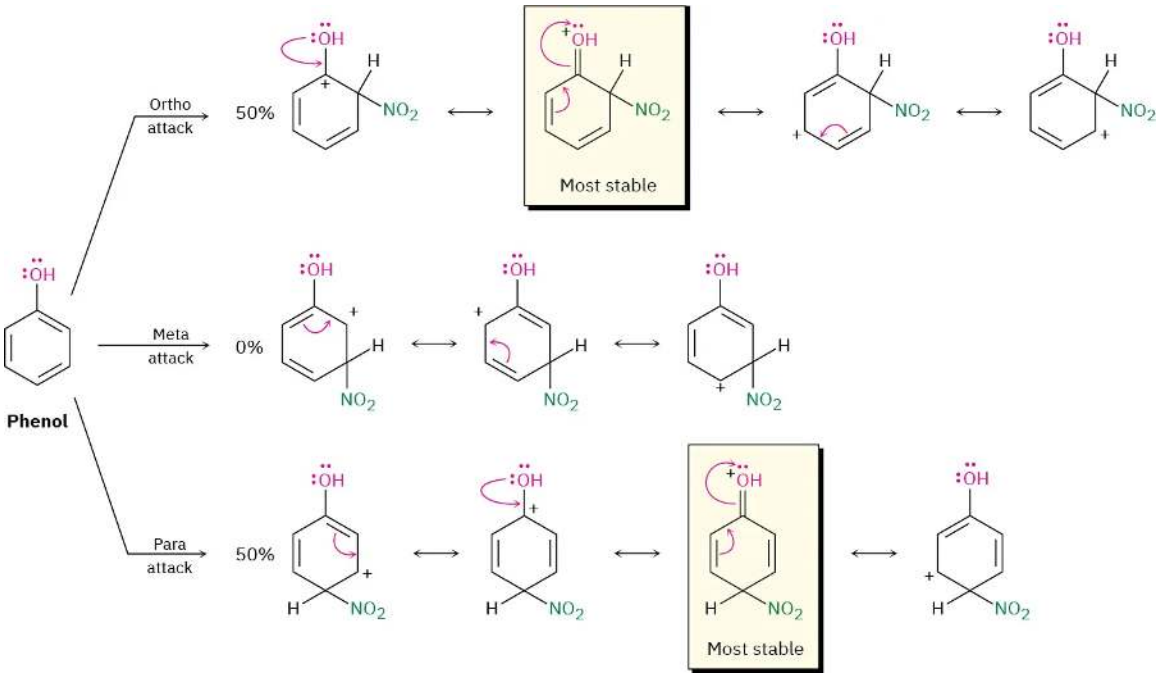
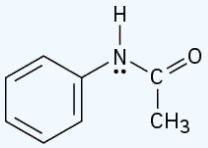


Figure 5.5.4: Carbocation intermediates in the nitration of phenol. The ortho and para intermediates are more stable than the meta intermediate because they have more resonance forms, including one particularly favorable form that involves electron donation from the oxygen atom.

? Exercise 5.5.5

Acetanilide is less reactive than aniline toward electrophilic substitution. Explain.



Acetanilide

Answer

The nitrogen electrons are donated to the nearby carbonyl group by resonance and are less available to the ring.

Ortho- and Para-Directing Deactivators: Halogens

Halogens are deactivating because their stronger electron-withdrawing inductive effect outweighs their weaker electron-donating resonance effect. Although weak, that electron-donating resonance effect is nevertheless felt only at the ortho and para positions and not at the meta position (Figure 5.5.5). Thus, a halogen substituent can stabilize the positive charge of the carbocation intermediates from ortho and para reaction in the same way that hydroxyl and amino substituents can. The meta intermediate, however, has no such stabilization and is therefore formed more slowly.

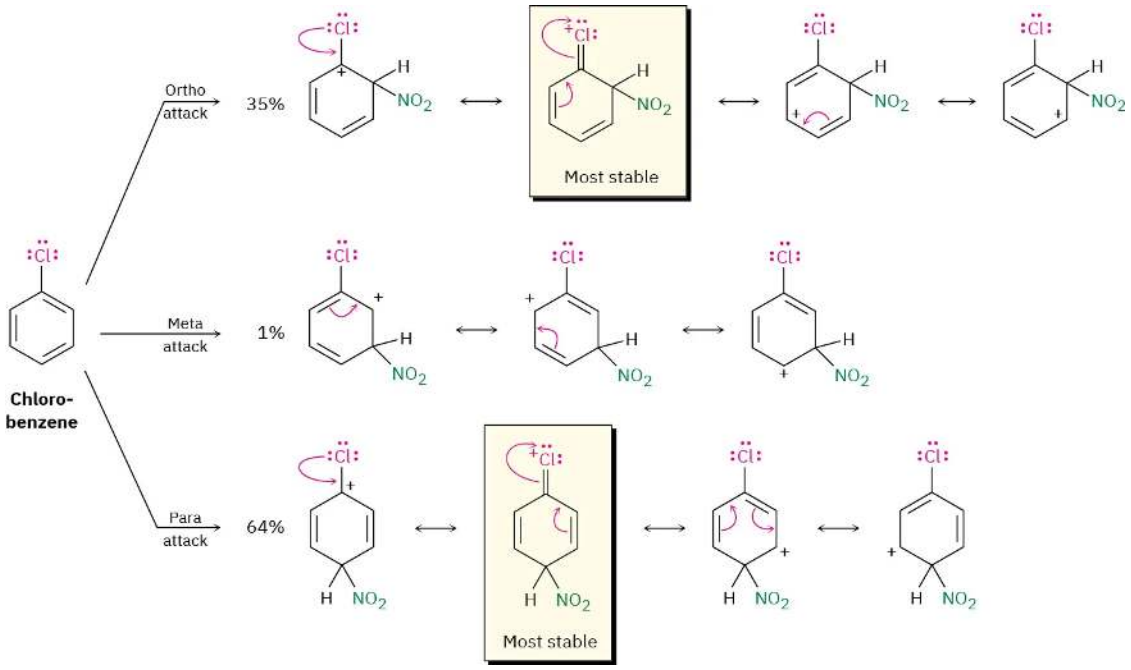


Figure 5.5.5: Carbocation intermediates in the nitration of chlorobenzene. The ortho and para intermediates are more stable than the meta intermediate because of electron donation of the halogen lone-pair electrons.

Note again that halogens, hydroxyl, alkoxyl, and amino groups all withdraw electrons inductively but donate electrons by resonance. Halogens have a stronger electron-withdrawing inductive effect but a weaker electron-donating resonance effect and are thus deactivators. Hydroxyl, alkoxyl, and amino groups have a weaker electron-withdrawing inductive effect but a stronger electron-donating resonance effect and are thus activators. All are ortho and para directors, however, because of the lone pair of electrons on the atom bonded to the aromatic ring.

Meta-Directing Deactivators

The influence of meta-directing substituents can be explained using the same kinds of arguments used for ortho and para directors. Look at the nitration of benzaldehyde, for instance (Figure 5.5.6). Of the three possible carbocation intermediates, the meta intermediate has three favorable resonance forms, whereas the ortho and para intermediates have only two. In both ortho and para intermediates, the third resonance form is unfavorable because it places the positive charge directly on the carbon that bears the aldehyde group, where it is disfavored by a repulsive interaction with the positively polarized carbon atom of the C=O group. Hence, the meta intermediate is more favored and is formed faster than the ortho and para intermediates.

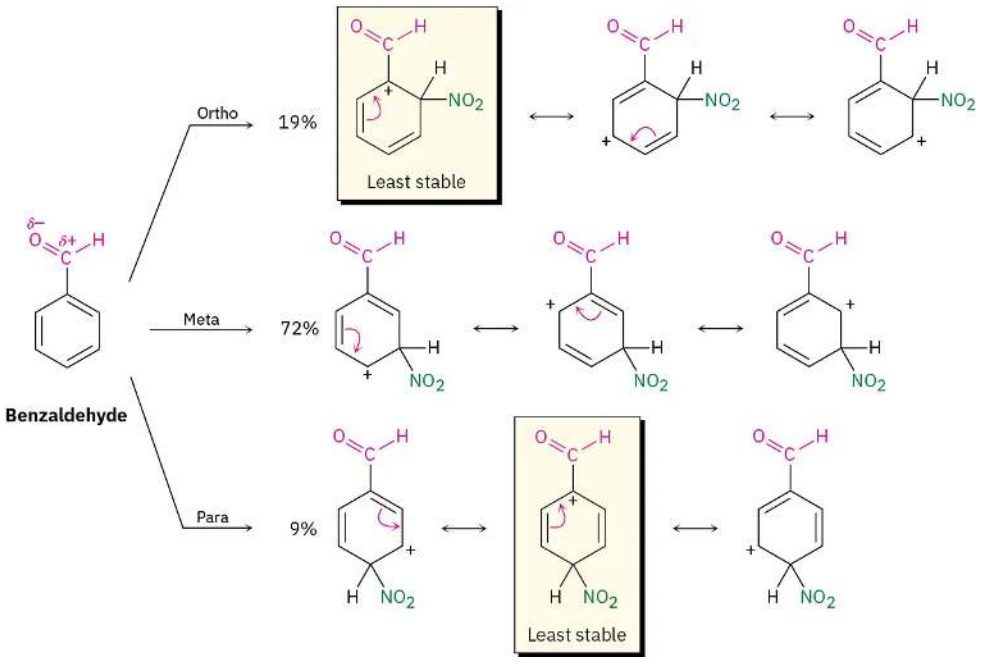


Figure 5.5.6: Carbocation intermediates in the nitration of benzaldehyde. The ortho and para intermediates are less stable than the meta intermediate. The meta intermediate is more favorable than ortho and para intermediates because it has three favorable resonance forms rather than two.

In general, any substituent that has a positively polarized atom (δ^+) directly attached to the ring will make one of the resonance forms of the ortho and para intermediates unfavorable and will thus act as a meta director.

? Exercise 5.5.6

Draw resonance structures for the intermediates from the reaction of an electrophile at the ortho, meta, and para positions of nitrobenzene. Which intermediates are most stable?

Answer

The meta intermediate is most favored.

A Summary of Substituent Effects in Electrophilic Aromatic Substitution

A summary of the activating and directing effects of substituents in electrophilic aromatic substitution is shown in Table 5.5.1.

Table 5.5.1: Substituent Effects in Electrophilic Aromatic Substitution

Substituent	Reactivity	Orienting effect	Inductive effect	Resonance effect
$-CH_3$	Activating	Ortho, para	Weak donating	—
$-OH$, $-NH_2$	Activating	Ortho, para	Weak withdrawing	Strong donating
–F, –Cl	Deactivating	Ortho, para	Strong withdrawing	Weak donating
–Br, –I				
$-NO_2$, –CN,	Deactivating	Meta	Strong withdrawing	Strong withdrawing
–CHO, $-CO_2R$				
–COR, $-CO_2H$				

This page titled 5.5: Substituent Effects in Electrophilic Substitutions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

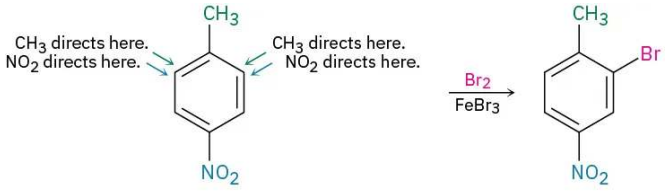
- **16.4: Substituent Effects in Electrophilic Substitutions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

5.6: Trisubstituted Benzenes- Additivity of Effects

Electrophilic substitution of a disubstituted benzene ring is governed by the same resonance and inductive effects that influence monosubstituted rings. The only difference is that it's necessary to consider the additive effects of two different groups. In practice, this isn't as difficult as it sounds; three rules are usually sufficient.

RULE 1

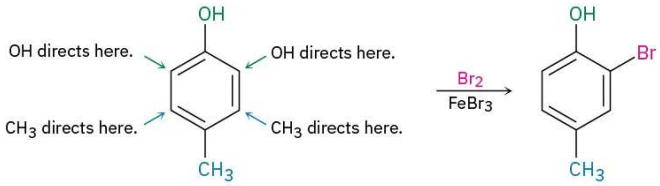
If the directing effects of the two groups reinforce each other, the situation is straightforward. In *p*-nitrotoluene, for example, both the methyl and the nitro group direct further substitution to the same position (ortho to the methyl = meta to the nitro). A single product is thus formed on electrophilic substitution.



***p*-Nitrotoluene** **2-Bromo-4-nitrotoluene**

RULE 2

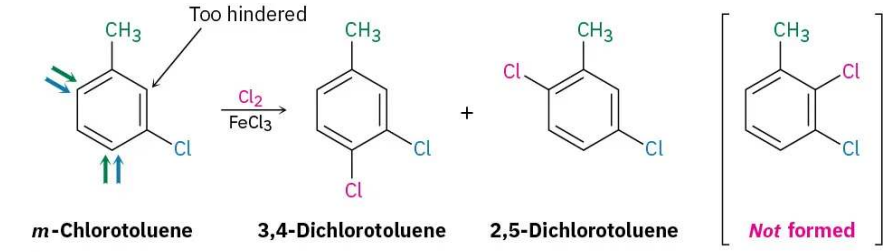
If the directing effects of the two groups oppose each other, the more powerful activating group has the dominant influence, but mixtures of products are often formed. For example, bromination of *p*-methylphenol yields primarily 2-bromo-4-methylphenol because –OH is a more powerful activator than $–CH_3$.



***p*-Methylphenol** **2-Bromo-4-methylphenol**

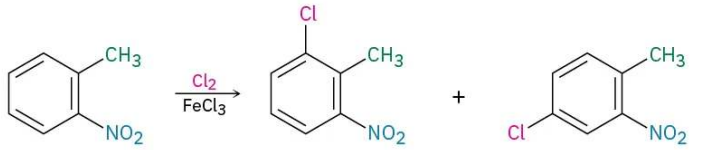
RULE 3

Further substitution rarely occurs between the two groups in a meta-disubstituted compound because this site is too hindered. Aromatic rings with three adjacent substituents must therefore be prepared by some other route, such as by substitution of an ortho-disubstituted compound.



***m*-Chlorotoluene** **3,4-Dichlorotoluene** **2,5-Dichlorotoluene** ***Not* formed**

But:



***o*-Nitrotoluene** **2-Chloro-6-nitrotoluene** **4-Chloro-2-nitrotoluene**

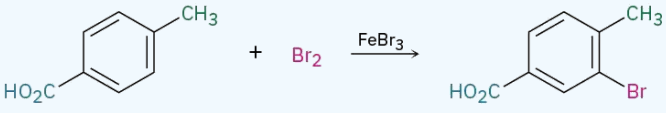
Worked Example 5.6.1: Predicting the Product of Substitution on a Disubstituted Benzene

What product would you expect from bromination of *p*-methylbenzoic acid?

Strategy

Identify the two substituents present on the ring, decide the directing effect of each and, if necessary, decide which substituent is the stronger activator. In the present case, the carboxyl group ($-CO_2H$) is a meta director and the methyl group is an ortho and para director. Both groups direct bromination to the position next to the methyl group, yielding 3-bromo-4-methylbenzoic acid.

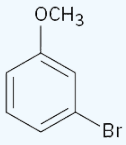
Solution

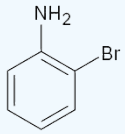


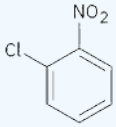
***p*-Methylbenzoic acid** **3-Bromo-4-methylbenzoic acid**

Exercise 5.6.1

At what position would you expect electrophilic substitution to occur in each of the following substances:

a. 

b. 

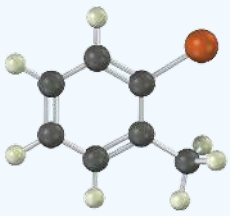
c. 

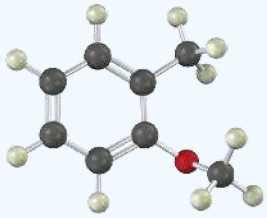
Answer

a. Ortho and para to $-OCH_3$
b. Ortho and para to $-NH_2$
c. Ortho and para to $-Cl$

Exercise 5.6.2

Show the major product(s) from reaction of the following substances with (1) CH_3CH_2Cl, $AlCl_3$ and (2) HNO_3, H_2SO_4:

a. 

b. 

Answer

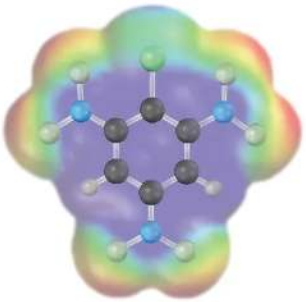
a. Reaction occurs ortho and para to the $-CH_3$ group.
b. Reaction occurs ortho and para to the $-OCH_3$ group.

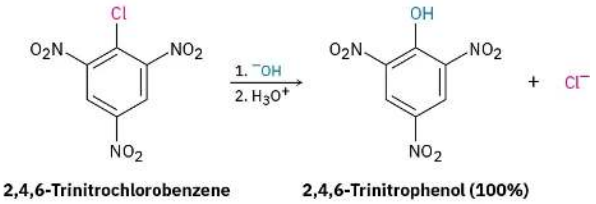
This page titled 5.6: Trisubstituted Benzenes- Additivity of Effects is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **16.5: Trisubstituted Benzenes- Additivity of Effects** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

5.7: Nucleophilic Aromatic Substitution

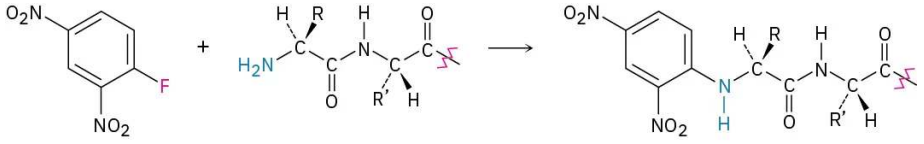
Although aromatic substitution reactions usually occur by an *electrophilic* mechanism, aryl halides that have electron-withdrawing substituents can also undergo a *nucleophilic* substitution reaction. For example, 2,4,6-trinitrochlorobenzene reacts with aqueous NaOH at room temperature to give 2,4,6-trinitrophenol. Here, the nucleophile OH^- substitutes for Cl^-.





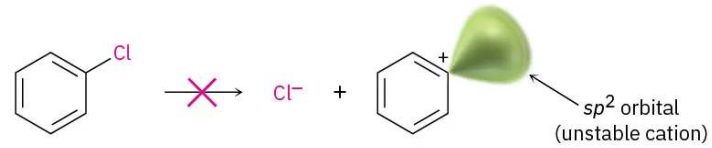
2,4,6-Trinitrochlorobenzene **2,4,6-Trinitrophenol (100%)**

Nucleophilic aromatic substitution is much less common than electrophilic substitution but nevertheless does have certain uses. One such use is the reaction of proteins with 2,4-dinitrofluorobenzene, known as *Sanger's reagent*, to attach a "label" to the terminal NH_2 group of the amino acid at one end of the protein chain.

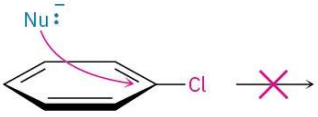


2,4-Dinitro-fluorobenzene **A protein** **A labeled protein**

Although the reaction appears superficially similar to the S_N1 and S_N2 nucleophilic substitutions of alkyl halides discussed in the chapter on Reactions of Alkyl Halides: Nucleophilic Substitutions and Eliminations, it must be different because aryl halides are inert to both S_N1 and S_N2 conditions. S_N1 reactions don't occur with aryl halides because dissociation of the halide is energetically unfavorable, due to the instability of the potential aryl cation product. S_N2 reactions don't occur with aryl halides because the halo-substituted carbon of the aromatic ring is sterically shielded from a backside approach. For a nucleophile to react with an aryl halide, it would have to approach directly through the aromatic ring and invert the stereochemistry of the aromatic ring carbon—a geometric impossibility.



Dissociation reaction does not occur because the aryl cation is unstable; therefore, no S_N1 reaction.



Backside displacement is sterically blocked; therefore, no S_N2 reaction.

Instead, nucleophilic substitutions on an aromatic ring proceed by the mechanism shown in Figure 5.7.1. The nucleophile first adds to the electron-deficient aryl halide, forming a resonance-stabilized, negatively charged intermediate called a *Meisenheimer complex* after its discoverer. Halide ion is then eliminated.

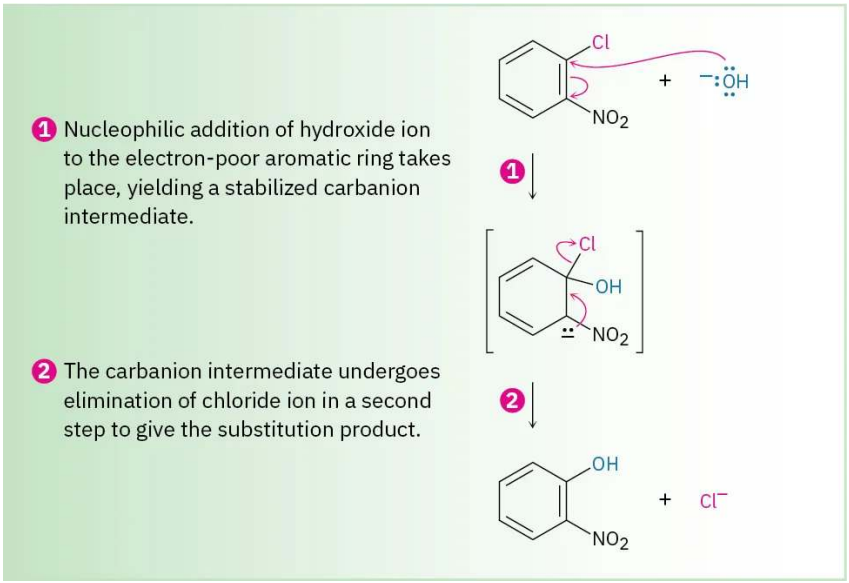


Figure 5.7.1: Mechanism of nucleophilic aromatic substitution. The reaction occurs in two steps and involves a resonance-stabilized carbanion intermediate.

Nucleophilic aromatic substitution occurs only if the aromatic ring has an electron-withdrawing substituent in a position ortho or para to the leaving group to stabilize the anion intermediate through resonance (Figure 5.7.2). A meta substituent offers no such resonance stabilization. Thus, *p*-chloronitrobenzene and *o*-chloronitrobenzene react with hydroxide ion at 130 °C to yield substitution products, but *m*-chloronitrobenzene is inert to OH^-.

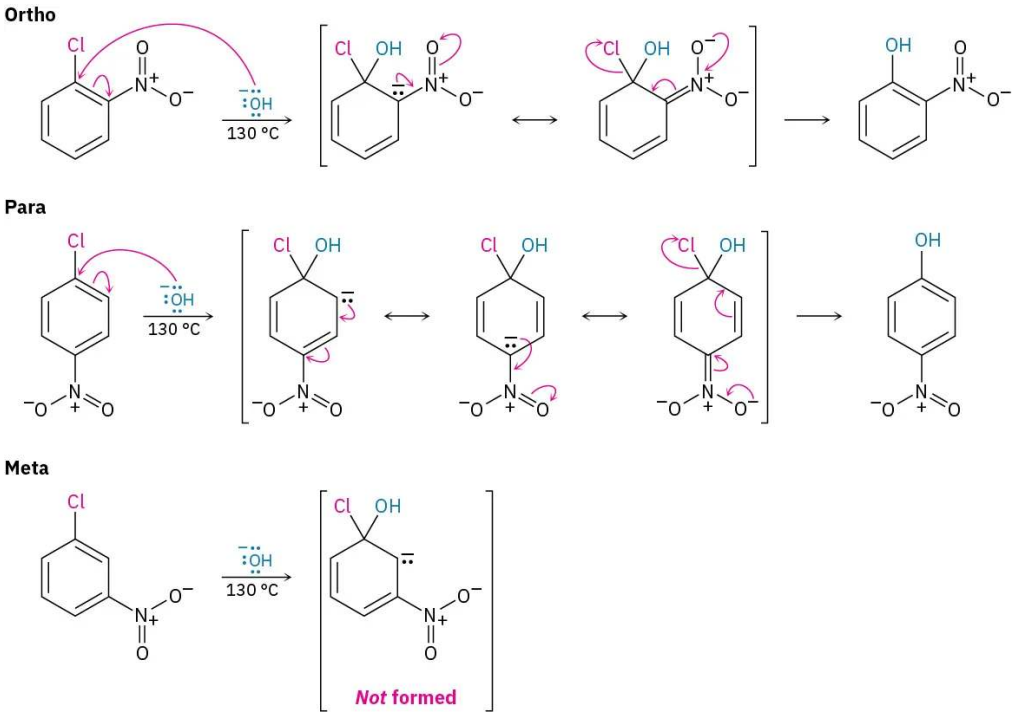


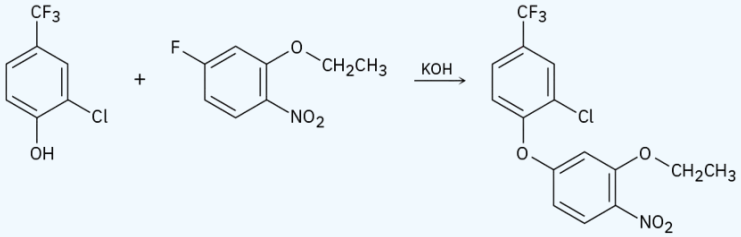
Figure 5.7.2: Nucleophilic aromatic substitution on nitrochlorobenzenes. Only in the ortho and para intermediates is the negative charge stabilized by a resonance interaction with the nitro group, so only the ortho and para isomers undergo reaction.

Note the differences between electrophilic and nucleophilic aromatic substitutions. Electrophilic substitutions are favored by electron-donating substituents, which stabilize a carbocation intermediate, while nucleophilic substitutions are favored by electron-withdrawing substituents, which stabilize a carbanion intermediate. Thus, the electron-withdrawing groups that deactivate rings for electrophilic substitution (nitro, carbonyl, cyano, and so forth) activate them for nucleophilic substitution. What's more, these functional groups are meta directors in electrophilic substitution but are ortho–para directors in nucleophilic substitution. And

finally, electrophilic substitutions replace hydrogen on the ring, while nucleophilic substitutions replace a leaving group, usually halide ion.

? Exercise 5.7.1

The herbicide oxyfluorfen can be prepared by reaction between a phenol and an aryl fluoride. Propose a mechanism.



Oxyfluorfen

Answer

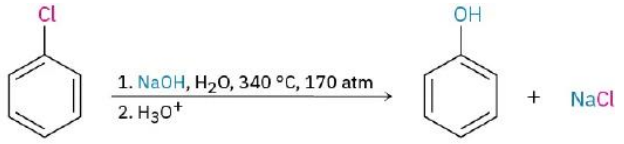
The phenol is deprotonated by KOH to give an anion that carries out a nucleophilic acyl substitution reaction on the 1-ethoxyl-5-fluoro-2-nitrobenzene.

This page titled 5.7: Nucleophilic Aromatic Substitution is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **16.6: Nucleophilic Aromatic Substitution** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

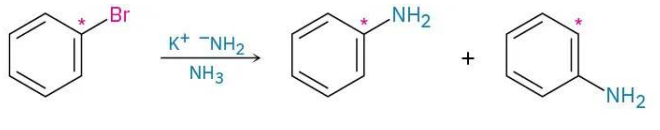
5.8: Benzyne

Halobenzenes without electron-withdrawing substituents don't react with nucleophiles under most conditions. At high temperature and pressure, however, even chlorobenzene can be forced to react. Chemists at the Dow Chemical Company discovered in 1928 that phenol could be prepared on an industrial scale by treatment of chlorobenzene with dilute aqueous NaOH at 340 °C under 170 atm pressure.



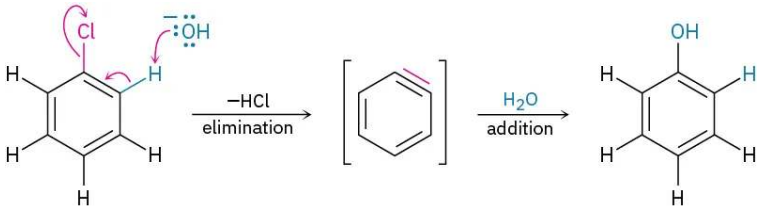
Chlorobenzene **Phenol**

A similar substitution reaction occurs with other strong bases. Treatment of bromobenzene with potassium amide (KNH_2) in liquid NH_3 solvent, for instance, gives aniline. Curiously, though, when using bromobenzene labeled with radioactive ^{14}C at the C1 position, the substitution product has equal amounts of the label at both C1 and C2, implying the presence of a symmetrical reaction intermediate in which C1 and C2 are equivalent.

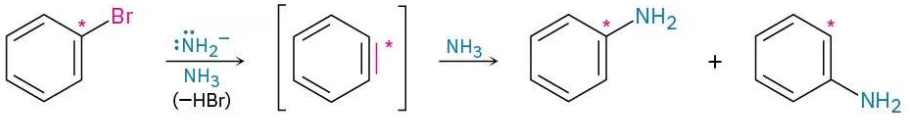


Bromobenzene **Aniline**

Further mechanistic evidence comes from trapping experiments. When bromobenzene is treated with KNH_2 in the presence of a conjugated diene, such as furan, a Diels–Alder reaction (Section 14.4) occurs, implying that the symmetrical intermediate is a benzyne, formed by elimination of HBr from bromobenzene. Benzyne is too reactive to be isolated as a pure compound but, in the presence of water, addition occurs to give phenol. In the presence of a diene, Diels–Alder cycloaddition takes place.



Chlorobenzene **Benzyne** **Phenol**



Bromobenzene **Benzyne (symmetrical)** **Aniline**

The electronic structure of benzyne, shown in Figure 5.8.1, is that of a highly distorted alkyne. Although a typical alkyne triple bond uses *sp*-hybridized carbon atoms, the benzyne triple bond uses sp^2-hybridized carbons. Furthermore, a typical alkyne triple bond has two mutually perpendicular π bonds formed by *p*–*p* overlap, but the benzyne triple bond has one π bond formed by *p*–*p* overlap and one π bond formed by sp^2–sp^2 overlap. The latter π bond is in the plane of the ring and is very weak.

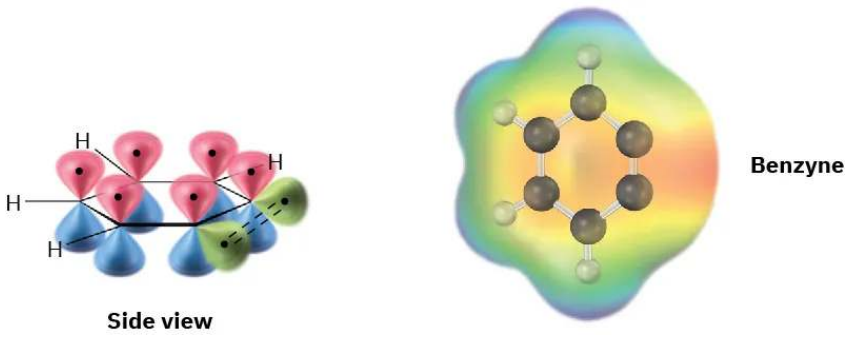


Figure 5.8.1: An orbital picture and electrostatic potential map of benzyne. The benzyne carbons are sp^2-hybridized, and the "third" bond results from weak overlap of two adjacent sp^2 orbitals.

? Exercise 5.8.1

Treatment of *p*-bromotoluene with NaOH at 300 °C yields a mixture of two products, but treatment of *m*-bromotoluene with NaOH yields a mixture of three products. Explain.

Answer

Only one benzyne intermediate can form from *p*-bromotoluene; two different benzyne intermediates can form from *m*-bromotoluene.

This page titled 5.8: Benzyne is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **16.7: Benzyne** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

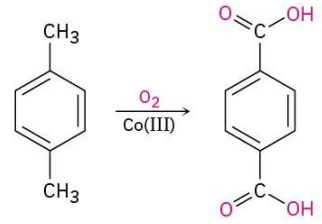
5.9: Oxidation of Aromatic Compounds

Oxidation of Alkyl Side Chains

Despite its unsaturation, the benzene ring is inert to strong oxidizing agents such as $KMnO_4$, which will cleave alkene carbon–carbon bonds (Section 8.8). It turns out, however, that the presence of the aromatic ring has a dramatic effect on the reactivity of alkyl side chains. These side chains react rapidly with oxidizing agents and are converted into carboxyl groups, $–CO_2H$.The net effect is conversion of an alkylbenzene into a benzoic acid, $Ar–R \rightarrow Ar–CO2HAr–R \rightarrow Ar–CO2H$. Butylbenzene is oxidized by aqueous $KMnO_4$ to give benzoic acid, for instance.

Butylbenzene **Benzoic acid (85%)**

A similar oxidation is employed industrially for the preparation of the terephthalic acid used in the production of polyester fibers. Worldwide, approximately 118 million tons per year of terephthalic acid is produced by oxidation of *p*-xylene, using air as the oxidant and Co(III) salts as catalyst.

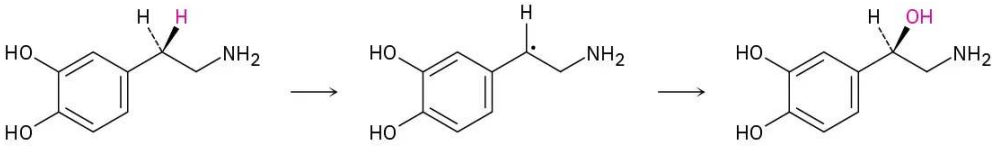


***p*-Xylene** **Terephthalic acid**

The mechanism of side-chain oxidation is complex and involves reaction of C–H bonds at the position next to the aromatic ring to form intermediate benzylic radicals. *tert*-Butylbenzene has no benzylic hydrogens, however, and is therefore inert.

***tert*-Butylbenzene**

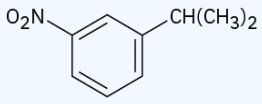
Analogous side-chain oxidations occur in various biosynthetic pathways. The neurotransmitter norepinephrine, for instance, is biosynthesized from dopamine by a benzylic hydroxylation reaction. The process is catalyzed by the copper-containing enzyme dopamine β-monooxygenase and occurs by a radical mechanism. A copper–oxygen species in the enzyme first abstracts the pro-R benzylic hydrogen to give a radical, and a hydroxyl is then transferred from copper to carbon.



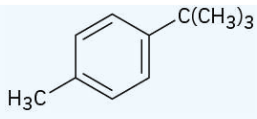
Dopamine **Norepinephrine**

? Exercise 5.9.1

What aromatic products would you obtain from the $KMnO_4$ oxidation of the following substances?



a.

b. 

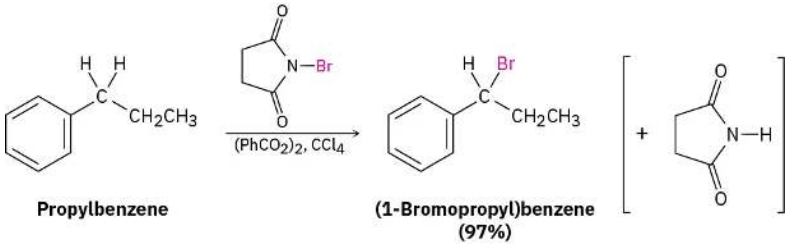
Answer

a. *m*-Nitrobenzoic acid

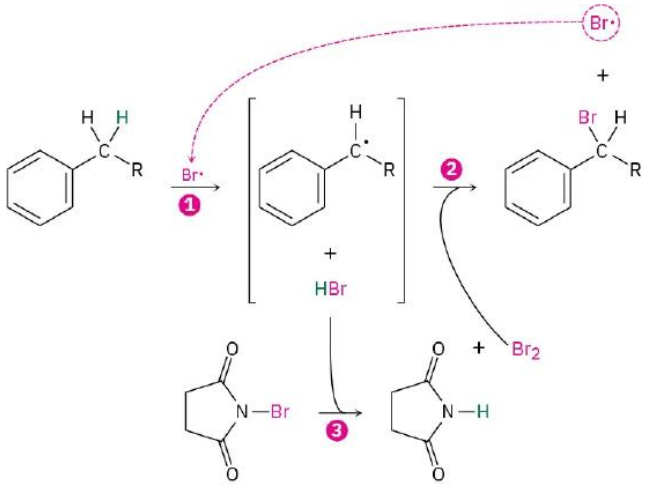
b. *p*-*tert*-Butylbenzoic acid

Bromination of Alkylbenzene Side Chains

Side-chain bromination at the benzylic position occurs when an alkylbenzene is treated with *N*-bromosuccinimide (NBS). For example, propylbenzene gives (1-bromopropyl)benzene in 97% yield on reaction with NBS in the presence of benzoyl peroxide, $(PhCO_2)_2$, as a radical initiator. Bromination occurs exclusively in the benzylic position next to the aromatic ring and does not give a mixture of products.



The mechanism of benzylic bromination is similar to that discussed in Section 10.3 for allylic bromination of alkenes. Abstraction of a benzylic hydrogen atom first generates an intermediate benzylic radical, which then reacts with Br_2 in step 2 to yield product and a Br· radical, which cycles back into the reaction to carry on the chain shown below as a summary. The Br_2 needed for reaction with the benzylic radical is produced in step 3 by a concurrent reaction of HBr with NBS.



Reaction occurs exclusively at the benzylic position because the benzylic radical intermediate is stabilized by resonance. Figure 5.9.1 shows how the benzyl radical is stabilized by overlap of its *p* orbital with the ringed π electron system.

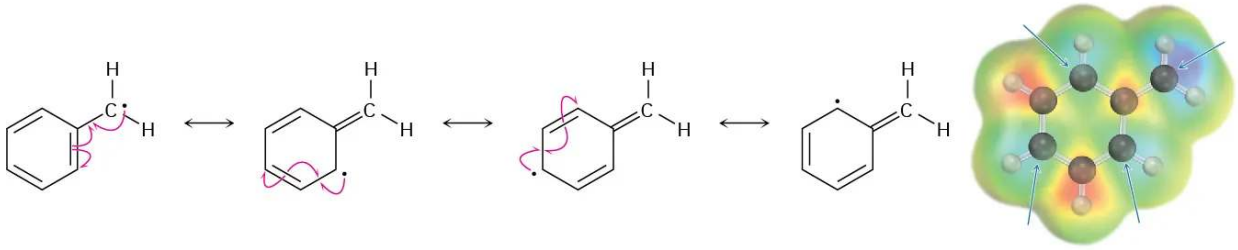


Figure 5.9.1: A resonance-stabilized benzylic radical. The spin-density surface shows that the **unpaired electron** is shared by the ortho and para carbons of the ring.

Exercise 5.9.2

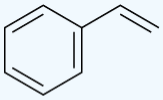
Refer to Table 6.3 for a quantitative idea of the stability of a benzyl radical. How much more stable (in kJ/mol) is the benzyl radical than a primary alkyl radical? How does a benzyl radical compare in stability to an allyl radical?

Answer

A benzyl radical is more stable than a primary alkyl radical by 52 kJ/mol and is similar in stability to an allyl radical.

Exercise 5.9.3

Styrene, the simplest alkenylbenzene, is prepared commercially for use in plastics manufacture by catalytic dehydrogenation of ethylbenzene. How might you prepare styrene from benzene using reactions you've studied?



Styrene

Answer

1. CH_3CH_2Cl, $AlCl_3$; 2. NBS; 3. KOH, ethanol.

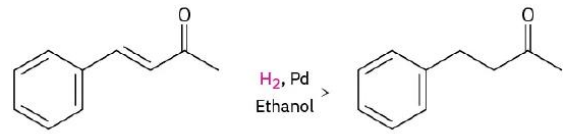
This page titled 5.9: Oxidation of Aromatic Compounds is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **16.8: Oxidation of Aromatic Compounds** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

5.10: Reduction of Aromatic Compounds

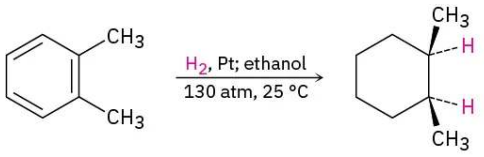
Catalytic Hydrogenation of Aromatic Rings

Just as aromatic rings are generally inert to oxidation, they're also inert to catalytic hydrogenation under conditions that reduce typical alkene double bonds. As a result, it's possible to reduce an alkene double bond selectively in the presence of an aromatic ring. For example, 4-phenyl-3-buten-2-one is reduced to 4-phenyl-2-butanone using a palladium catalyst at room temperature and atmospheric pressure. Neither the benzene ring nor the ketone carbonyl group is affected.

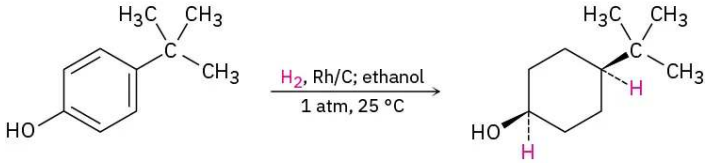


4-Phenyl-3-buten-2-one **4-Phenyl-2-butanone (100%)**

To hydrogenate an aromatic ring, it's necessary either to use a platinum catalyst with hydrogen gas at a pressure of several hundred atmospheres or to use a more effective catalyst such as rhodium on carbon. Under these conditions, aromatic rings are converted into cyclohexanes. For example, *o*-xylene yields 1,2-dimethylcyclohexane, and 4-*tert*-butylphenol gives 4-*tert*-butylcyclohexanol.



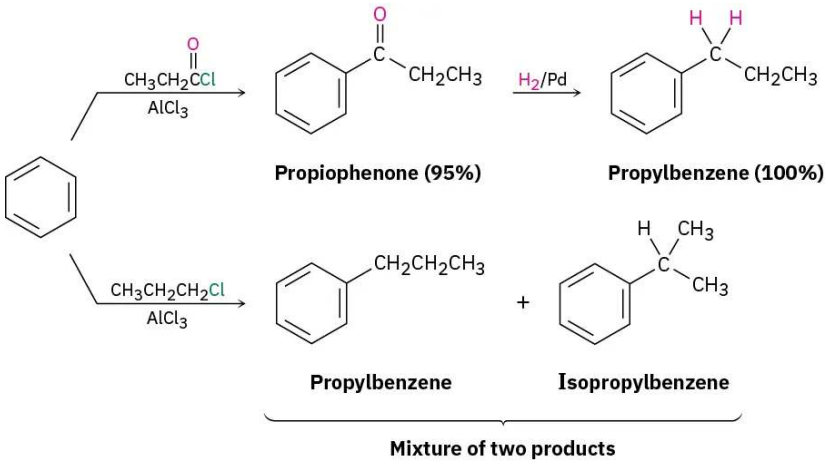
***o*-Xylene** ***cis*-1,2-Dimethyl-cyclohexane**



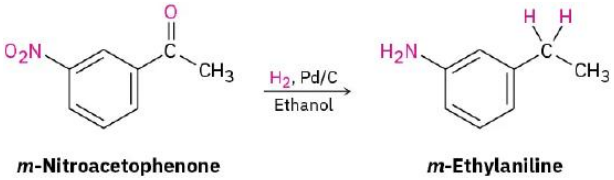
4-*tert*-Butylphenol ***cis*-4-*tert*-Butyl-cyclohexanol**

Reduction of Aryl Alkyl Ketones

In the same way that an aromatic ring activates a neighboring (benzylic) C–H toward oxidation, it also activates a benzylic carbonyl group toward reduction. Thus, an aryl alkyl ketone prepared by Friedel–Crafts acylation of an aromatic ring can be converted into an alkylbenzene by catalytic hydrogenation over a palladium catalyst. Propiophenone, for instance, is reduced to propylbenzene by catalytic hydrogenation. Because the net effect of Friedel–Crafts acylation followed by reduction is the preparation of a primary alkylbenzene, this two-step sequence of reactions makes it possible to circumvent the carbocation rearrangement problems associated with direct Friedel–Crafts alkylation using a primary alkyl halide (Section 16.3).



The conversion of a carbonyl group into a methylene group (C=O →) by catalytic hydrogenation is limited to *aryl* alkyl ketones; dialkyl ketones are not reduced under these conditions. Furthermore, the catalytic reduction of aryl alkyl ketones is not compatible with the presence of a nitro substituent on the aromatic ring because a nitro group is reduced to an amino group under reaction conditions. We'll see a more general method for reducing ketone carbonyl groups to yield alkanes in **Section 19.9**.



? Exercise 5.10.1

How would you prepare diphenylmethane, $(Ph)_2CH_2$, from benzene and an acid chloride?

Answer

1. PhCOCl, $AlCl_3$; 2. H_2/Pd

This page titled 5.10: Reduction of Aromatic Compounds is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **16.9: Reduction of Aromatic Compounds** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

5.11: Synthesis of Polysubstituted Benzenes

As discussed in the **Introduction to Organic Synthesis** in Section 9.9, one of the surest ways to learn organic chemistry is to work synthesis problems. The ability to plan a successful multistep synthesis of a complex molecule requires a working knowledge of the uses and limitations of a great many organic reactions. Not only must you know which reactions to use, you must also know when to use them because the order in which reactions are carried out is often critical to the success of the overall scheme.

The ability to plan a sequence of reactions in the right order is particularly important in the synthesis of substituted aromatic rings, where the introduction of a new substituent is strongly affected by the directing effects of other substituents. Planning syntheses of substituted aromatic compounds is therefore a good way to gain confidence in using the many reactions discussed in the past few chapters.

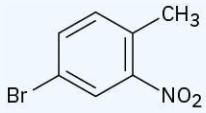
As we said in Section 9.9, it's usually best to work a synthesis problem backward, or *retrosynthetically.* Look at the target molecule and ask yourself, "What is an immediate precursor of this compound?" Choose a likely answer and continue working backward, one step at a time, until you arrive at a simple starting material. Let's try some examples.

Worked Example 5.11.1: Synthesizing a Polysubstituted Benzene

How would you synthesize 4-bromo-2-nitrotoluene from benzene?

Strategy

Draw the target molecule, identify the substituents, and recall how each group can be introduced separately. Then plan retrosynthetically.

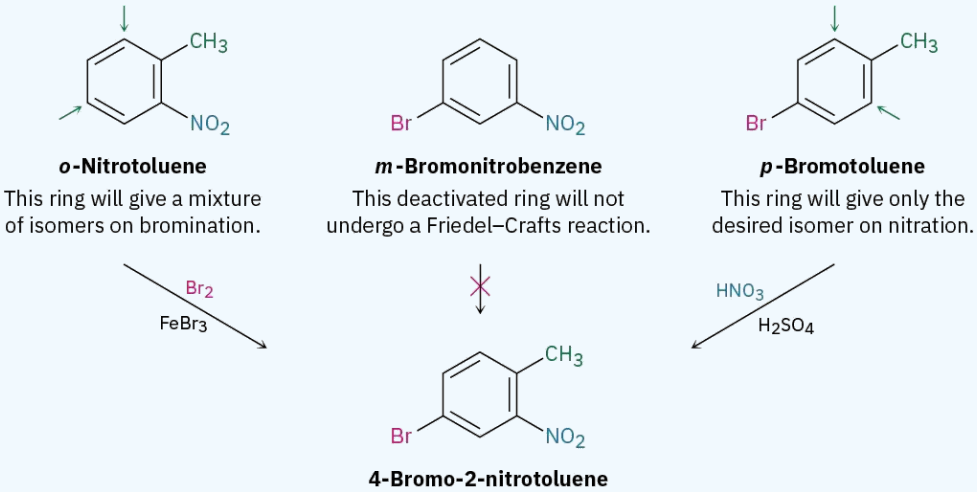


4-Bromo-2-nitrotoluene

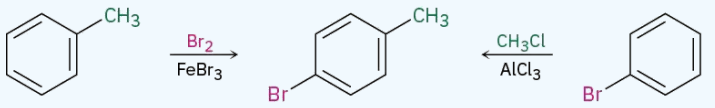
The three substituents on the ring are a bromine, a methyl group, and a nitro group. A bromine can be introduced by bromination with $Br_2/FeBr_3$, a methyl group can be introduced by Friedel–Crafts alkylation with $CH_3Cl/AlCl_3$, and a nitro group can be introduced by nitration with HNO_3/H_2SO_4.

Solution

Ask yourself, "What is an immediate precursor of the target?" The final step will involve introduction of one of three groups—bromine, methyl, or nitro—so we have to consider three possibilities. Of the three, the bromination of *o*-nitrotoluene could be used because the activating methyl group would dominate the deactivating nitro group and direct bromination to the correct position. Unfortunately, a mixture of product isomers would be formed. A Friedel–Crafts reaction can't be used as the final step because this reaction doesn't work on a nitro-substituted (strongly deactivated) benzene. The best precursor of the desired product is probably *p*-bromotoluene, which can be nitrated ortho to the activating methyl group to give a single product.



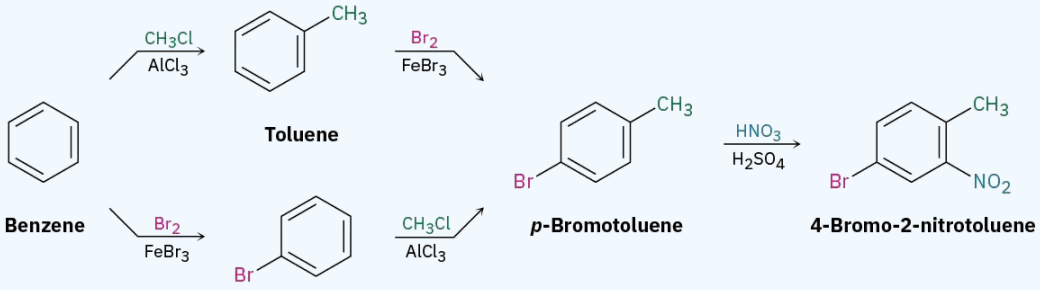
Next ask, "What is an immediate precursor of *p*-bromotoluene?" Perhaps toluene is an immediate precursor because the methyl group would direct bromination to the ortho and para positions. Alternatively, bromobenzene might be an immediate precursor because we could carry out a Friedel–Crafts methylation and obtain a mixture of ortho and para products. Both answers are satisfactory, although both would also lead unavoidably to a mixture of products that would have to be separated.



Toluene | ***p*-Bromotoluene (+ ortho isomer)** | **Bromobenzene**

"What is an immediate precursor of toluene?" Benzene, which could be methylated in a Friedel–Crafts reaction. Alternatively, "What is an immediate precursor of bromobenzene?" Benzene, which could be brominated.

The retrosynthetic analysis has provided two valid routes from benzene to 4-bromo-2-nitrotoluene.

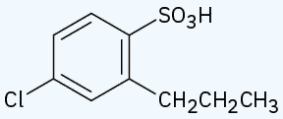


Worked Example 5.11.2: Synthesizing a Polysubstituted Benzene

Synthesize 4-chloro-2-propylbenzenesulfonic acid from benzene.

Strategy

Draw the target molecule, identify its substituents, and recall how each of the three can be introduced. Then plan retrosynthetically.

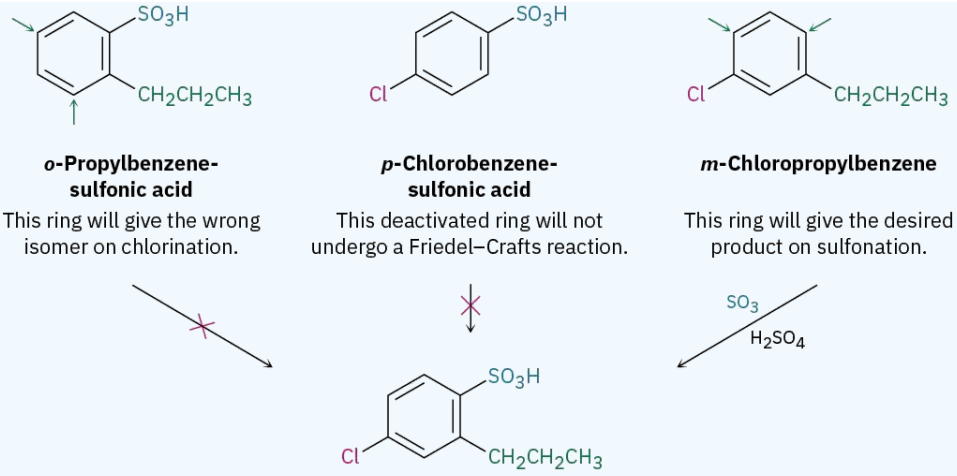


4-Chloro-2-propylbenzenesulfonic acid

The three substituents on the ring are a chlorine, a propyl group, and a sulfonic acid group. A chlorine can be introduced by chlorination with $Cl_2/FeCl_3$, a propyl group can be introduced by Friedel–Crafts acylation with $CH_3CH_2COCl/AlCl_3$ followed by reduction with H_2/Pd, and a sulfonic acid group can be introduced by sulfonation with SO_3/H_2SO_4.

Solution

"What is an immediate precursor of the target?" The final step will involve introduction of one of three groups—chlorine, propyl, or sulfonic acid—so we have to consider three possibilities. Of the three, the chlorination of *o*-propylbenzenesulfonic acid can't be used because the reaction would occur at the wrong position. Similarly, a Friedel–Crafts reaction can't be used as the final step because this reaction doesn't work on sulfonic-acid-substituted (strongly deactivated) benzenes. Thus, the immediate precursor of the desired product is probably *m*-chloropropylbenzene, which can be sulfonated to give a mixture of product isomers that must then be separated.



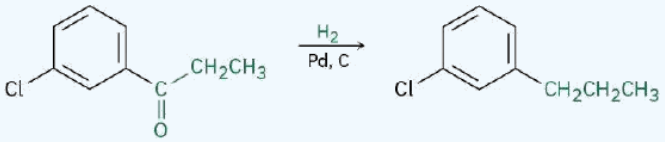
***o*-Propylbenzene-sulfonic acid**
This ring will give the wrong isomer on chlorination.

***p*-Chlorobenzene-sulfonic acid**
This deactivated ring will not undergo a Friedel–Crafts reaction.

***m*-Chloropropylbenzene**
This ring will give the desired product on sulfonation.

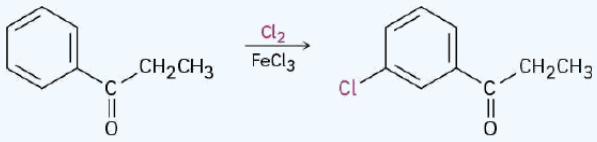
4-Chloro-2-propylbenzenesulfonic acid

"What is an immediate precursor of *m*-chloropropylbenzene?" Because the two substituents have a meta relationship, the first substituent placed on the ring must be a meta director so that the second substitution will take place at the proper position. Furthermore, because primary alkyl groups such as propyl can't be introduced directly by Friedel–Crafts alkylation, the precursor of *m*-chloropropylbenzene is probably *m*-chloropropiophenone, which could be catalytically reduced.



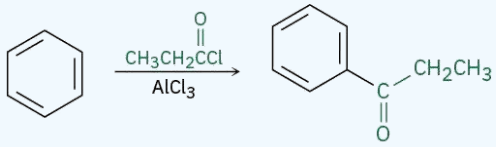
***m*-Chloropropiophenone** ***m*-Chloropropylbenzene**

"What is an immediate precursor of *m*-chloropropiophenone?" Propiophenone, which could be chlorinated in the meta position.



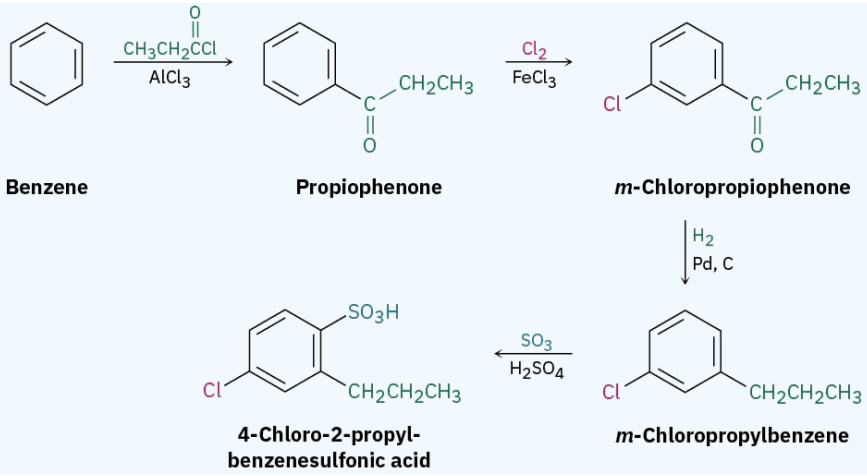
Propiophenone ***m*-Chloropropiophenone**

"What is an immediate precursor of propiophenone?" Benzene, which could undergo Friedel–Crafts acylation with propanoyl chloride and $AlCl_3$.



Benzene **Propiophenone**

The final synthesis is a four-step route from benzene:



Planning an organic synthesis has been compared with playing chess. There are no tricks; all that's required is a knowledge of the allowable moves (the organic reactions) and the discipline to plan ahead, carefully evaluating the consequences of each move. Practicing may not be easy, but it's a great way to learn organic chemistry.

? Exercise 5.11.1

How might you synthesize the following substances from benzene?

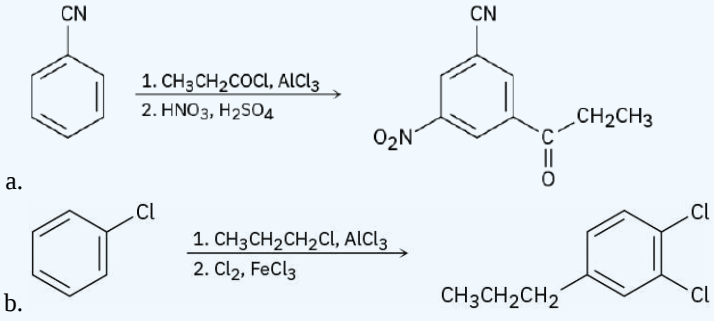
a. *m*-Chloronitrobenzene
b. *m*-Chloroethylbenzene
c. 4-Chloro-1-nitro-2-propylbenzene
d. 3-Bromo-2-methylbenzenesulfonic acid

Answer

a. 1. HNO_3, H_2SO_4; 2. Cl_2, $FeCl_3$
b. 1. CH_3COCl, $AlCl_3$; 2. Cl_2, $FeCl_3$; 3. H_2/Pd
c. 1. CH_3CH_2COCl, $AlCl_3$; 2. Cl_2, $FeCl_3$; 3. H_2/Pd; 4. HNO_3, H_2SO_4
d. 1. CH_3Cl, $AlCl_3$; 2. Br_2, $FeBr_3$; 3. SO_3, H_2SO_4

? Exercise 5.11.2

In planning a synthesis, it's as important to know what not to do as to know what to do. As written, the following reaction schemes have flaws in them. What is wrong with each?



Answer

a. Friedel–Crafts acylation does not occur on a deactivated ring.
b. Rearrangement occurs during Friedel–Crafts alkylation with primary halides; chlorination occurs ortho to the alkyl group.

https://chem.libretexts.org/@go/page/564198

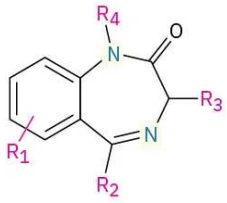
This page titled 5.11: Synthesis of Polysubstituted Benzenes is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **16.10: Synthesis of Polysubstituted Benzenes** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

5.12: Chemistry Matters—Combinatorial Chemistry

Traditionally, organic compounds have been synthesized one at a time. This works well for preparing large amounts of a few substances, but it doesn't work so well for preparing small amounts of a great many substances. This latter goal is particularly important in the pharmaceutical industry, where vast numbers of structurally similar compounds must be synthesized and screened to find an optimum drug candidate.

To speed the process of drug discovery, combinatorial chemistry has been developed to prepare what are called *combinatorial libraries*, in which anywhere from a few dozen to several hundred thousand substances are prepared simultaneously. Among the early successes of combinatorial chemistry is the development of a benzodiazepine library, a class of aromatic compounds commonly used as antianxiety agents.



Benzodiazepine library (R_1–R_4 are various organic substituents)

Two main approaches to combinatorial chemistry are used—*parallel synthesis* and *split synthesis*. In parallel synthesis, each compound is prepared independently. Typically, a reactant is first linked to the surface of polymer beads, which are then placed into small wells on a 96-well glass plate. Programmable robotic instruments add different sequences of building blocks to the different wells, thereby making 96 different products. When the reaction sequences are complete, the polymer beads are washed and their products are released.

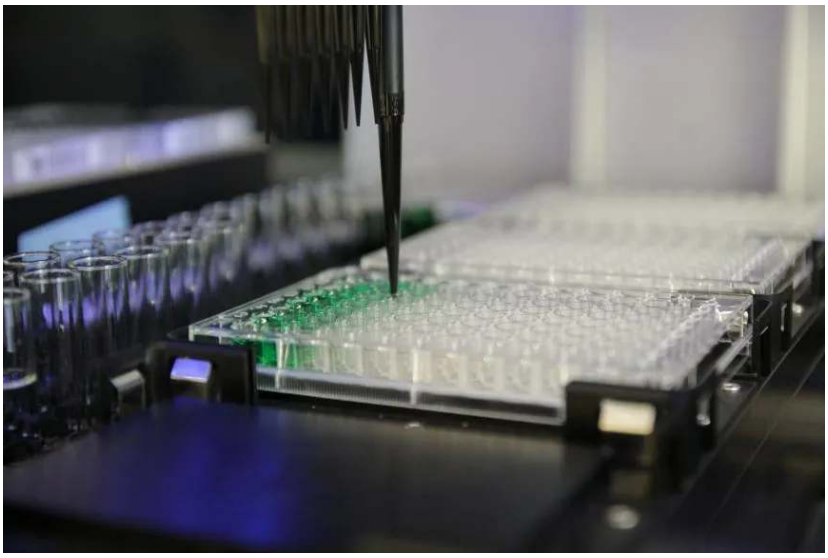


Figure 5.12.1: Organic chemistry by robot means no spilled flasks!

In split synthesis, the initial reactant is again linked to the surface of polymer beads, which are then divided into several groups. A different building block is added to each group of beads, the different groups are combined, and the reassembled mix is again split to form new groups. Another building block is added to each group, the groups are again combined and redivided, and the process continues. If, for example, the beads are divided into four groups at each step, the number of compounds increases in the progression 4 → 16 → 64 → 256. After 10 steps, more than 1 million compounds have been prepared (Figure 5.12.2).

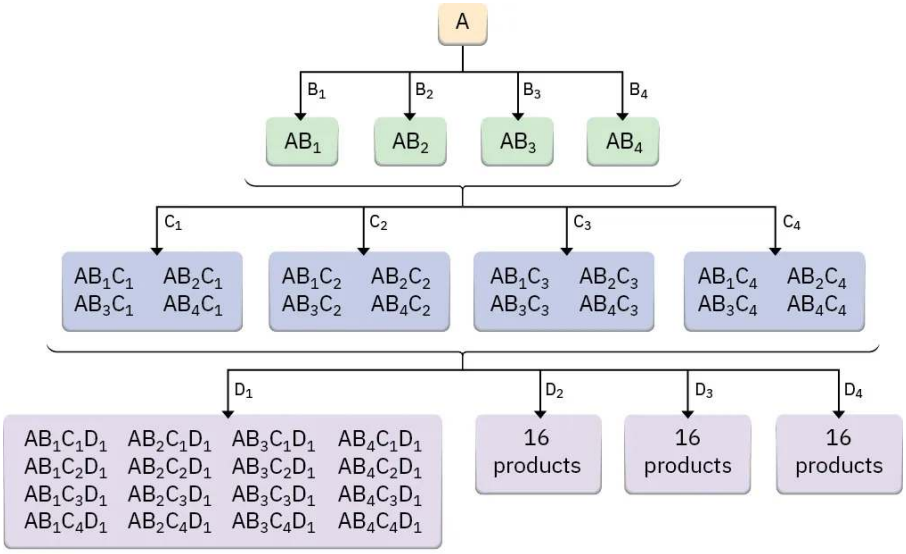


Figure 5.12.2: The results of split combinatorial synthesis. Assuming that 4 different building blocks are used at each step, 64 compounds result after 3 steps, and more than one million compounds result after 10 steps.

Of course, with so many different final products mixed together, the problem is to identify them. What structure is linked to what bead? Several approaches to this problem have been developed, all of which involve the attachment of encoding labels to each polymer bead to keep track of the chemistry each has undergone. Encoding labels used thus far have included proteins, nucleic acids, halogenated aromatic compounds, and even computer chips.

This page titled 5.12: Chemistry Matters—Combinatorial Chemistry is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **16.11: Chemistry Matters—Combinatorial Chemistry** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

5.13: Key Terms

- acyl group
- acylation
- alkylation
- benzyne
- combinatorial chemistry
- electrophilic aromatic substitution
- Friedel–Crafts reaction
- inductive effect
- nucleophilic aromatic substitution
- resonance effect

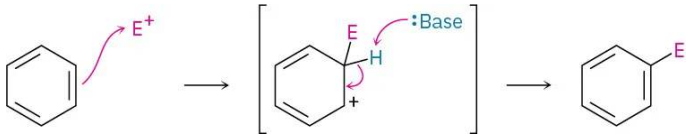
This page titled 5.13: Key Terms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **16.12: Key Terms** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

5.14: Summary

We've continued the coverage of aromatic molecules in this chapter, shifting focus to concentrate on reactions. In particular, we've looked at the relationship between aromatic structure and reactivity, a relationship critical to understanding how numerous biological molecules and pharmaceutical agents are synthesized and why they behave as they do.

An **electrophilic aromatic substitution reaction** takes place in two steps—initial reaction of an electrophile, $\mathbf{E}^+$, with the aromatic ring, followed by loss of H^+ from the resonance-stabilized carbocation intermediate to regenerate the aromatic ring.



Many variations of the reaction can be carried out, including halogenation, nitration, and sulfonation. **Friedel–Crafts alkylation** and **acylation** reactions, which involve reaction of an aromatic ring with carbocation electrophiles, are particularly useful. They are limited, however, by the fact that the aromatic ring must be at least as reactive as a halobenzene. In addition, polyalkylation and carbocation rearrangements often occur in Friedel–Crafts alkylation.

Substituents on the benzene ring affect both the reactivity of the ring toward further substitution and the orientation of that substitution. Groups can be classified as ortho- and para-directing activators, ortho- and para-directing deactivators, or meta-directing deactivators. Substituents influence aromatic rings by a combination of resonance and inductive effects. **Resonance effects** are transmitted through π bonds; **inductive effects** are transmitted through σ bonds.

Halobenzenes undergo **nucleophilic aromatic substitution** through either of two mechanisms. If the halobenzene has a strongly electron-withdrawing substituent in the ortho or para position, substitution occurs by addition of a nucleophile to the ring, followed by elimination of halide from the intermediate anion. If the halobenzene is not activated by an electron-withdrawing substituent, substitution can occur by elimination of HX to give a **benzyne**, followed by addition of a nucleophile.

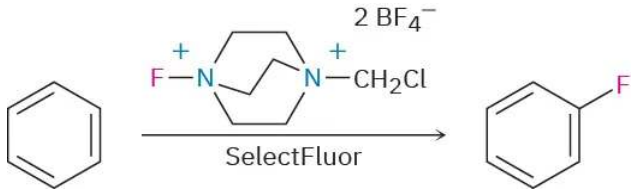
The benzylic position of an alkylbenzene can be brominated by reaction with *N*-bromosuccinimide, and the entire side chain can be degraded to a carboxyl group by oxidation with aqueous $KMnO_4$. Aromatic rings can also be reduced to cyclohexanes by hydrogenation over a platinum or rhodium catalyst, and aryl alkyl ketones are reduced to alkylbenzenes by hydrogenation over a platinum catalyst.

This page titled 5.14: Summary is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

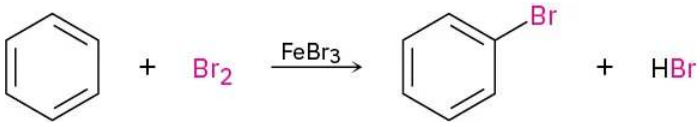
- **16.13: Summary** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

5.15: Summary of Reactions

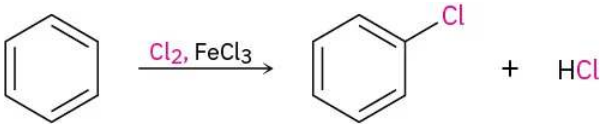
1. Electrophilic aromatic substitution
   a. Fluorination (Section 16.2)



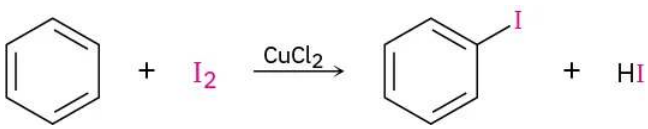
- Bromination (Section 16.1)



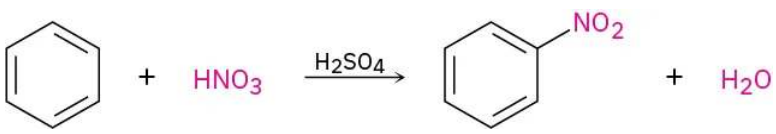
- Chlorination (Section 16.2)



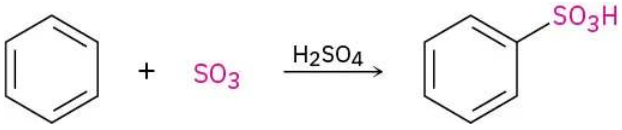
- Iodination (Section 16.2)



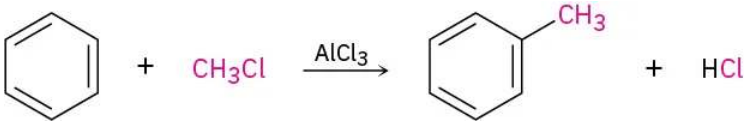
- Nitration (Section 16.2)



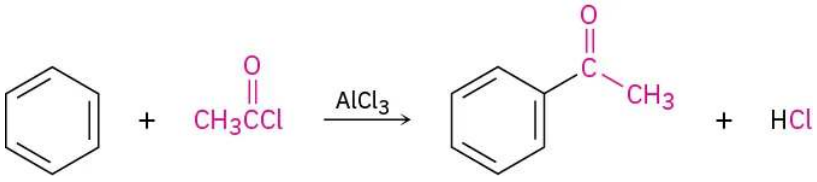
- Sulfonation (Section 16.2)



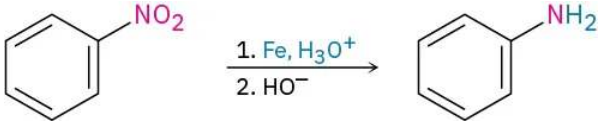
- Friedel–Crafts alkylation (Section 16.3)



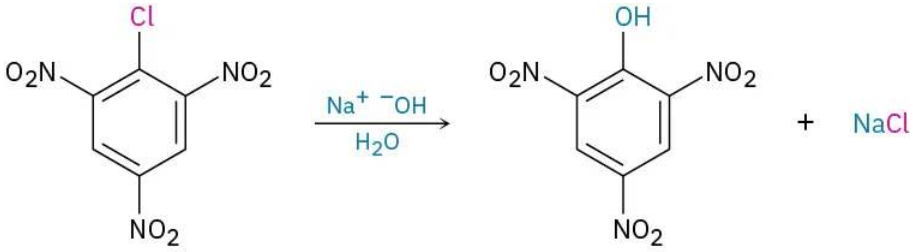
- Friedel–Crafts acylation (Section 16.3)



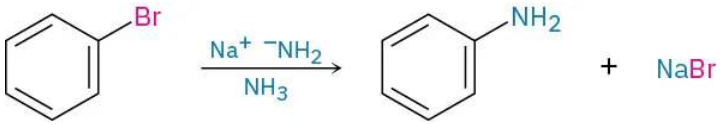
- Reduction of aromatic nitro groups (Section 16.2)



- Nucleophilic aromatic substitution
  a. By addition to activated aryl halides (Section 16.6)

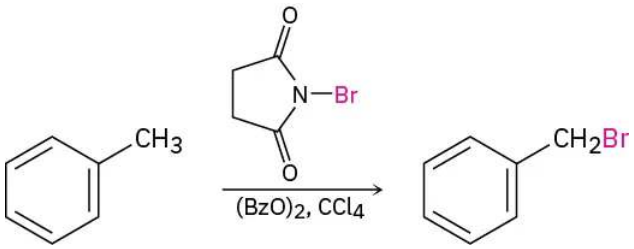


b. By formation of benzyne intermediate from unactivated aryl halide (Section 16.7)

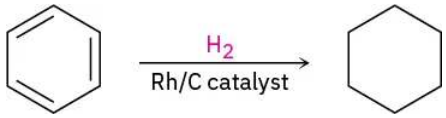


- Oxidation of alkylbenzene side chain (Section 16.8)

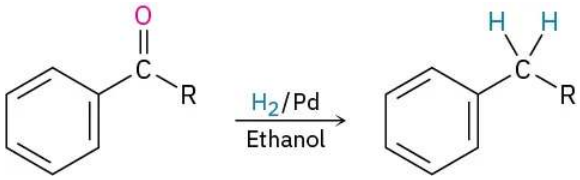
- Benzylic bromination of alkylbenzene side chain (Section 16.8)



- Catalytic hydrogenation of aromatic ring (Section 16.9)



- Reduction of aryl alkyl ketones (Section 16.9)



This page titled 5.15: Summary of Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

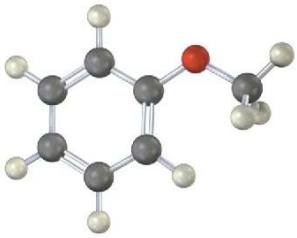
- **16.14: Summary of Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

5.16: Additional Problems

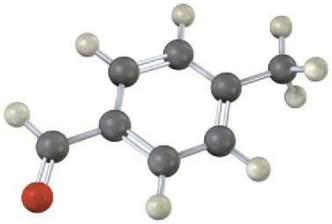
16 • Additional Problems

Visualizing Chemistry

PROBLEM 16-24 Draw the product from reaction of each of the following substances with (1) Br_2, $FeBr_3$ and (2) CH_3COCl, $AlCl_3$.

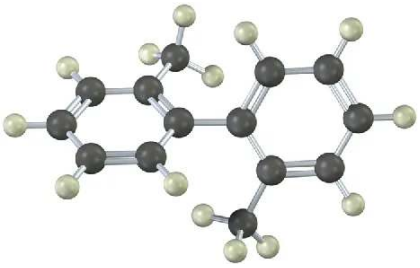


(a)

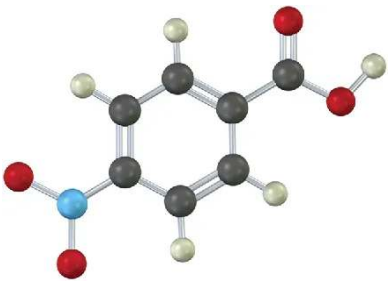


(b)

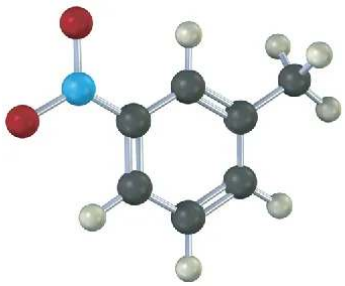
PROBLEM 16-25 The following molecular model of a dimethyl-substituted biphenyl represents the lowest-energy conformation of the molecule. Why are the two benzene rings tilted at a 63° angle to each other rather than being in the same plane so that their *p* orbitals overlap? Why doesn't complete rotation around the single bond joining the two rings occur?



PROBLEM 16-26 How would you synthesize the following compound starting from benzene? More than one step is needed.



PROBLEM 16-27 The following compound can't be synthesized using the methods discussed in this chapter. Why not?



Mechanisms of Electrophilic Substitutions

PROBLEM 16-28 Aromatic iodination can be carried out with a number of reagents, including iodine monochloride, ICl. What is the direction of polarization of ICl? Propose a mechanism for the iodination of an aromatic ring with ICl.

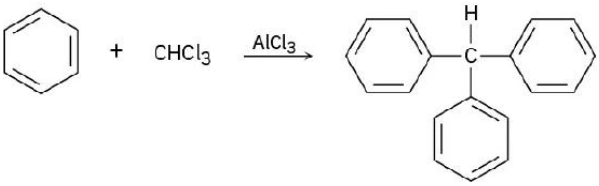
PROBLEM 16-29 The sulfonation of an aromatic ring with SO_3 and H_2SO_4 is reversible. That is, heating benzenesulfonic acid with H_2SO_4 yields benzene. Show the mechanism of the desulfonation reaction. What is the electrophile?

PROBLEM 16-30 The carbocation electrophile in a Friedel–Crafts reaction can be generated by an alternate means than reaction of an alkyl chloride with $AlCl_3$. For example, reaction of benzene with 2-methylpropene in the presence of H_3PO_4 yields *tert*-butylbenzene. Propose a mechanism for this reaction.

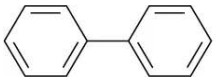
PROBLEM 16-31 The *N*,*N*,*N*-trimethylammonium group, $-\overset{+}{N}(CH_3)_3$, is one of the few groups that is a meta-directing deactivator yet has no electron-withdrawing resonance effect. Explain.

PROBLEM 16-32 The nitroso group, –N=O, is one of the few nonhalogens that is an ortho- and para-directing deactivator. Explain this behavior by drawing resonance structures of the carbocation intermediates in ortho, meta, and para electrophilic reaction on nitrosobenzene, $C_6H_5N{=}O$.

PROBLEM 16-33 Triphenylmethane can be prepared by reaction of benzene and chloroform in the presence of $AlCl_3$. Propose a mechanism for the reaction.

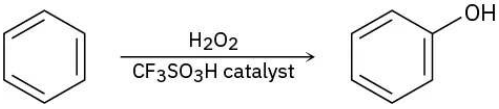


PROBLEM 16-34 Using resonance structures of the intermediates, explain why bromination of biphenyl occurs at ortho and para positions rather than at meta.



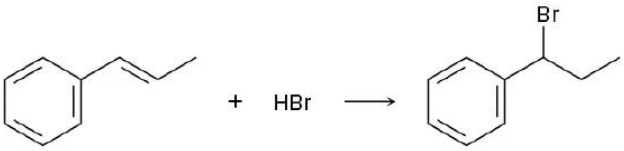
Biphenyl

PROBLEM 16-35 Benzene and alkyl-substituted benzenes can be hydroxylated by reaction with H_2O_2 in the presence of an acidic catalyst. What is the structure of the reactive electrophile? Propose a mechanism for the reaction.

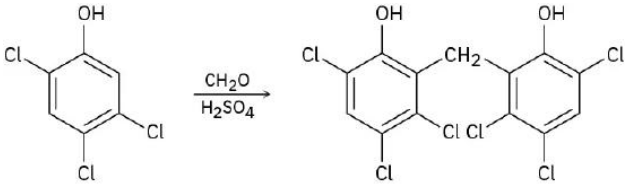


Additional Mechanism Practice

PROBLEM 16-36 Addition of HBr to 1-phenylpropene yields only (1-bromopropyl)benzene. Propose a mechanism for the reaction, and explain why none of the other regioisomer is produced.

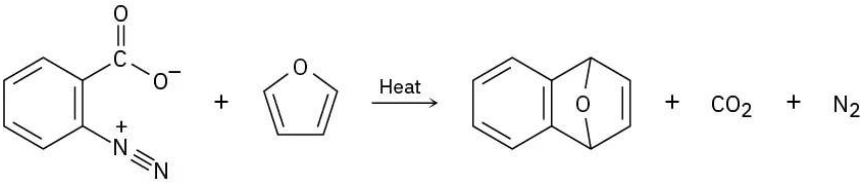


PROBLEM 16-37 Hexachlorophene, a substance used in the manufacture of germicidal soaps, is prepared by reaction of 2,4,5-trichlorophenol with formaldehyde in the presence of concentrated sulfuric acid. Propose a mechanism for the reaction.



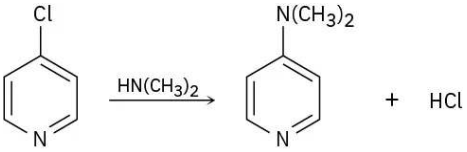
Hexachlorophene

PROBLEM 16-38 Benzenediazonium carboxylate decomposes when heated to yield N_2, CO_2, and a reactive substance that can't be isolated. When benzene-diazonium carboxylate is heated in the presence of furan, the following reaction is observed:

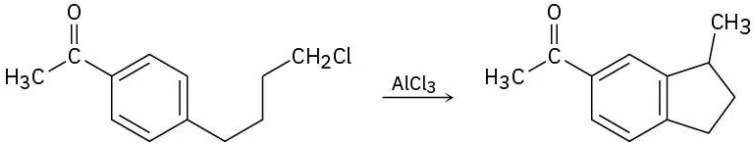


What intermediate is involved in this reaction? Propose a mechanism for its formation.

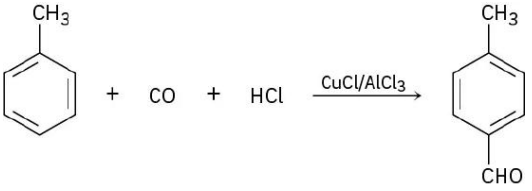
PROBLEM 16-39 4-Chloropyridine undergoes reaction with dimethylamine to yield 4-dimethylaminopyridine. Propose a mechanism for the reaction.



PROBLEM 16-40 Propose a mechanism to account for the following reaction:

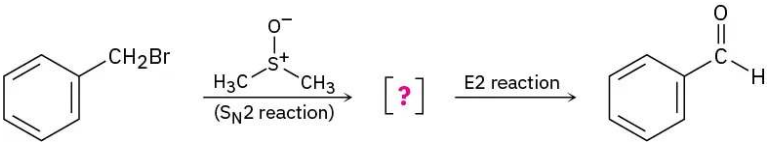


PROBLEM 16-41 In the *Gatterman–Koch reaction*, a formyl group (–CHO) is introduced directly onto a benzene ring. For example, reaction of toluene with CO and HCl in the presence of mixed $CuCl/AlCl_3$ gives *p*-methylbenzaldehyde. Propose a mechanism.

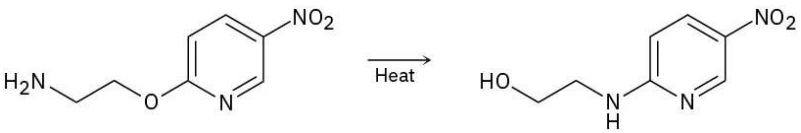


PROBLEM 16-42 Treatment of *p-tert*-butylphenol with a strong acid such as H_2SO_4 yields phenol and 2-methylpropene. Propose a mechanism.

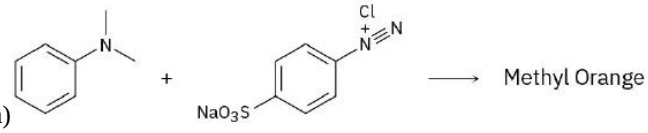
PROBLEM 16-43 Benzyl bromide is converted into benzaldehyde by heating in dimethyl sulfoxide. Propose a structure for the intermediate, and show the mechanisms of the two steps in the reaction.

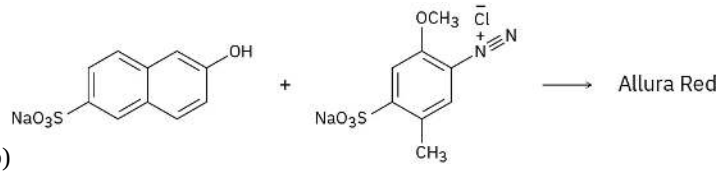


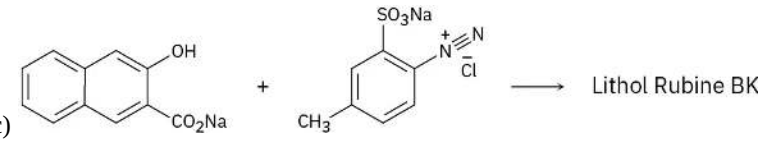
PROBLEM 16-44 Propose a mechanism for the *Smiles rearrangement* below.



PROBLEM 16-44 Because of their conjugation, azo dyes are highly colored compounds and the major artificial color source for textiles and food. Azo dyes are produced by the reaction of aryl diazonium salts with a second aromatic compound. In the product, the aromatic rings are linked by a diazo bridge (–N=N–). From the reactants provided, propose a structure for each azo dye and draw the electron-pushing mechanism.

(a)


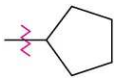
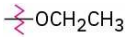
(b)


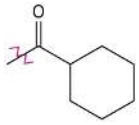
(c)


Reactivity and Orientation of Electrophilic Substitutions

PROBLEM 16-46 Identify each of the following groups as an activator or deactivator and as an *o*,*p*-director or *m*-director:

(a)

(b) 
(c) 

(d) 

PROBLEM 16-47 Predict the major product(s) of nitration of the following substances. Which react faster than benzene, and which slower?

(a) Bromobenzene (b) Benzonitrile (c) Benzoic acid (d) Nitrobenzene (e) Benzenesulfonic acid (f) ethoxybenzene

PROBLEM 16-48 Rank the compounds in each group according to their reactivity toward electrophilic substitution.

- (a) Chlorobenzene, *o*-dichlorobenzene, benzene
- (b) *p*-Bromonitrobenzene, nitrobenzene, phenol
- (c) Fluorobenzene, benzaldehyde, *o*-xylene
- (d) Benzonitrile, *p*-methylbenzonitrile, *p*-methoxybenzonitrile

PROBLEM 16-49 Predict the major monoalkylation products you would expect to obtain from reaction of the following substances with chloromethane and $AlCl_3$:

(a) Bromobenzene (b) *m*-Bromophenol (c) *p*-Chloroaniline (d) 2,4-Dichloronitrobenzene

(e) 2,4-Dichlorophenol (f) Benzoic acid (g) *p*-Methylbenzenesulfonic acid (h) 2,5-Dibromotoluene

PROBLEM 16-50 Name and draw the major product(s) of electrophilic chlorination of the following compounds:

(a) *m*-Nitrophenol (b) *o*-Xylene (c) *p*-Nitrobenzoic acid (d) *p*-Bromobenzenesulfonic acid

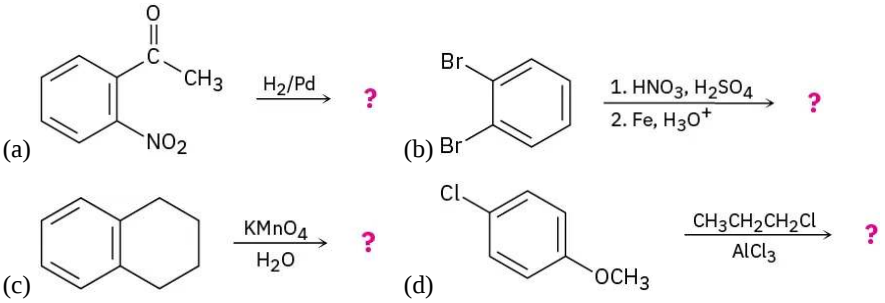
PROBLEM 16-51 Predict the major product(s) you would obtain from sulfonation of the following compounds:

(a) Fluorobenzene (b) *m*-Bromophenol (c) *m*-Dichlorobenzene (d) 2,4-Dibromophenol

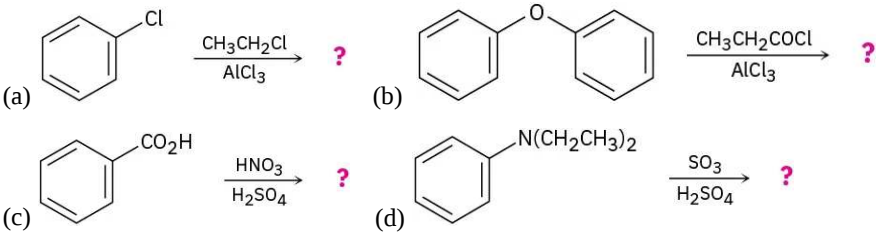
PROBLEM 16-52 Rank the following aromatic compounds in the expected order of their reactivity toward Friedel–Crafts alkylation. Which compounds are unreactive?

(a) Bromobenzene (b) Toluene (c) Phenol (d) Aniline (e) Nitrobenzene (f) *p*-Bromotoluene

PROBLEM 16-53 What product(s) would you expect to obtain from the following reactions:



PROBLEM 16-54 Predict the mayor product(s) of the following reactions:



Organic Synthesis

PROBLEM 16-55 How would you synthesize the following substances starting from benzene or phenol? Assume that ortho- and para-substitution products can be separated. (a) *o*-Bromobenzoic acid (b) *p*-Methoxytoluene (c) 2,4,6-Trinitrobenzoic acid (d) *m*-Bromoaniline

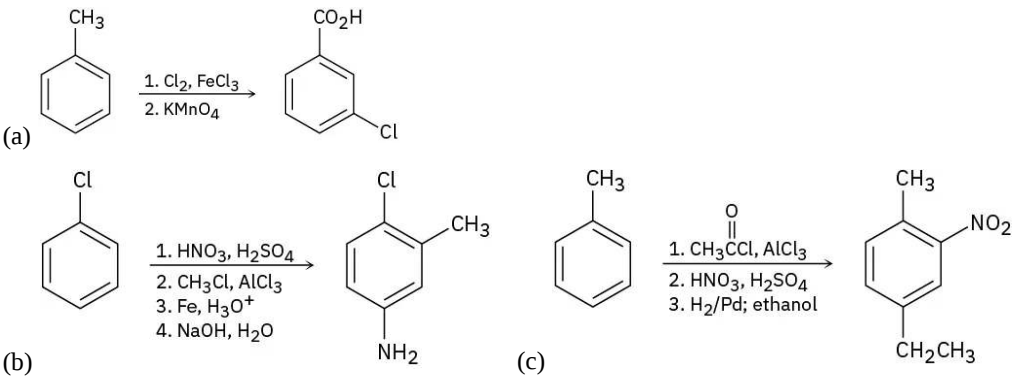
PROBLEM 16-56 Starting with benzene as your only source of aromatic compounds, how would you synthesize the following substances? Assume that you can separate ortho and para isomers if necessary.

(a) *p*-Chloroacetophenone (b) *m*-Bromonitrobenzene (c) *o*-Bromobenzenesulfonic acid (d) *m*-Chlorobenzenesulfonic acid

PROBLEM 16-57 Starting with either benzene or toluene, how would you synthesize the following substances: Assume that ortho and para isomers can be separated.

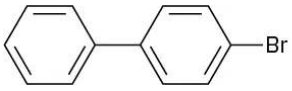
(a) 2-Bromo-4-nitrotoluene (b) 1,3,5-Trinitrobenzene (c) 2,4,6-Tribromoaniline (d) *m*-Fluorobenzoic acid

PROBLEM 16-58 As written, the following syntheses have flaws. What is wrong with each?



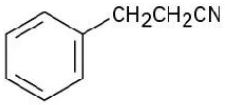
General Problems

PROBLEM 16-59 At what position and on what ring do you expect nitration of 4-bromo-biphenyl to occur? Explain, using resonance structures of the potential intermediates.

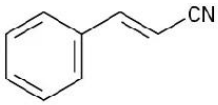


4-Bromobiphenyl

PROBLEM 16-60 Electrophilic substitution on 3-phenylpropanenitrile occurs at the ortho and para positions, but reaction with 3-phenylpropenenitrile occurs at the meta position. Explain, using resonance structures of the intermediates.



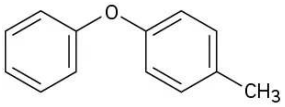
3-Phenylpropanenitrile



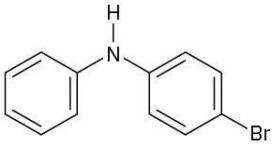
3-Phenylpropenenitrile

PROBLEM 16-61 At what position, and on what ring, would you expect the following substances to undergo electrophilic substitution?

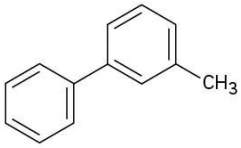
(a)



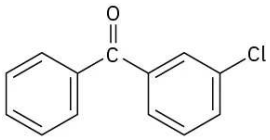
(b)



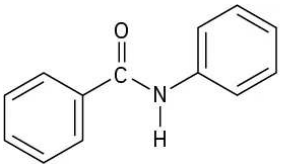
(c)



(d)



PROBLEM 16-62 At what position, and on what ring, would you expect bromination of benzanilide to occur? Explain by drawing resonance structures of the intermediates.

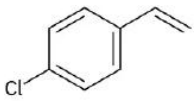


Benzanilide

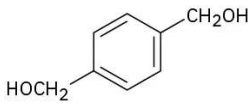
PROBLEM 16-63 Would you expect the Friedel–Crafts reaction of benzene with (*R*)-2- chlorobutane to yield optically active or racemic product? Explain.

PROBLEM 16-64 How would you synthesize the following substances starting from benzene?

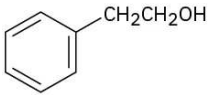
(a)



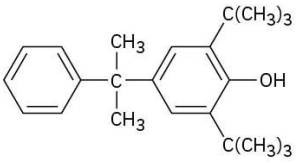
(b)



(c)



PROBLEM 16-65 The compound MON-0585 is a nontoxic, biodegradable larvicide that is highly selective against mosquito larvae. Synthesize MON-0585 using either benzene or phenol as a source of the aromatic rings.

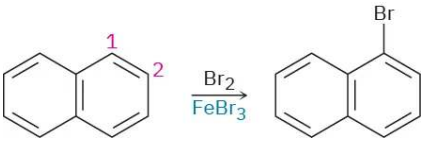


MON-0585

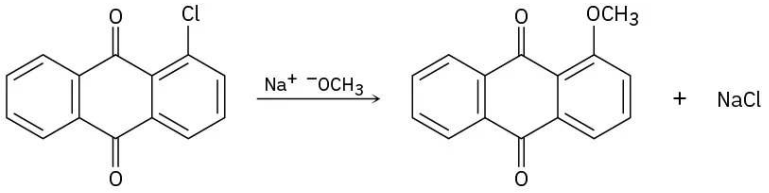
https://chem.libretexts.org/@go/page/564203

PROBLEM 16-66 Phenylboronic acid, $C_6H_5B(OH)_2$, is nitrated to give 15% ortho- substitution product and 85% meta. Explain the meta-directing effect of the $–B(OH)_2$ group.

PROBLEM 16-67 Draw resonance structures of the intermediate carbocations in the bromination of naphthalene, and account for the fact that naphthalene undergoes electrophilic substitution at C1 rather than C2.



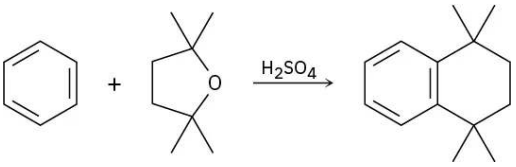
PROBLEM 16-68 Propose a mechanism for the reaction of 1-chloroanthraquinone with methoxide ion to give the substitution product 1-methoxyanthraquinone. Use curved arrows to show the electron flow in each step.



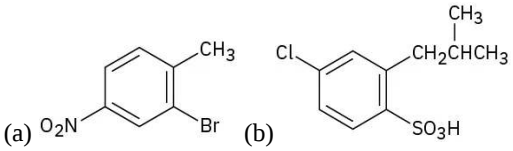
1-Chloroanthraquinone **1-Methoxyanthraquinone**

PROBLEM 16-69 *p*-Bromotoluene reacts with potassium amide to give a mixture of *m*- and *p*-methylaniline. Explain.

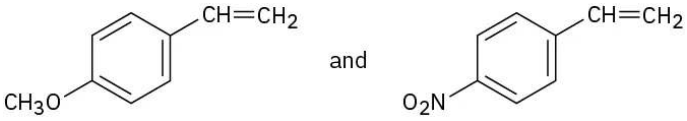
PROBLEM 16-70 Propose a mechanism to account for the reaction of benzene with 2,2,5,5-tetramethyltetrahydrofuran.



PROBLEM 16-71 How would you synthesize the following compounds from benzene? Assume that ortho and para isomers can be separated.



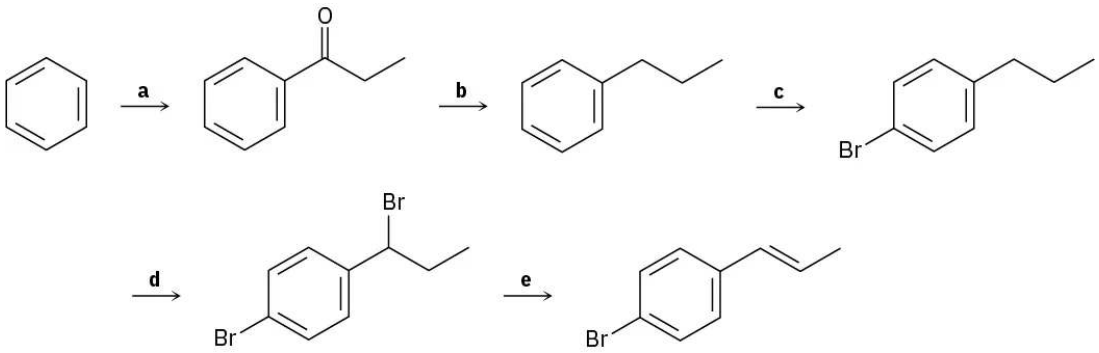
PROBLEM 16-72 You know the mechanism of HBr addition to alkenes, and you know the effects of various substituent groups on aromatic substitution. Use this knowledge to predict which of the following two alkenes reacts faster with HBr. Explain your answer by drawing resonance structures of the carbocation intermediates.



PROBLEM 16-73 Use your knowledge of directing effects, along with the following data, to deduce the directions of the dipole moments in aniline, bromobenzene, and bromoaniline.

μ = 1.53 D **μ = 1.52 D** **μ = 2.91 D**

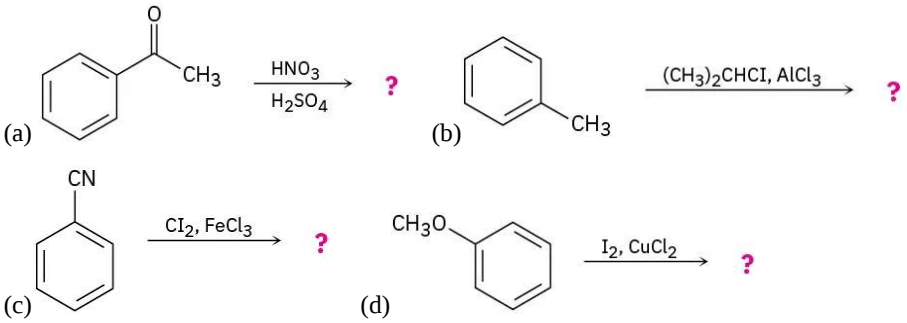
PROBLEM 16-74 Identify the reagents represented by the letters **a**–**e** in the following scheme:



PROBLEM 16-75 Phenols (ArOH) are relatively acidic, and the presence of a substituent group on the aromatic ring has a large effect. The pK_a of unsubstituted phenol, for example, is 9.89, while that of *p*-nitrophenol is 7.15. Draw resonance structures of the corresponding phenoxide anions and explain the data.

PROBLEM 16-76 Would you expect *p*-methylphenol to be more acidic or less acidic than unsubstituted phenol? Explain. (See Problem 16-75.)

PROBLEM 16-77 Predict the product(s) for each of the following reactions. In each case, draw the resonance forms of the intermediate to explain the observed regiochemistry.



This page titled 5.16: Additional Problems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **16.15: Additional Problems** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

CHAPTER OVERVIEW

6: Alcohols and Phenols

Learning Objectives

When you have completed Chapter 17, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design a multi-step synthesis using any of the reactions introduced in this chapter, together with any number of the reactions discussed in *Chemistry 350*.
3. solve "road-map" problems that require a knowledge of the chemistry of alcohols and phenols, in addition to the chemistry of the other classes of compounds discussed in *Chemistry 350*.
4. define, and use in context, the key terms introduced in this chapter.

In this chapter, we examine the chemistry of the alcohol family of compounds. Alcohols can undergo a wide variety of reactions, and because of this reactivity and because they can be prepared in a number of different ways, alcohols occupy an important position in organic chemistry.

The discussion begins with an outline of the nomenclature of alcohols and phenols. We review the physical properties of these compounds, and discuss methods used to obtain the lower members of the series on an industrial scale. A detailed discussion of the laboratory preparation of alcohols follows, with particular emphasis on those methods that involve either the reduction of a carbonyl compound or the use of a Grignard reagent.

Certain reactions of alcohols were discussed in previous chapters. In this chapter, we concentrate on the oxidation of alcohols to carbonyl compounds. We also introduce the concept of protecting a sensitive functional group during an organic synthesis. The discussion then turns to the uses of phenols, their preparation and their chemical reactivity.

Infrared, nuclear magnetic resonance and mass spectroscopy each can provide valuable information about alcohols and phenols, and we illustrate the application of these techniques to the identification of unknown alcohols and phenols with a number of examples.

6.1: Why This Chapter?
6.2: Naming Alcohols and Phenols
6.3: Properties of Alcohols and Phenols
6.4: Preparation of Alcohols- A Review
6.5: Alcohols from Carbonyl Compounds - Reduction
6.6: Alcohols from Carbonyl Compounds - Grignard Reagents
6.7: Reactions of Alcohols
6.8: Oxidation of Alcohols
6.9: Protection of Alcohols
6.10: Phenols and Their Uses
6.11: Reactions of Phenols
6.12: Spectroscopy of Alcohols and Phenols
6.13: Chemistry Matters—Ethanol- Chemical, Drug, and Poison
6.14: Key Terms
6.15: Summary
6.16: Summary of Reactions
6.17: Additional Problems

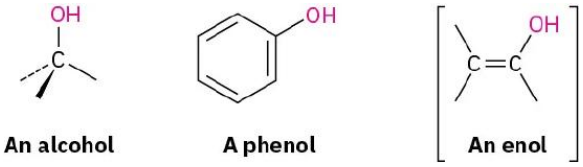
This page titled 6: Alcohols and Phenols is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

6.1: Why This Chapter?

Up to this point, we've focused on developing some general ideas of organic reactivity, looking at the chemistry of hydrocarbons and alkyl halides, and examining some of the tools used in structural studies. With that background, it's now time to begin a study of the oxygen-containing functional groups that lie at the heart of organic and biological chemistry. We'll look at alcohols in this chapter and move on to carbonyl compounds in Chapters 19 through 23.

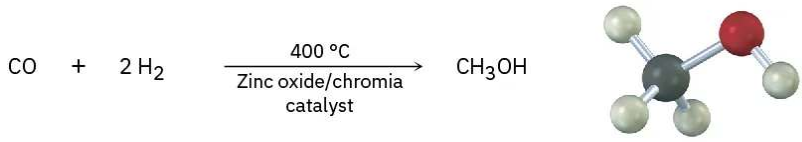
Figure 6.1.1: The phenol resveratrol, found in the skin of red grapes, continues to be studied for its potential anti-cancer, antiarthritic, and hypoglycemic properties. (credit: "Weinreben-Ötlingen" by Pierre Likissas/Wikimedia Commons, CC BY 3.0)

Alcohols and phenols can be thought of as organic derivatives of water in which one of water's hydrogens is replaced by an organic group: H–O–H versus R–O–H and Ar–O–H. In practice, the name *alcohol* is restricted to compounds that have their –OH group bonded to a saturated, sp^3-hybridized carbon atom, while compounds with their –OH group bonded to a vinylic, sp^2-hybridized carbon are called *enols*. We'll look at enols in Chapter 22.



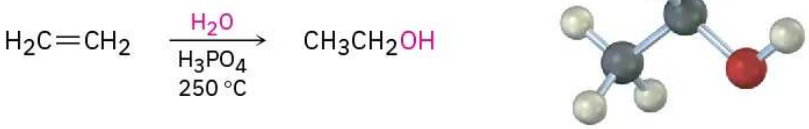
An alcohol **A phenol** **An enol**

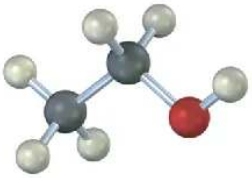
Alcohols occur widely in nature and have many industrial and pharmaceutical applications. Methanol, for instance, is one of the most important of all industrial chemicals. Historically, methanol was prepared by heating wood in the absence of air and thus came to be called *wood alcohol*. Today, approximately 173 million tons (50 billion gallons) of methanol is manufactured worldwide each year, most of it by catalytic reduction of carbon monoxide with hydrogen gas. Methanol is toxic to humans, causing blindness in small doses (15 mL) and death in larger amounts (100–250 mL). Industrially, it is used both as a solvent and as a starting material for production of formaldehyde (CH_2O) and acetic acid (CH_3CO_2H).



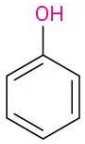
Ethanol was one of the first organic chemicals to be prepared and purified. Its production by fermentation of grains and sugars has been carried out for perhaps 9000 years, and its purification by distillation goes back at least as far as the 12th century. Today, approximately 88 million tons (26 billion gallons) of ethanol are produced worldwide each year, most of it by fermentation of corn, barley, sorghum, and other plant sources. Almost all of this ethanol is used for bus and automobile fuel.

Ethanol for industrial use as a solvent or chemical intermediate is largely obtained by acid-catalyzed hydration of ethylene at high temperature.

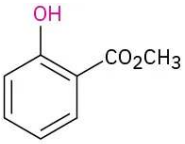




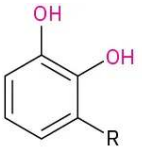
Phenols occur widely throughout nature and also serve as intermediates in the industrial synthesis of products as diverse as adhesives and antiseptics. Phenol itself is a general disinfectant found in coal tar; methyl salicylate is a flavoring agent found in oil of wintergreen; and urushiols are the allergenic constituents of poison oak and poison ivy. Note that the word *phenol* is the name both of the specific compound (hydroxybenzene) and of the class of compounds.



Phenol (also known as carbolic acid)



Methyl salicylate



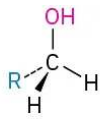
Urushiols (R = different C_{15} alkyl and alkenyl chains)

This page titled 6.1: Why This Chapter? is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

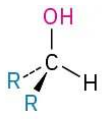
- **17.0: Why This Chapter?** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

6.2: Naming Alcohols and Phenols

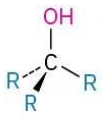
Alcohols are classified as primary (1°), secondary (2°), or tertiary (3°), depending on the number of organic groups bonded to the hydroxyl-bearing carbon.



A primary (1°) alcohol



A secondary (2°) alcohol



A tertiary (3°) alcohol

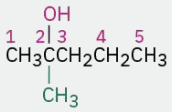
Simple alcohols are named in the IUPAC system as derivatives of the parent alkane, using the suffix *-ol*.

Alcohol Nomenclature

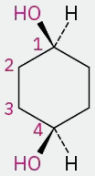
RULE 1: Select the longest carbon chain containing the hydroxyl group, and derive the parent name by replacing the *-e* ending of the corresponding alkane with *-ol*. The *-e* is deleted to prevent the occurrence of two adjacent vowels: propanol rather than propaneol, for example.

RULE 2: Number the alkane chain beginning at the end nearer the hydroxyl group.

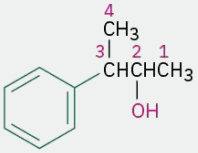
RULE 3: Number the substituents according to their position on the chain, and write the name, listing the substituents in alphabetical order and identifying the position to which the –OH is bonded. Note that in naming *cis*-1,4-cyclohexanediol, the final *-e* of cyclohexane is not deleted because the next letter, *d*, is not a vowel; that is, cyclohexanediol rather than cyclohexandiol. Also, as with alkenes (Section 7.3), newer IUPAC naming recommendations place the locant immediately before the suffix rather than before the parent.



2-Methyl-2-pentanol
(New: 2-Methylpentan-2-ol)

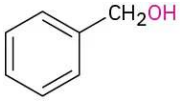


***cis*-1,4-Cyclohexanediol**
(New: *cis*-Cyclohexane-1,4-diol)

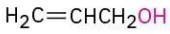


3-Phenyl-2-butanol
(New: 3-Phenylbutan-2-ol)

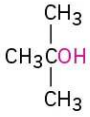
Some simple and widely occurring alcohols have common names that are accepted by IUPAC. For example:



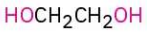
Benzyl alcohol
(phenylmethanol)



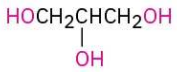
Allyl alcohol
(2-propen-1-ol)



***tert*-Butyl alcohol**
(2-methyl-2-propanol)

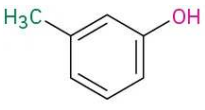


Ethylene glycol
(1,2-ethanediol)

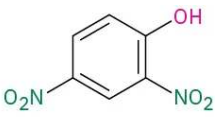


Glycerol
(1,2,3-propanetriol)

Phenols are named as described previously for aromatic compounds according to the rules discussed in Section 15.1, with *-phenol* used as the parent name rather than *-benzene*.



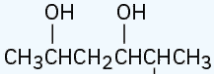
***m*-Methylphenol**
(*m*-Cresol)



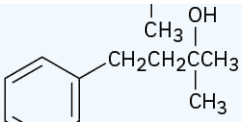
2,4-Dinitrophenol

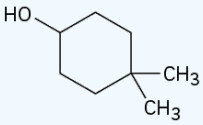
Exercise 6.2.1

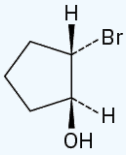
Give IUPAC names for the following compounds:



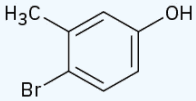
https://chem.libretexts.org/@go/page/564206

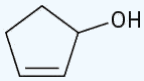
a. 

b. 

c. 

d.

e. 

f. 

Answer

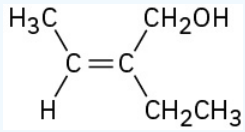
a. 5-Methyl-2,4-hexanediol
b. 2-Methyl-4-phenyl-2-butanol
c. 4,4-Dimethylcyclohexanol
d. *trans*-2-Bromocyclopentanol
e. 4-Bromo-3-methylphenol
f. 2-Cyclopenten-1-ol

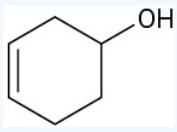
Exercise 6.2.2

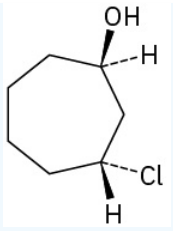
Draw structures corresponding to the following IUPAC names:

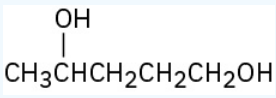
a. (Z)-2-Ethyl-2-buten-1-ol
b. 3-Cyclohexen-1-ol
c. *trans*-3-Chlorocycloheptanol
d. 1,4-Pentanediol
e. 2,6-Dimethylphenol
f. o-(2-Hydroxyethyl)phenol

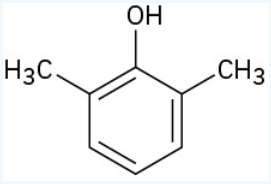
Answer

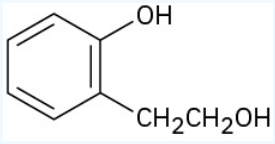
a. 

b. 

c. 

d. 

e. 

f. 

This page titled 6.2: Naming Alcohols and Phenols is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **17.1: Naming Alcohols and Phenols** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

6.3: Properties of Alcohols and Phenols

Alcohols and phenols have nearly the same geometry around the oxygen atom as water. The R–O–H bond angle has an approximately tetrahedral value (108.5° in methanol, for instance), and the oxygen atom is sp^3-hybridized.

Also like water, alcohols and phenols have higher boiling points than might be expected, because of hydrogen-bonding (Section 2.12). A positively polarized –OH hydrogen atom from one molecule is attracted to a lone pair of electrons on the electronegative oxygen atom of another molecule, resulting in a weak force that holds the molecules together (Figure 6.3.1). These intermolecular attractions must be overcome for a molecule to break free from the liquid and enter the vapor state, so the boiling temperature is raised. For example, 1-propanol (MW = 60), butane (MW = 58), and chloroethane (MW = 65) have similar molecular weights, yet 1-propanol boils at 97 °C, compared with –0.5 °C for the alkane and 12.5 °C for the chloroalkane.

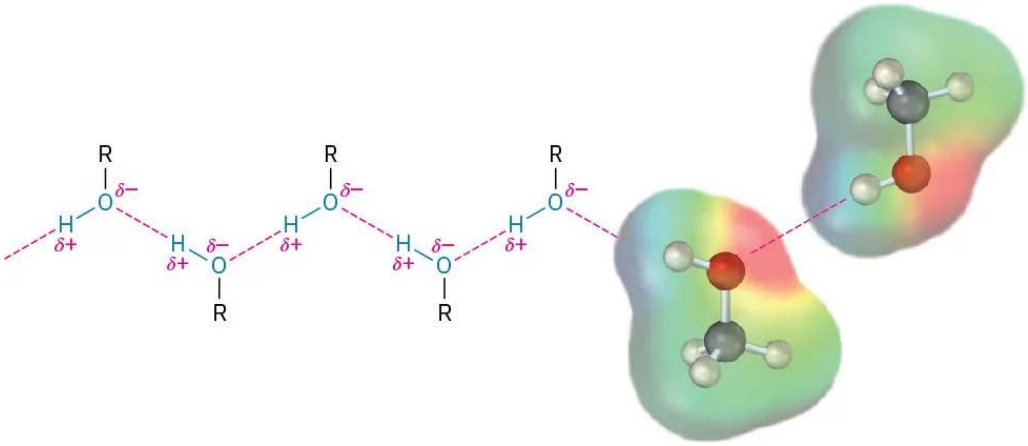
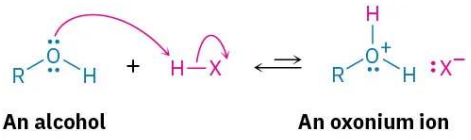
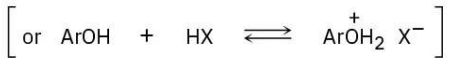


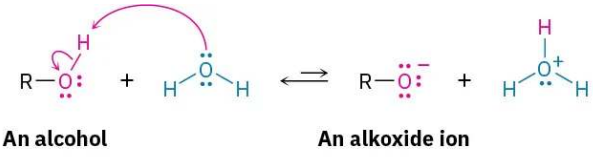
Figure 6.3.1: Hydrogen-bonding in alcohols and phenols. Attraction between a positively polarized –OH hydrogen and a negatively polarized oxygen holds molecules together. The electrostatic potential map of methanol shows the **positively polarized** –OH hydrogen and the **negatively polarized** oxygen.

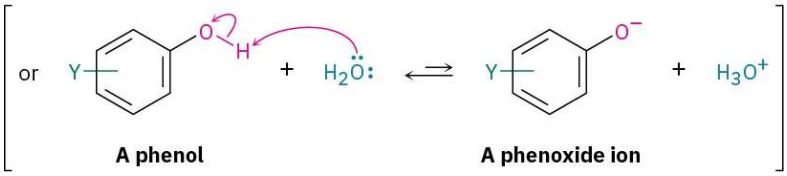
Another similarity with water is that alcohols and phenols are both weakly basic and weakly acidic. As weak bases, they are reversibly protonated by strong acids to yield oxonium ions, ROH_2^+.





As weak acids, they dissociate slightly in dilute aqueous solution by donating a proton to water, generating H_3O^+ and an alkoxide ion, $RO^–$, or a phenoxide ion, $ArO^–$.





Recall from the earlier discussion of acidity in Section 2.7 to Section 2.11 that the strength of any acid HA in water can be expressed by an acidity constant, K_a.

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

with

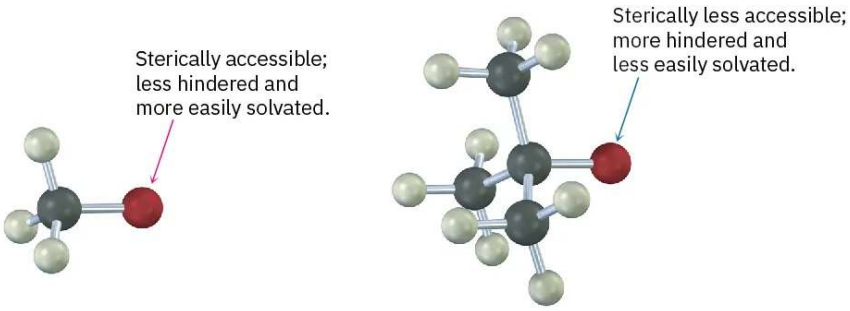
$$pK_a = -\log K_a$$

Compounds with a smaller K_a and larger pK_a are less acidic, whereas compounds with a larger K_a and smaller pK_a are more acidic. As shown in Table 6.3.1, simple alcohols like methanol and ethanol are about as acidic as water, but the more highly substituted *tert*-butyl alcohol is somewhat weaker. Substituent groups also have a significant effect: 2,2,2-trifluoroethanol is approximately 3700 times stronger than ethanol, for instance. Phenols and *thiols*, the sulfur analogs of alcohols, are substantially more acidic than water.

Table 6.3.1 Acidity Constants of Some Alcohols and Phenols

Compound	pK_a
$(CH_3)_3COH$	18
CH_3CH_2OH	16
H_2O	15.74
CH_3OH	15.54
CF_3CH_2OH	12.43
p-Aminophenol	10.46
CH_3SH	10.3
p-Methylphenol	10.17
Phenol	9.89
p-Chlorophenol	9.38
p-Nitrophenol	7.15

The effect of alkyl substitution on alcohol acidity is due primarily to solvation of the alkoxide ion formed on acid dissociation. The more readily the alkoxide ion is solvated by water, the more stable it is, the more its formation is energetically favored, and the greater the acidity of the parent alcohol. For example, the oxygen atom of an unhindered alkoxide ion, such as that from methanol, is sterically accessible and is easily solvated by water. The oxygen atom of a hindered alkoxide ion, however, such as that from *tert*-butyl alcohol, is less easily solvated and is therefore less stable.



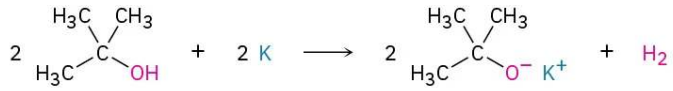
Methoxide ion, CH_3O^- (pK_a = 15.54) **_tert_-Butoxide ion, $(CH_3)_3CO^-$ (pK_a = 18)**

Inductive effects (Section 16.4) are also important in determining alcohol acidities. Electron-withdrawing halogen substituents, for instance, stabilize an alkoxide ion by spreading the charge over a larger volume, thus making the alcohol more acidic. Compare, for instance, the acidities of ethanol (pK_a = 16) and 2,2,2-trifluoroethanol (pK_a = 12.43), or of *tert*-butyl alcohol (pK_a = 18) and nonafluoro-*tert*-butyl alcohol (pK_a = 5.4).

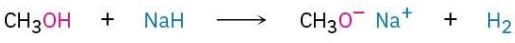
Electron-withdrawing groups stabilize the alkoxide ion and lower the pK_a of the alcohol.

pK_a = 5.4 pK_a = 18

Because alcohols are weak acids, they don't react with weak bases, such as amines or bicarbonate ion, and they only react to a limited extent with metal hydroxides such as NaOH. Alcohols do, however, react with alkali metals and with strong bases such as sodium hydride (NaH), sodium amide ($NaNH_2$), and Grignard reagents (RMgX). Alkoxides are themselves bases that are frequently used as reagents in organic chemistry. They are named systematically by adding the *-ate* suffix to the name of the alcohol. Methanol becomes methanolate, for instance.

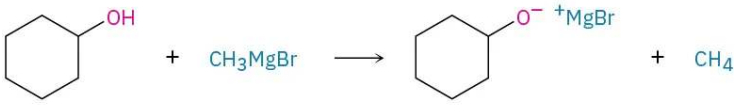


***tert*-Butyl alcohol (2-methyl-2-propanol)** **Potassium *tert*-butoxide (potassium 2-methyl-2-propanolate)**



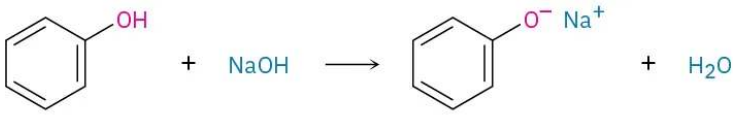
Methanol **Sodium methoxide (sodium methanolate)**

Ethanol **Sodium ethoxide (sodium ethanolate)**



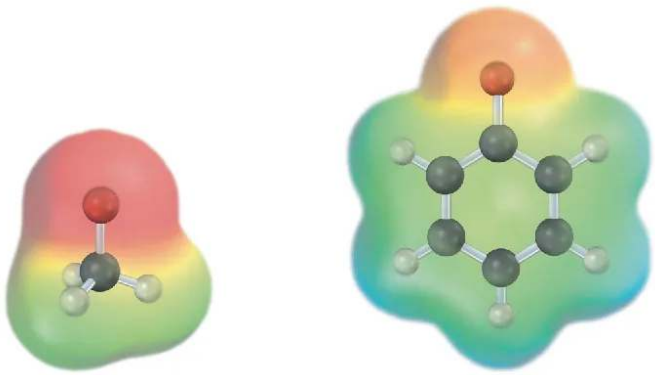
Cyclohexanol **Bromomagnesium cyclohexanolate**

Phenols are about a million times more acidic than alcohols (Table 6.3.1). They are therefore soluble in dilute aqueous NaOH and can often be separated from a mixture simply by basic extraction into aqueous solution, followed by reacidification.



Phenol **Sodium phenoxide (sodium phenolate)**

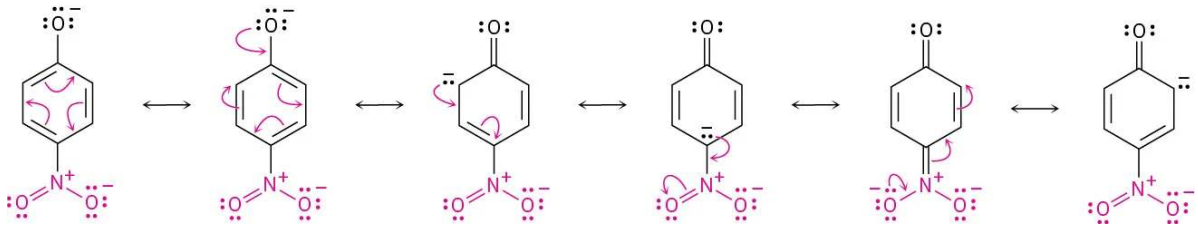
Phenols are more acidic than alcohols because the phenoxide anion is resonance-stabilized. Delocalization of the negative charge over the ortho and para positions of the aromatic ring results in increased stability of the phenoxide anion relative to undissociated phenol and in a consequently lower $\Delta G°$ for dissociation. Figure 6.3.2 compares electrostatic potential maps of an alkoxide ion (CH_3O^-) with phenoxide ion to show how the negative charge in phenoxide ion is delocalized from oxygen to the ring.



CH_3O^- **$C_6H_5O^-$**

Figure 6.3.2: The resonance-stabilized phenoxide ion is more stable than an alkoxide ion. Electrostatic potential maps show how the **negative charge** is concentrated on oxygen in the methoxide ion but is spread over the aromatic ring in the phenoxide ion.

Substituted phenols can be either more acidic or less acidic than phenol itself, depending on whether the substituent is electron-withdrawing or electron-donating (Section 16.4). Phenols with an electron-withdrawing substituent are more acidic because these substituents delocalize the negative charge; phenols with an electron-donating substituent are less acidic because these substituents concentrate the charge. The acidifying effect of an electron-withdrawing substituent is particularly noticeable in phenols with a nitro group at the ortho or para position.



Worked Example 6.3.1: Predicting the Relative Acidity of a Substituted Phenol

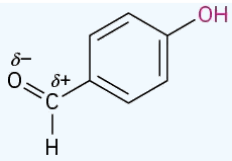
Is *p*-hydroxybenzaldehyde more acidic or less acidic than phenol?

Strategy

Identify the substituent on the aromatic ring, and decide whether it is electron-donating or electron-withdrawing. Electron-withdrawing substituents make the phenol more acidic by stabilizing the phenoxide anion, and electron-donating substituents make the phenol less acidic by destabilizing the anion.

Solution

We saw in Section 16.4 that a carbonyl group is electron-withdrawing. Thus, *p*-hydroxybenzaldehyde is more acidic (pK_a = 7.9) than phenol (pK_a = 9.89).



***p*-Hydroxybenzaldehyde**
(pK_a = 7.9)

? Exercise 6.3.1

The following data for isomeric four-carbon alcohols show that there is a decrease in boiling point with increasing substitution of the OH-bearing carbon. How might you account for this trend?

1-Butanol, bp 117.5 °C
2-Butanol, bp 99.5 °C
2-Methyl-2-propanol, bp 82.2 °C

Answer

Hydrogen-bonding is more difficult in hindered alcohols.

? Exercise 6.3.2

Rank the following substances in order of increasing acidity:

a. $(CH_3)_2CHOH$, $HC{\equiv}CH$, $(CF_3)_2CHOH$, CH_3OH
b. Phenol, p-methylphenol, p-(trifluoromethyl)phenol
c. Benzyl alcohol, phenol, p-hydroxybenzoic acid

Answer

1. $HC{\equiv}CH < (CH_3)_2CHOH < CH_3OH < (CF_3)_2CHOH$
2. p-Methylphenol < Phenol < p-(Trifluoromethyl)phenol
3. Benzyl alcohol < Phenol < p-Hydroxybenzoic acid

? Exercise 6.3.3

p-Nitrobenzyl alcohol is more acidic than benzyl alcohol, but *p*-methoxybenzyl alcohol is less acidic. Explain.

Answer

The electron-withdrawing nitro group stabilizes an alkoxide ion, but the electron-donating methoxyl group destabilizes the anion.

This page titled 6.3: Properties of Alcohols and Phenols is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **17.2: Properties of Alcohols and Phenols** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

6.4: Preparation of Alcohols- A Review

Alcohols occupy a central position in organic chemistry. They can be prepared from many other kinds of compounds (alkenes, alkyl halides, ketones, esters, and aldehydes, among others), and they can be transformed into an equally wide assortment of compounds (Figure 6.4.1).

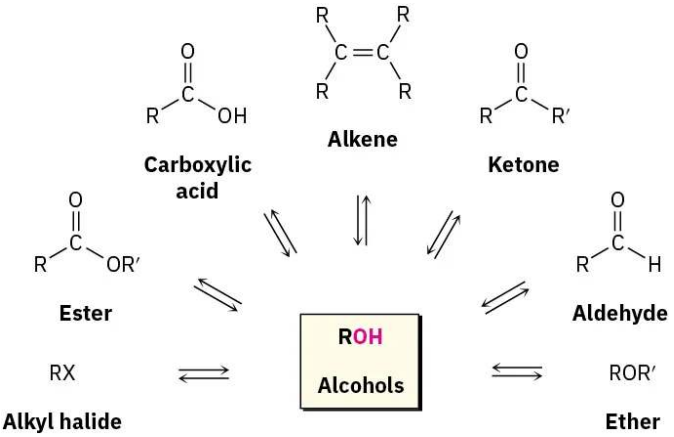
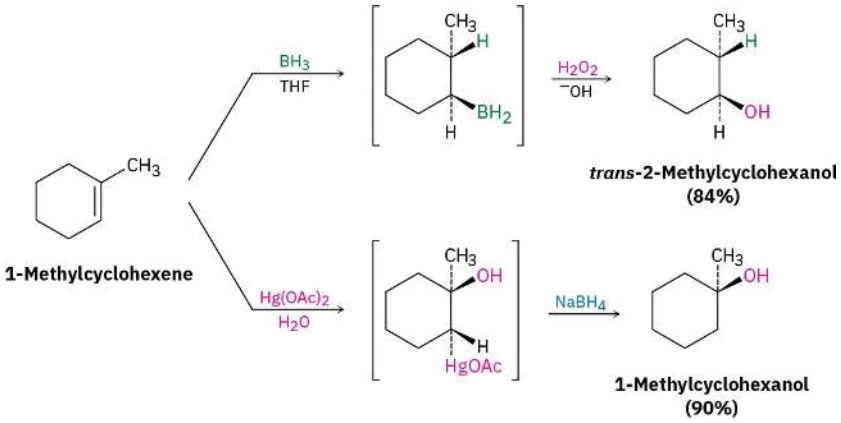


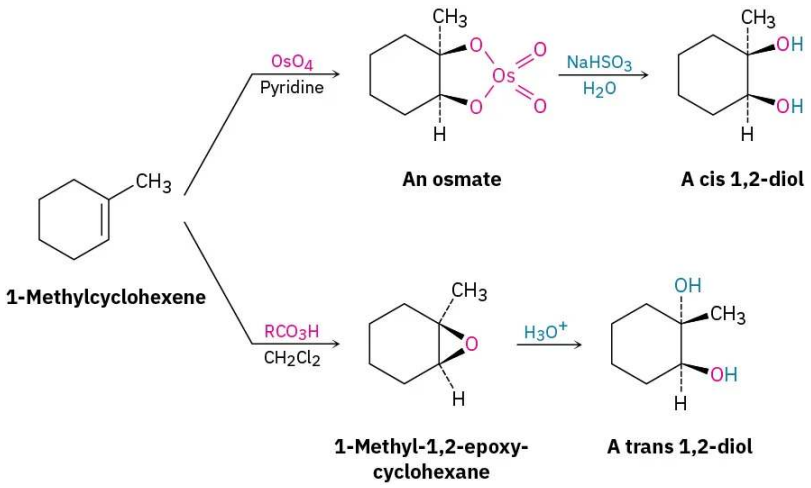
Figure 6.4.1: The central position of alcohols in organic chemistry. Alcohols can be prepared from, and converted into, many other kinds of compounds.

We've already seen several methods of alcohol synthesis:

- Alcohols can be prepared by hydration of alkenes. Because the direct hydration of alkenes with aqueous acid is generally a poor reaction in the laboratory, two indirect methods are commonly used. Hydroboration–oxidation yields the syn, non-Markovnikov hydration product (Section 8.5), whereas oxymercuration–demercuration yields the Markovnikov hydration product (Section 8.4).

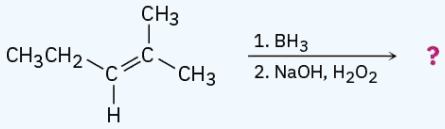


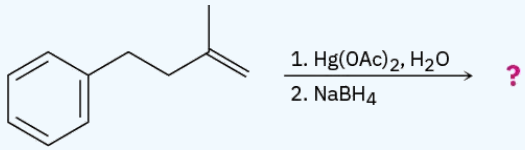
- 1,2-Diols can be prepared either by direct hydroxylation of an alkene with OsO_4 followed by reduction with $NaHSO_3$ or by acid-catalyzed hydrolysis of an epoxide (Section 8.7). The OsO_4 reaction occurs with syn stereochemistry to give a cis diol, and epoxide opening occurs with anti stereochemistry to give a trans diol.

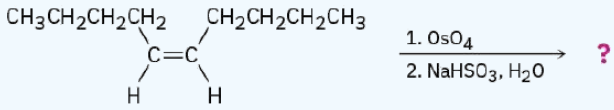


Exercise 6.4.1

Predict the products of the following reactions:

a. 

b. 

c. 

Answer

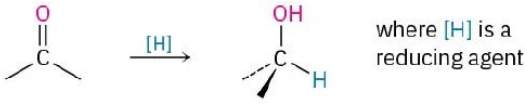
a. 2-Methyl-3-pentanol
b. 2-Methyl-4-phenyl-2-butanol
c. meso-5,6-Decanediol

This page titled 6.4: Preparation of Alcohols- A Review is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **17.3: Preparation of Alcohols- A Review** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

6.5: Alcohols from Carbonyl Compounds - Reduction

The most general method for preparing alcohols, both in the laboratory and in living organisms, is by reduction of a carbonyl compound. Just as reduction of an alkene adds hydrogen to a C=C bond to give an alkane (Section 8.6), reduction of a carbonyl compound adds hydrogen to a C=O bond to give an alcohol. All kinds of carbonyl compounds can be reduced, including aldehydes, ketones, carboxylic acids, and esters.



A carbonyl compound **An alcohol**

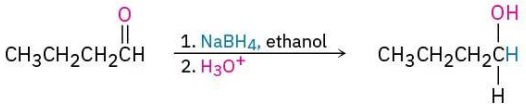
Reduction of Aldehydes and Ketones

Aldehydes are easily reduced to give primary alcohols, and ketones are reduced to give secondary alcohols.

An aldehyde **A primary alcohol** **A ketone** **A secondary alcohol**

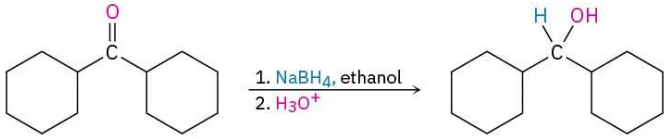
Dozens of reagents are used in the laboratory to reduce aldehydes and ketones, depending on the circumstances, but sodium borohydride, $NaBH_4$, is usually chosen because of its safety and ease of handling. Sodium borohydride is a white, crystalline solid that can be weighed in the open atmosphere and used in either water or alcohol solution.

Aldehyde reduction



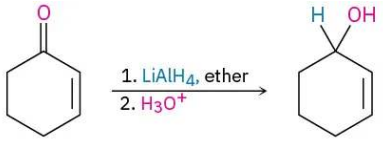
Butanal **1-Butanol (85%) (a 1° alcohol)**

Ketone reduction



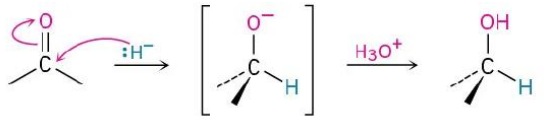
Dicyclohexyl ketone **Dicyclohexylmethanol (88%) (a 2° alcohol)**

Lithium aluminum hydride, $LiAlH_4$, is another reducing agent often used for reduction of aldehydes and ketones. A grayish powder that is soluble in ether and tetrahydrofuran, $LiAlH_4$ is much more reactive than $NaBH_4$ but also much more dangerous. It reacts violently with water and decomposes explosively when heated above 120 °C.



2-Cyclohexenone **2-Cyclohexenol (94%)**

We'll defer a detailed discussion of these reductions until Chapter 19. For the moment, we'll simply note that they involve the addition of a nucleophilic hydride ion ($:H^-$) to the positively polarized, electrophilic carbon atom of the carbonyl group. The initial product is an alkoxide ion, which is protonated by addition of H_3O^+ in a second step to yield the alcohol product.



In living organisms, aldehyde and ketone reductions are carried out by either of the coenzymes NADH (reduced nicotinamide adenine dinucleotide) or NADPH (reduced nicotinamide adenine dinucleotide phosphate). Although these biological "reagents" are much more complex structurally than $NaBH_4$ or $LiAlH_4$, the mechanisms of laboratory and biological reactions are similar. The coenzyme acts as a hydride-ion donor to give an alkoxide anion, and the intermediate anion is then protonated by acid. An example is the reduction of acetoacetyl ACP to β-hydroxybutyryl ACP, a step in the biological synthesis of fats (Figure 6.5.1). Note that the pro-*R* hydrogen of NADPH is the one transferred in this example. Enzyme-catalyzed reactions usually occur with high specificity, although it's not usually possible to predict the stereochemical result before the fact.

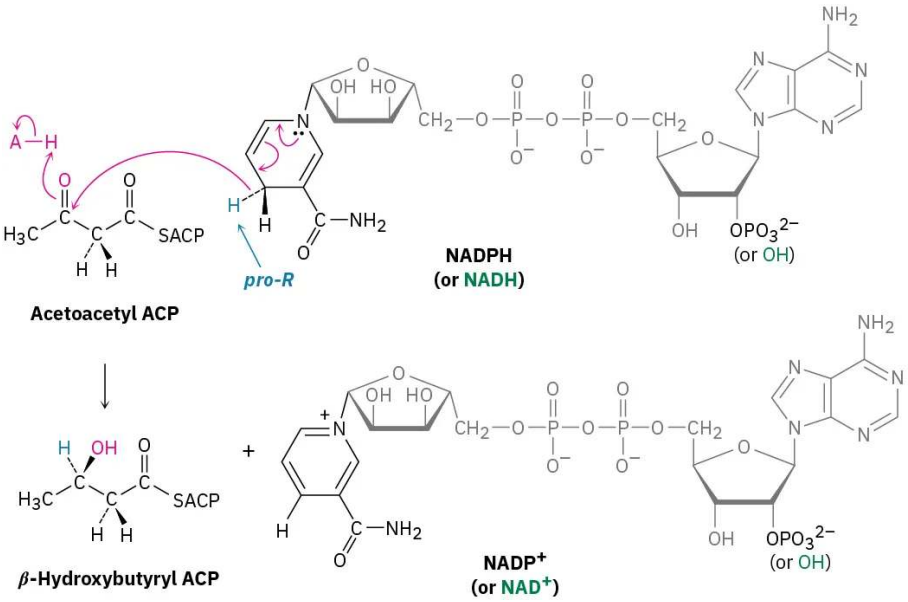
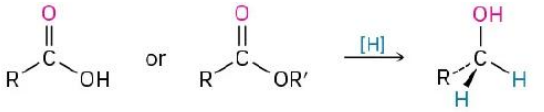


Figure 6.5.1: The biological reduction of a ketone (acetoacetyl ACP) to an alcohol (β-hydroxybutyryl ACP) by NADPH.

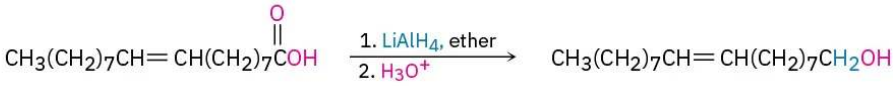
Reduction of Carboxylic Acids and Esters

Carboxylic acids and esters are reduced to give primary alcohols.



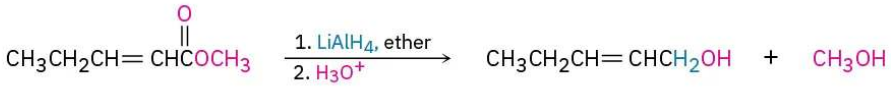
These reactions aren't as rapid as the reductions of aldehydes and ketones. $NaBH_4$ reduces esters very slowly and does not reduce carboxylic acids at all. Instead, carboxylic acid and ester reductions are usually carried out with the more reactive reducing agent $LiAlH_4$. All carbonyl groups, including acids, esters, ketones, and aldehydes, are reduced by $LiAlH_4$. Note that one hydrogen atom is delivered to the carbonyl carbon atom during aldehyde and ketone reductions but that two hydrogens become bonded to the former carbonyl carbon during carboxylic acid and ester reductions. We'll defer a discussion of the mechanisms of these reactions until Chapter 21.

Carboxylic acid reduction



9-Octadecenoic acid (oleic acid) → **9-Octadecen-1-ol (87%)**

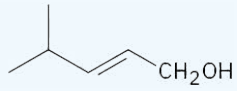
Ester reduction

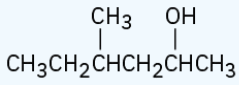


Methyl 2-pentenoate → **2-Penten-1-ol (91%)**

Worked Example 6.5.1: Identifying a Reactant, Given the Product

What carbonyl compounds would you reduce to obtain the following alcohols?

a. 

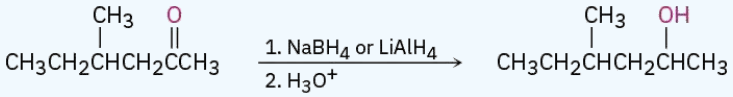
b. 

Strategy

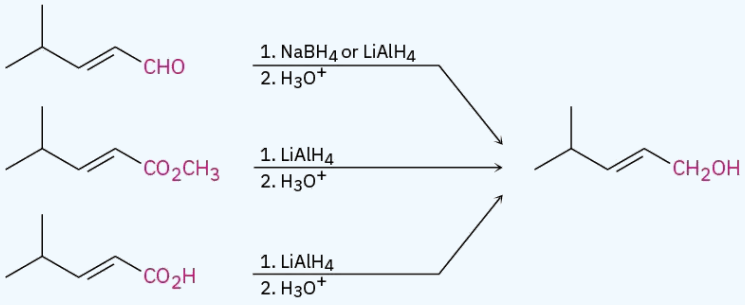
Identify the target alcohol as primary, secondary, or tertiary. A primary alcohol can be prepared by reduction of an aldehyde, an ester, or a carboxylic acid; a secondary alcohol can be prepared by reduction of a ketone; and a tertiary alcohol can't be prepared by reduction.

Solution

a. The target molecule is a secondary alcohol, which can be prepared only by reduction of a ketone. Either $NaBH_4$ or $LiAlH_4$ can be used.



a. The target molecule is a primary alcohol, which can be prepared by reduction of an aldehyde, an ester, or a carboxylic acid. $LiAlH_4$ is needed for the ester and carboxylic acid reductions.

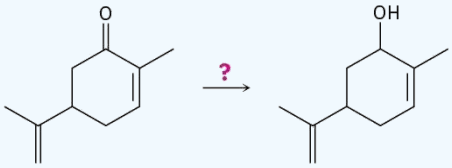


Exercise 6.5.1

What reagent would you use to accomplish each of the following reactions?

a.

b.

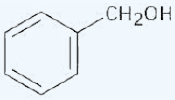
c. 

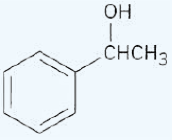
Answer

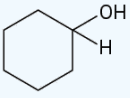
a. $NaBH_4$
b. $LiAlH_4$
c. $LiAlH_4$

Exercise 6.5.2

What carbonyl compounds give the following alcohols on reduction with $LiAlH_4$? Show all possibilities.

a. 

b. 

c. 

d. $(CH_3)_2CHCH_2OH$

Answer

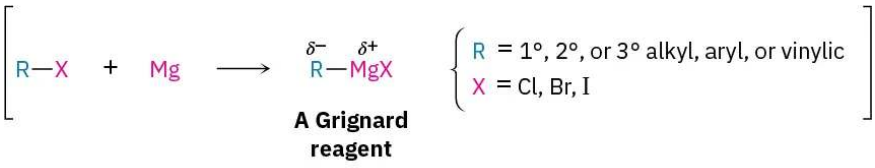
a. Benzaldehyde or benzoic acid (or ester)
b. Acetophenone
c. Cyclohexanone
d. 2-Methylpropanal or 2-methylpropanoic acid (or ester)

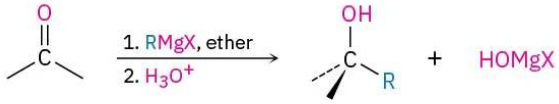
This page titled 6.5: Alcohols from Carbonyl Compounds - Reduction is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **17.4: Alcohols from Carbonyl Compounds - Reduction** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

6.6: Alcohols from Carbonyl Compounds - Grignard Reagents

Grignard reagents (RMgX), prepared by reaction of organohalides with magnesium (Section 10.6), react with carbonyl compounds to yield alcohols in much the same way that hydride reducing agents do. Just as carbonyl reduction involves addition of a hydride ion nucleophile to the C=O bond, Grignard reaction involves addition of a carbanion nucleophile ($R:^{-}{}^{+}MgX$).

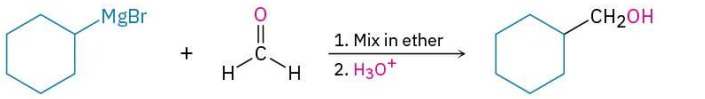




The nucleophilic addition reaction of Grignard reagents to carbonyl compounds has no direct counterpart in biological chemistry because organomagnesium compounds are too strongly basic to exist in an aqueous medium. Nevertheless, the reaction is worth understanding for two reasons. First, the reaction is an unusually broad and useful method of alcohol synthesis and demonstrates again the relative freedom with which chemists can operate in the laboratory. Second, the reaction does have an indirect biological counterpart, for we'll see in Chapter 23 that the addition of stabilized carbon nucleophiles to carbonyl compounds is used in almost all metabolic pathways as the major process for forming carbon–carbon bonds.

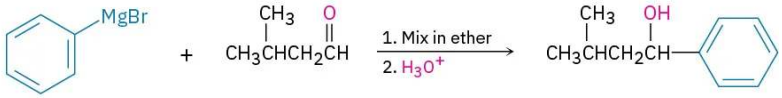
As examples of their addition to carbonyl compounds, Grignard reagents react with formaldehyde, $H_2C{=}O$, to give primary alcohols, with aldehydes to give secondary alcohols, and with ketones to give tertiary alcohols.

Formaldehyde reaction



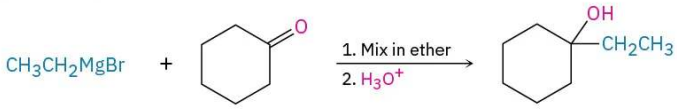
Cyclohexyl-magnesium bromide | **Formaldehyde** | **Cyclohexylmethanol (65%) (a 1° alcohol)**

Aldehyde reaction



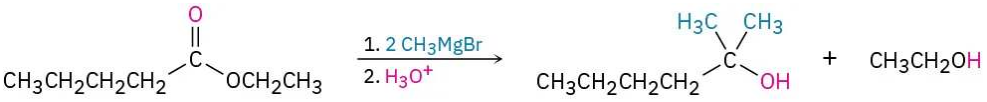
Phenylmagnesium bromide | **3-Methylbutanal** | **3-Methyl-1-phenyl-1-butanol (73%) (a 2° alcohol)**

Ketone reaction



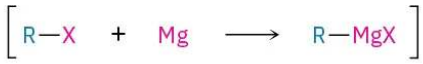
Ethylmagnesium bromide | **Cyclohexanone** | **1-Ethylcyclohexanol (89%) (a 3° alcohol)**

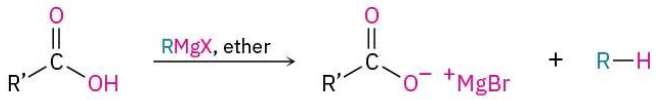
Esters react with Grignard reagents to yield tertiary alcohols in which two of the substituents bonded to the hydroxyl-bearing carbon have come from the Grignard reagent, just as $LiAlH_4$ reduction of an ester adds two hydrogens.



Ethyl pentanoate — 2-Methyl-2-hexanol (85%) (a 3° alcohol)

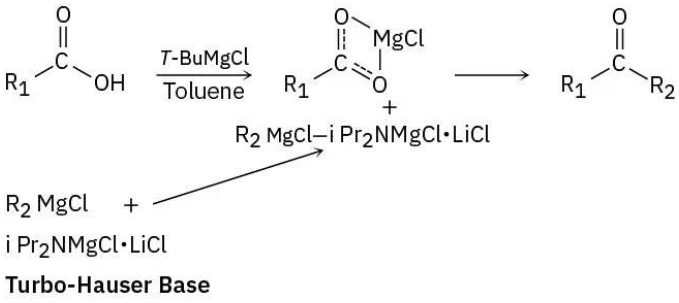
Carboxylic acids don't give addition products when treated directly with Grignard reagents because the acidic carboxyl hydrogen reacts with the basic Grignard reagent to yield a hydrocarbon and the magnesium salt of the acid.





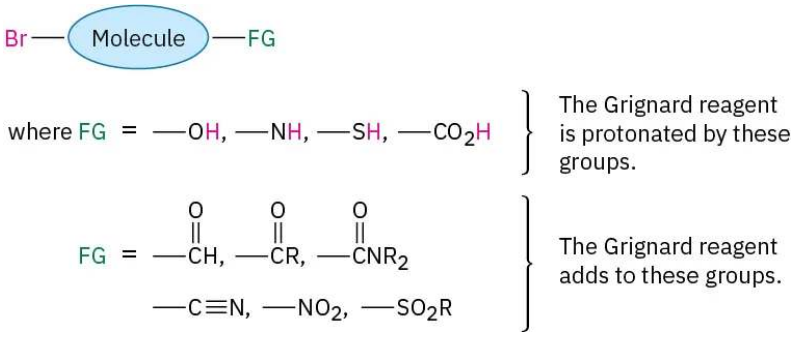
A carboxylic acid **A carboxylic acid salt**

Carboxylic acids do, however, react with Grignard reagents to give ketones if they are first treated with *i*-Pr_2NMgCl-LiCl, called the *turbo*-Hauser base, to form a complex and increase the electrophilicity of the carboxylate anion toward nucleophilic addition with a Grignard reagent.

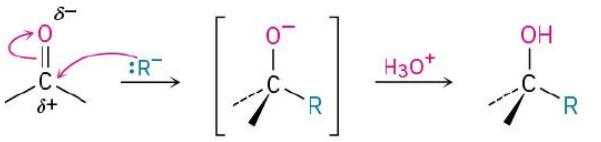


Turbo-Hauser Base

The Grignard reaction, although useful, does have limitations. One major problem is that a Grignard reagent can't be prepared from an organohalide if other reactive functional groups are present in the same molecule. For example, a compound that is both an alkyl halide and a ketone can't form a Grignard reagent because it would react with itself. Similarly, a compound that is both an alkyl halide and a carboxylic acid, alcohol, or amine can't form a Grignard reagent because the acidic $RCO_2\mathbf{H}$, RO**H**, or $RN\mathbf{H}_2$ hydrogen present in the same molecule would react with the basic Grignard reagent as rapidly as it forms. In general, Grignard reagents can't be prepared from alkyl halides that contain the following functional groups (FG):



As with the reduction of carbonyl compounds discussed in the previous section, we'll defer a detailed treatment of the Grignard reactions until Chapter 19. For the moment, it's sufficient to note that Grignard reagents act as nucleophilic carbanions (**:**R^-) and that their addition to a carbonyl compound is analogous to the addition of hydride ion. The intermediate is an alkoxide ion, which is protonated by addition of H_3O^+ in a second step.



A carbonyl compound **An alkoxide ion intermediate** **An alcohol**

Worked Example 17.3: Using a Grignard Reaction to Synthesize an Alcohol

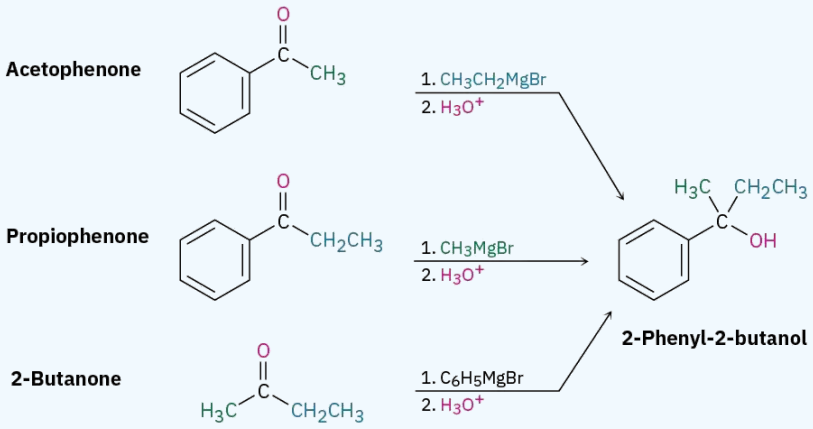
How could you use the addition of a Grignard reagent to a ketone to synthesize 2-phenyl-2-butanol?

Strategy

Draw the product, and identify the three groups bonded to the alcohol carbon atom. One of the three will have come from the Grignard reagent, and the remaining two will have come from the ketone.

Solution

2-Phenyl-2-butanol has a methyl group, an ethyl group, and a phenyl group ($–C_6H_5$) attached to the alcohol carbon atom. Thus, the possibilities are addition of ethylmagnesium bromide to acetophenone, addition of methylmagnesium bromide to propiophenone, and addition of phenylmagnesium bromide to 2-butanone.



Worked Example 17.4: Using a Grignard Reaction to Synthesize an Alcohol

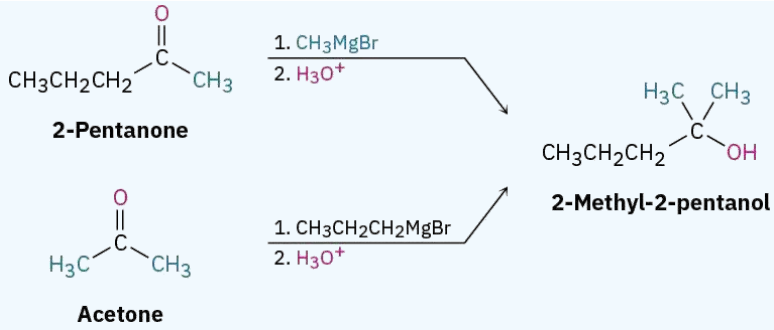
How could you use the reaction of a Grignard reagent with a carbonyl compound to synthesize 2-methyl-2-pentanol?

Strategy

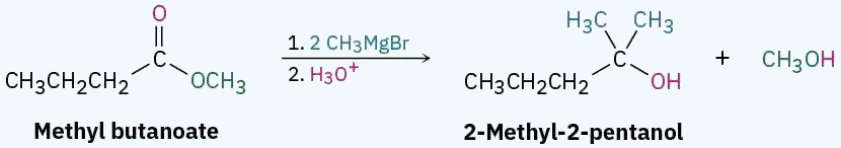
Draw the product, and identify the three groups bonded to the alcohol carbon atom. If the three groups are all different, the starting carbonyl compound must be a ketone. If two of the three groups are identical, the starting carbonyl compound could be either a ketone or an ester.

Solution

In the present instance, the product is a tertiary alcohol with two methyl groups and one propyl group. Starting from a ketone, the possibilities are addition of methylmagnesium bromide to 2-pentanone and addition of propylmagnesium bromide to acetone.



Starting from an ester, the only possibility is addition of methylmagnesium bromide to an ester of butanoic acid, such as methyl butanoate.



Exercise 6.6.1

Show the products obtained from addition of methylmagnesium bromide to the following compounds:

a. Cyclopentanone
b. Benzophenone (diphenyl ketone)
c. 3-Hexanone

Answer

a. 1-Methylcyclopentanol
b. 1,1-Diphenylethanol
c. 3-Methyl-3-hexanol

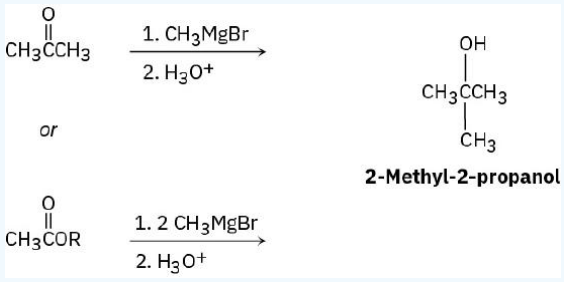
Exercise 6.6.2

Use a Grignard reaction to prepare the following alcohols:

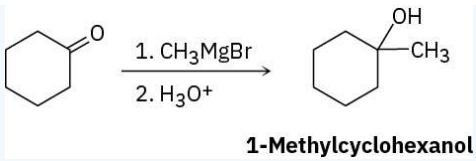
a. 2-Methyl-2-propanol
b. 1-Methylcyclohexanol
c. 3-Methyl-3-pentanol
d. 2-Phenyl-2-butanol
e. Benzyl alcohol
f. 4-Methyl-1-pentanol

Answer

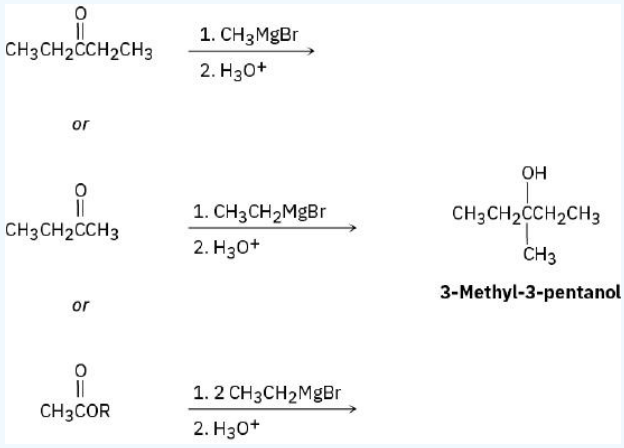
a.



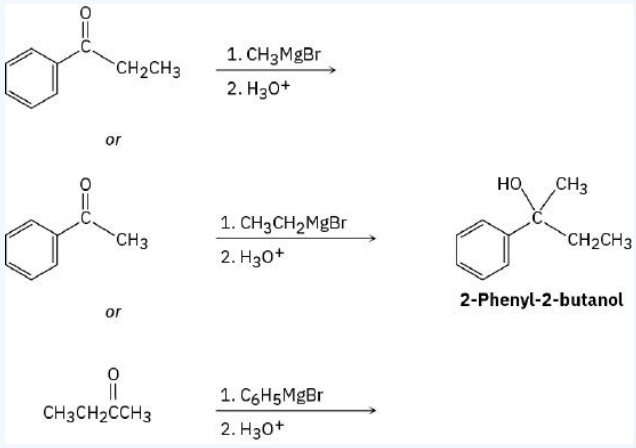
https://chem.libretexts.org/@go/page/564210

b. 

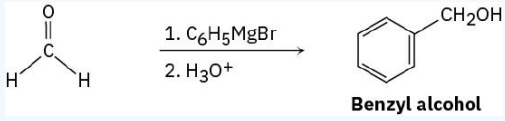
1-Methylcyclohexanol

c. 

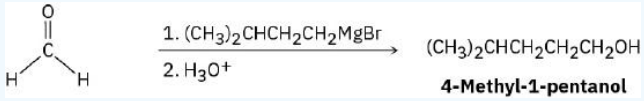
3-Methyl-3-pentanol

d. 

2-Phenyl-2-butanol

e. 

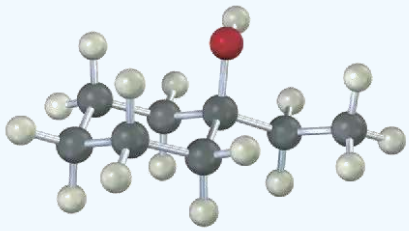
Benzyl alcohol

f. 

4-Methyl-1-pentanol

? Exercise 6.6.3

Use the reaction of a Grignard reagent with a carbonyl compound to synthesize the following compound:



Answer

Cyclohexanone + CH_3CH_2MgBr

This page titled 6.6: Alcohols from Carbonyl Compounds - Grignard Reagents is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **17.5: Alcohols from Carbonyl Compounds - Grignard Reagents** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

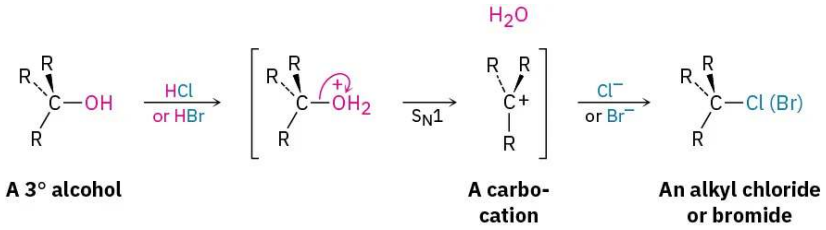
6.7: Reactions of Alcohols

We've already seen several reactions of alcohols—their conversion into alkyl halides and tosylates in Section 10.5 and their dehydration to give alkenes in Section 8.1—albeit without mechanistic details. Let's now look at those details.

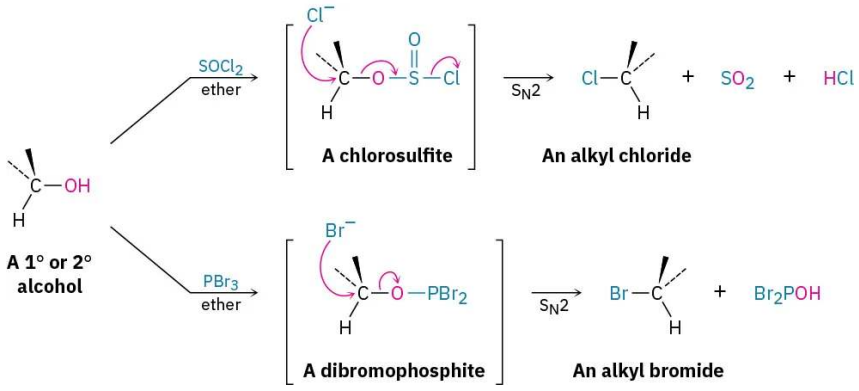
Conversion of Alcohols into Alkyl Halides

Tertiary alcohols react with either HCl or HBr at 0 °C by an S_N1 mechanism through a carbocation intermediate. Primary and secondary alcohols are much more resistant to acid, however, and are best converted into halides by treatment with either $SOCl_2$ or PBr_3 through an S_N2 mechanism.

The reaction of a tertiary alcohol with HX takes place by an S_N1 mechanism when acid protonates the hydroxyl oxygen atom. Water is expelled to generate a carbocation, and the cation reacts with nucleophilic halide ion to give the alkyl halide product.

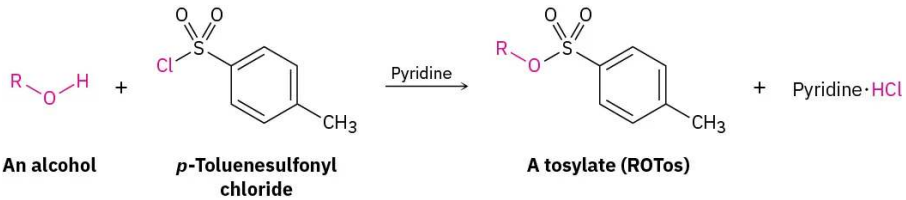


The reactions of primary and secondary alcohols with $SOCl_2$ and PBr_3 take place by S_N2 mechanisms. Hydroxide ion itself is too poor a leaving group to be displaced by nucleophiles in S_N2 reactions, but reaction of an alcohol with $SOCl_2$ or PBr_3 converts the –OH into a much better leaving group, either a chlorosulfite (–OSOCl) or a dibromophosphite ($–OPBr_2$), which is readily expelled by backside nucleophilic substitution.



Conversion of Alcohols into Tosylates

Alcohols react with *p*-toluenesulfonyl chloride (tosyl chloride, *p*-TosCl) in pyridine solution to yield alkyl tosylates, ROTos (Section 11.1). Only the O–H bond of the alcohol is broken in this reaction; the C–O bond remains intact, so no change of configuration occurs if the oxygen is attached to a chirality center. The resultant alkyl tosylates behave much like alkyl halides, undergoing both S_N1 and S_N2 substitution reactions.



One of the most important reasons for using tosylates in S_N2 reactions is stereochemical. The S_N2 reaction of an alcohol with an alkyl halide proceeds with two inversions of configuration—one to make the halide from the alcohol and one to substitute the halide—and yields a product with the same stereochemistry as the starting alcohol. The S_N2 reaction of an alcohol with a tosylate,

however, proceeds with only one inversion and yields a product of opposite stereochemistry to the starting alcohol. Figure 6.7.1 shows a series of reactions on the *R* enantiomer of 2-octanol that illustrates these stereochemical relationships.

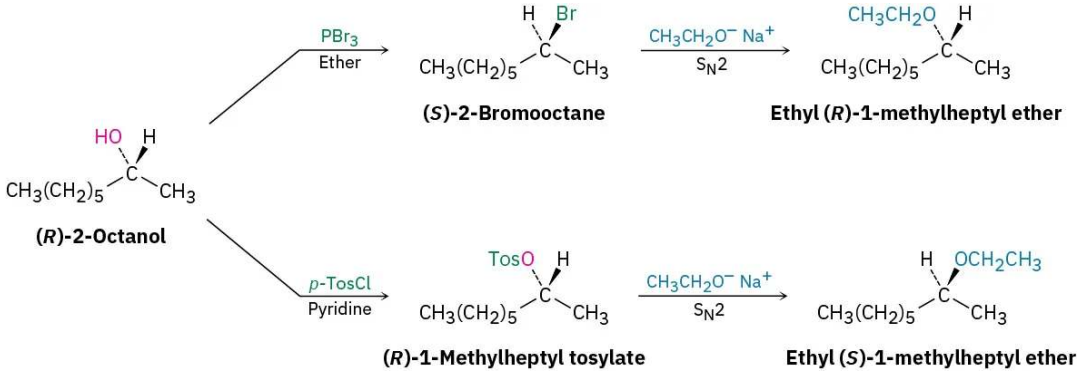
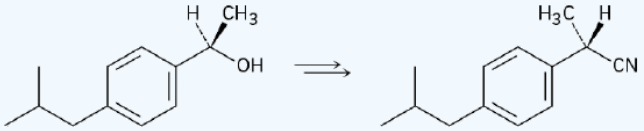


Figure 6.7.1: Stereochemical consequences of S_N2 reactions on derivatives of (*R*)-2-octanol. Substitution through the halide gives a product with the same stereochemistry as the starting alcohol; substitution through the tosylate gives a product with opposite stereochemistry to the starting alcohol.

? Exercise 6.7.1

How would you carry out the following transformation, a step used in the commercial synthesis of (*S*)-ibuprofen?

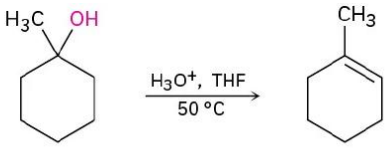


Answer

1. p-TosCl, pyridine; 2. NaCN

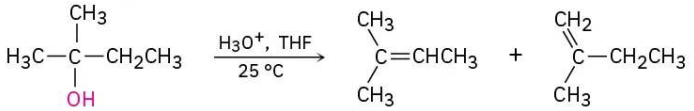
Dehydration of Alcohols to Yield Alkenes

A third important reaction of alcohols, both in the laboratory and in biological pathways, is their dehydration to give alkenes. Because of the usefulness of the reaction, a number of methods have been devised for carrying out dehydrations. One method that works particularly well for tertiary alcohols is the acid-catalyzed reaction discussed in Section 8.1. For example, treatment of 1-methylcyclohexanol with warm, aqueous sulfuric acid in a solvent such as tetrahydrofuran results in loss of water and formation of 1-methylcyclohexene.



1-Methylcyclohexanol **1-Methylcyclohexene (91%)**

Acid-catalyzed dehydrations usually follow Zaitsev's rule (Section 11.7) and yield the more stable alkene as the major product. Thus, 2-methyl-2-butanol gives primarily 2-methyl-2-butene (trisubstituted double bond) rather than 2-methyl-1-butene (disubstituted double bond).



2-Methyl-2-butanol **2-Methyl-2-butene (trisubstituted)** **2-Methyl-1-butene (disubstituted)**

Major product **Minor product**

https://chem.libretexts.org/@go/page/564211

This reaction is an E1 process (Section 11.10) and occurs by the three-step mechanism shown in Figure 6.7.2 on the next page. Protonation of the alcohol oxygen is followed by unimolecular loss of water to generate a carbocation intermediate and final loss of a proton from the neighboring carbon atom to complete the process. As with most E1 reactions, tertiary alcohols react fastest because they lead to stabilized, tertiary carbocation intermediates. Secondary alcohols can be made to react, but the conditions are severe (75% H_2SO_4, 100 °C) and sensitive molecules don't survive.

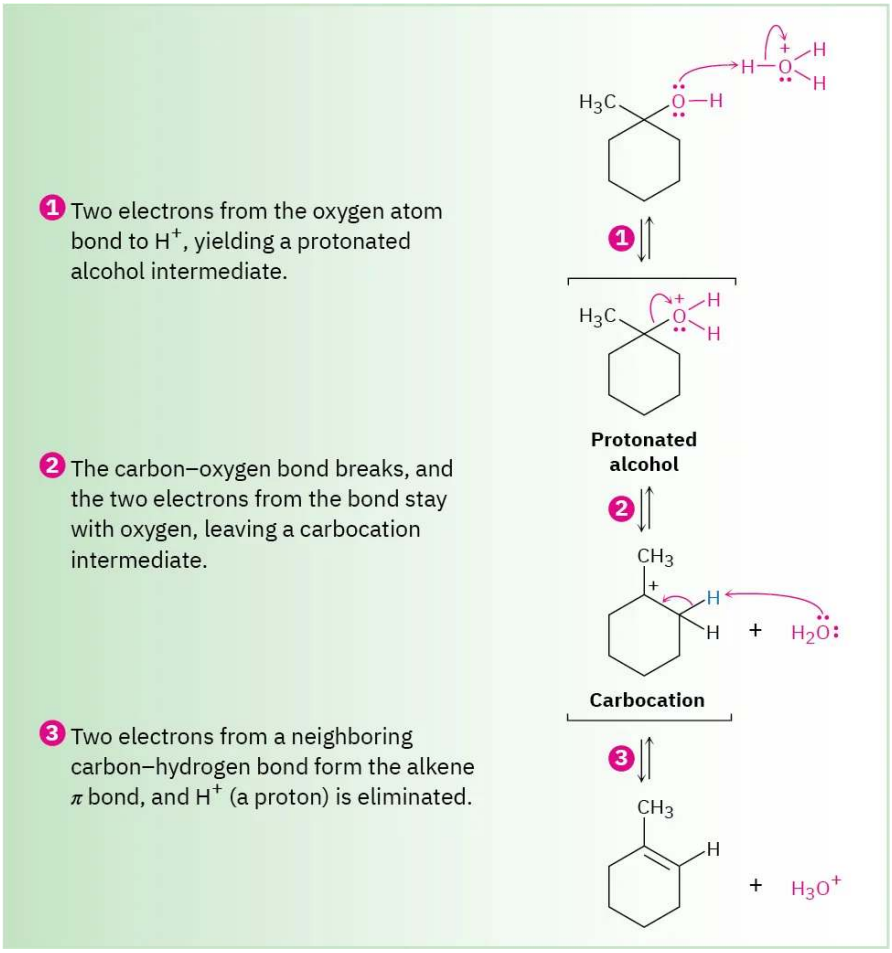
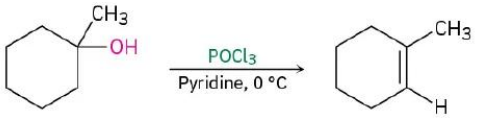


Figure 6.7.2: Mechanism for the acid-catalyzed dehydration of a tertiary alcohol to yield an alkene. The process is an E1 reaction and involves a carbocation intermediate.

To circumvent the need for strong acid and allow the dehydration of secondary alcohols in a gentler way, reagents have been developed that are effective under mild, basic conditions. One such reagent, phosphorus oxychloride ($POCl_3$) in the basic amine solvent pyridine, is often able to effect the dehydration of secondary and tertiary alcohols at 0 °C.



1-Methylcyclohexanol **1-Methylcyclohexene (96%)**

Alcohol dehydrations carried out with $POCl_3$ in pyridine take place by an E2 mechanism, as shown in Figure 6.7.3. Because hydroxide ion is a poor leaving group (Section 11.3), direct E2 elimination of water from an alcohol does not occur. On reaction with $POCl_3$, however, the –OH group is converted into a dichlorophosphate (–$OPOCl_2$), which is a good leaving group and is readily eliminated. Pyridine is both the reaction solvent and the base that removes a neighboring proton in the E2 elimination step.

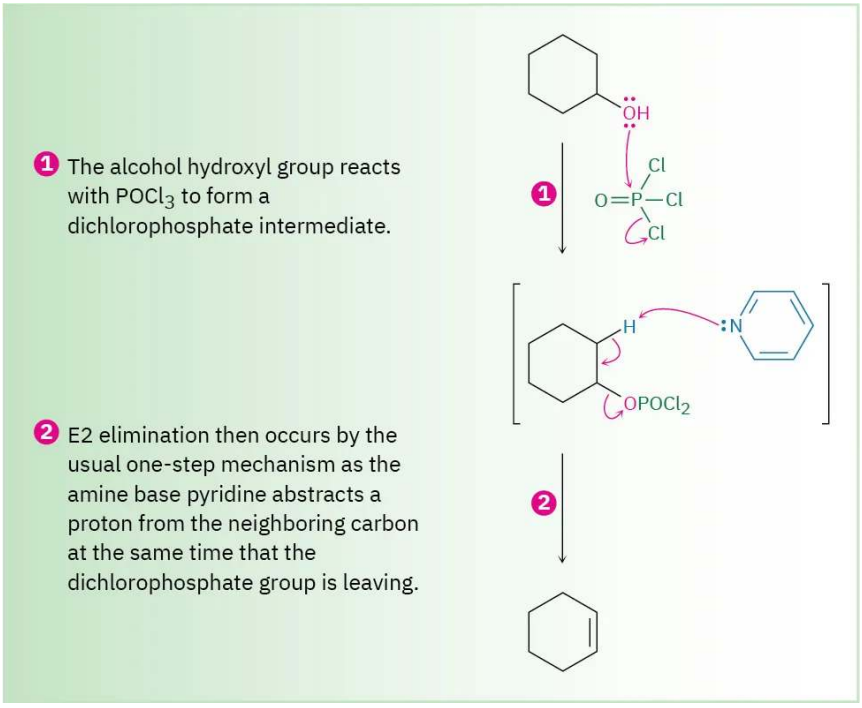
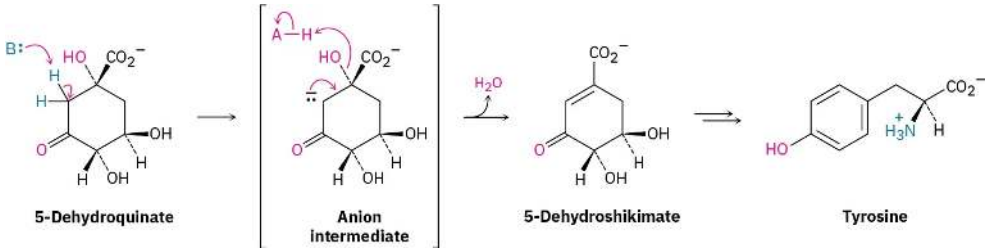


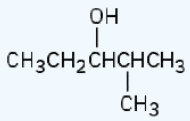
Figure 6.7.3: Mechanism for the dehydration of secondary and tertiary alcohols by reaction with $POCl_3$ in pyridine. The reaction is an E2 process.

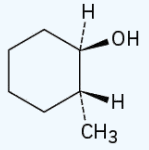
As noted in Section 11.11, biological dehydrations are also common and usually occur by an E1cB mechanism on a substrate in which the –OH group is two carbons away from a carbonyl group. One example occurs in the biosynthesis of the aromatic amino acid tyrosine. A base (:B) first abstracts a proton from the carbon adjacent to the carbonyl group, and the anion intermediate then expels the –OH group with simultaneous protonation by an acid (HA) to form water.

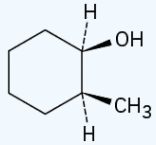


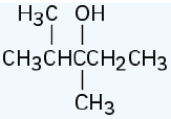
? Exercise 6.7.2

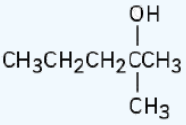
What product(s) would you expect from dehydration of the following alcohols with $POCl_3$ in pyridine? Indicate the major product in each case.

a. 

b. 

c. 

d. 

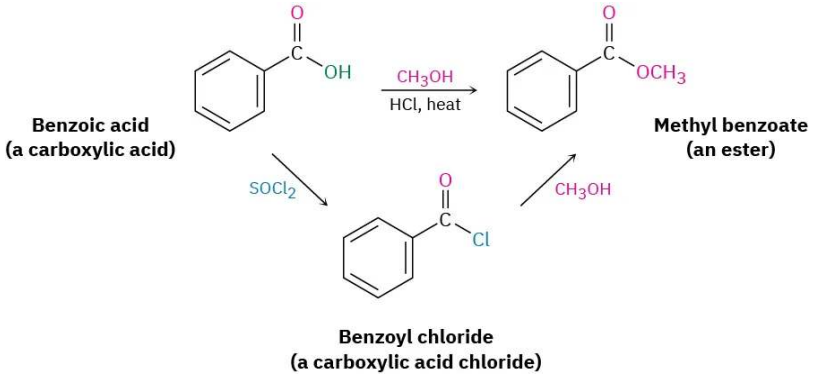
e. 

Answer

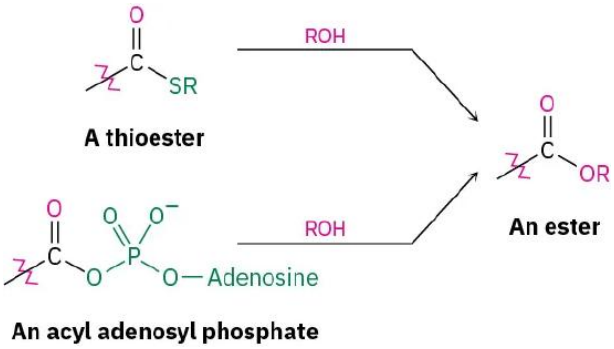
a. 2-Methyl-2-pentene
b. 3-Methylcyclohexene
c. 1-Methylcyclohexene
d. 2,3-Dimethyl-2-pentene
e. 2-Methyl-2-pentene

Conversion of Alcohols into Esters

Alcohols react with carboxylic acids to give esters, a reaction that is common in both the laboratory and living organisms. In the laboratory, the reaction can be carried out in a single step if a strong acid is used as catalyst. More frequently, though, the reactivity of the carboxylic acid is enhanced by first converting it into a carboxylic acid chloride, which then reacts with the alcohol.



In living organisms, a similar process occurs, though a thioester or acyl adenosyl phosphate acts as substrate rather than a carboxylic acid chloride. We'll look at the mechanisms of these reactions in Chapter 21.

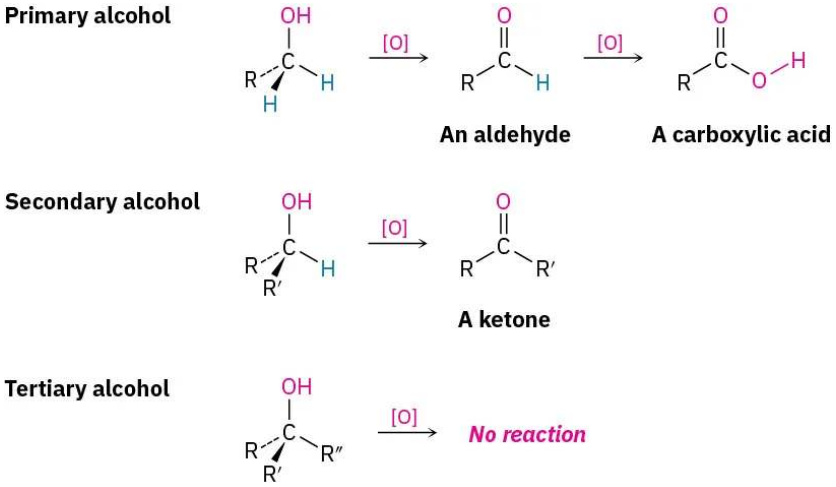


This page titled 6.7: Reactions of Alcohols is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

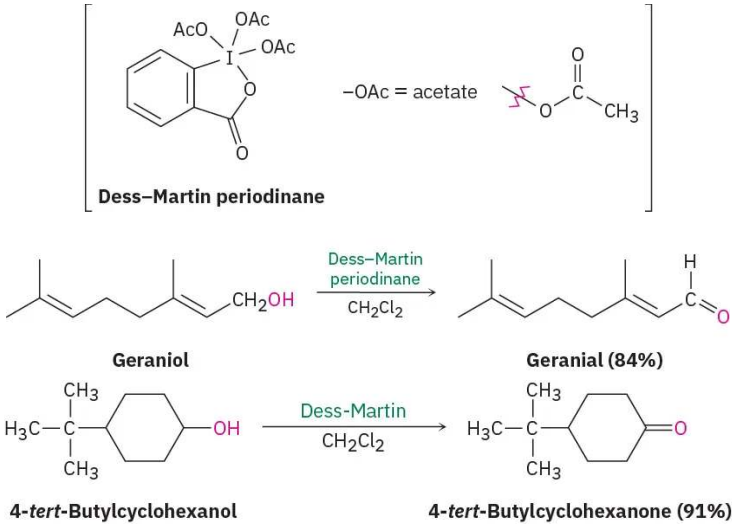
- **17.6: Reactions of Alcohols** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

6.8: Oxidation of Alcohols

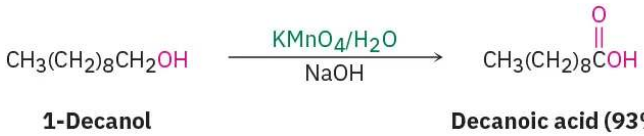
Perhaps the most valuable reaction of alcohols is their oxidation to give carbonyl compounds—the opposite of the reduction of carbonyl compounds to give alcohols. Primary alcohols are oxidized either to aldehydes or carboxylic acids, and secondary alcohols are oxidized to ketones, but tertiary alcohols don't normally react with most oxidizing agents.



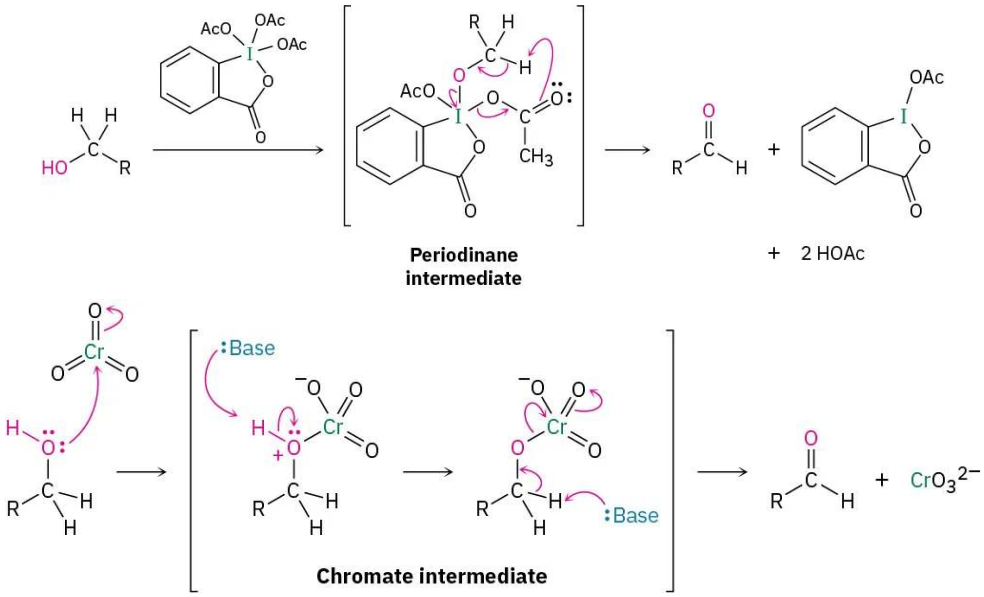
Primary and secondary alcohols can be oxidized by any of a number of reagents, including CrO_3 in aqueous acetic acid and $KMnO_4$ in aqueous NaOH, but chromium-based reagents are rarely used today because of their toxicity and fire danger. Today, primary and secondary alcohols are oxidized to aldehydes and ketones, respectively, using the iodine-containing *Dess–Martin periodinane* in dichloromethane solution.



Primary alcohols are oxidized to carboxylic acids by heating with $KMnO_4$ in a basic aqueous solution. An aldehyde is involved as an intermediate in the $KMnO_4$ reaction but can't usually be isolated because it is further oxidized too rapidly.



All these oxidations occur by a mechanism that is closely related to the E2 reaction (Section 11.8). In the Dess–Martin oxidation, for instance, the first step involves a substitution reaction between the alcohol and the I(V) reagent to form a new periodinane intermediate, followed by expulsion of reduced I(III) as the leaving group. Similarly, when a Cr(VI) reagent, such as CrO_3, is the oxidant, reaction with the alcohol gives a chromate intermediate followed by expulsion of a reduced Cr(VI) species.



Biological alcohol oxidations are the opposite of biological carbonyl reductions and are facilitated by the coenzymes NAD^+ and $NADP^+$. A base removes the –OH proton, and the alkoxide ion transfers a hydride ion to the coenzyme. An example is the oxidation of *sn*-glycerol 3-phosphate to dihydroxyacetone phosphate, a step in the biological metabolism of fats (Figure 6.8.1). Note that addition occurs exclusively on the Re face of the NAD^+ ring, adding a hydrogen with pro-*R* stereochemistry.

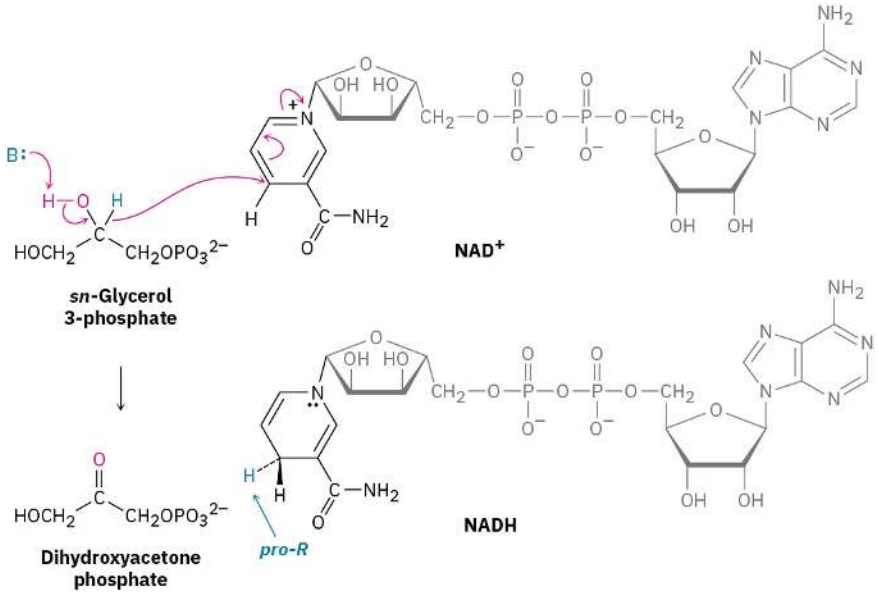
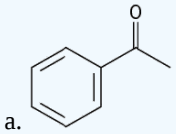
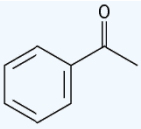


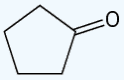
Figure 6.8.1: The biological oxidation of an alcohol (*sn*-glycerol 3-phosphate) to give a ketone (dihydroxyacetone phosphate). This mechanism is the exact opposite of the ketone reduction shown previously in Figure 17.5.

Exercise 6.8.1

What alcohols would give the following products on oxidation?

a. 

b. 

c. 

Answer

a. 1-Phenylethanol
b. 2-Methyl-1-propanol
c. Cyclopentanol

? Exercise 6.8.2

What products would you expect from oxidation of the following compounds with the Dess–Martin periodinane?

a. 1-Hexanol
b. 2-Hexanol
c. Hexanal

Answer

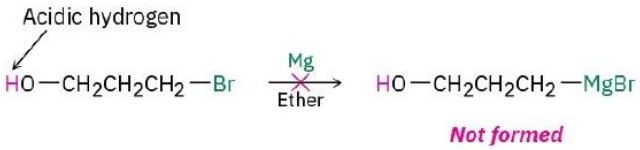
a. Hexanoic acid, hexanal
b. 2-Hexanone
c. Hexanoic acid, no reaction

This page titled 6.8: Oxidation of Alcohols is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **17.7: Oxidation of Alcohols** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

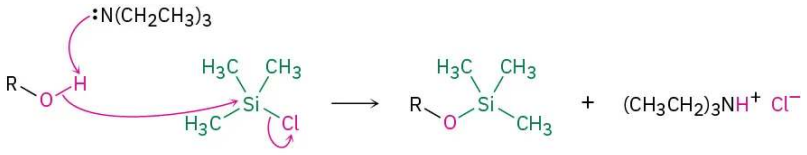
6.9: Protection of Alcohols

It often happens, particularly during the synthesis of complex molecules, that one functional group in a molecule interferes with an intended reaction on another functional group elsewhere in the same molecule. We saw earlier in this chapter, for instance, that a Grignard reagent can't be prepared from an alcohol-containing halidel because the C–Mg bond is not compatible with the presence of an acidic –OH group in the same molecule.



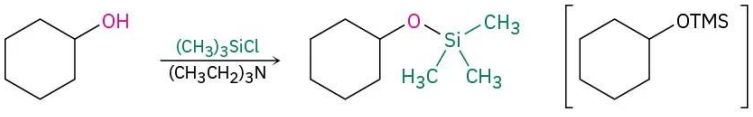
When this kind of incompatibility arises, it's sometimes possible to circumvent the problem by *protecting* the interfering functional group. Protection involves three steps: (**1**) introducing a protecting group to block the interfering function, (**2**) carrying out the desired reaction, and (**3**) removing the protecting group.

One of the more common methods of alcohol protection involves reaction with a chlorotrialkylsilane, Cl–SiR_3, to yield a trialkylsilyl ether, R′–O–SiR_3. (Chloro-*tert*-butyldimethylsilane), usually abbreviated either TBS or TBDMS is often used, as is chlorotrimethylsilane (TMS), and the reaction is carried out in the presence of a base, such as triethylamine, to help form the alkoxide anion from the alcohol and to remove the HCl by-product from the reaction.



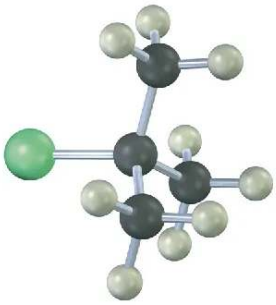
An alcohol **Chlorotrimethyl-silane** **A trimethylsilyl (TMS) ether**

For example:

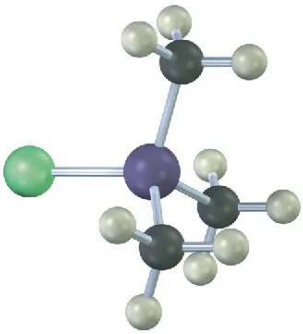


Cyclohexanol **Cyclohexyl trimethylsilyl ether (94%)**

The ether-forming step is an S_N2-like reaction of the alkoxide ion on the silicon atom, with concurrent loss of the leaving chloride anion. Unlike most S_N2 reactions, though, this reaction takes place at a *tertiary* center—a trialkyl-substituted silicon atom. The reaction occurs because silicon, a third-row atom, is larger than carbon and forms longer bonds. In addition, three alkyl substituents attached to silicon offer little steric hindrance to ether formation.



C–C bond length: 154 pm



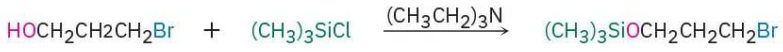
C–Si bond length: 195 pm

Like most other ethers, which we'll study in the next chapter, trialkylsilylethers are relatively unreactive. They have no acidic hydrogens and don't react with oxidizing agents, reducing agents, or Grignard reagents. They do, however, react with aqueous acid or with fluoride ion to regenerate the alcohol. Tetrabutylammonium fluoride is often used.

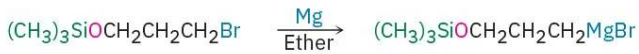
Cyclohexyl trimethylsilyl ether **Cyclohexanol**

To solve the problem posed at the beginning of this section, note that it's possible to use an alcohol-containing halide in a Grignard reaction by employing a protection sequence. For example, we can add 3-bromo-1-propanol to acetaldehyde by the route shown in Figure 6.9.1.

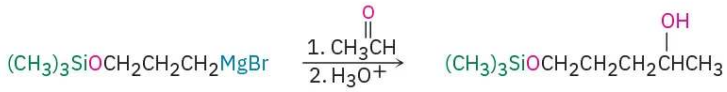
Step 1 Protect alcohol:



Step 2a Form Grignard reagent:



Step 2b Do Grignard reaction:



Step 3 Remove protecting group:

Figure 6.9.1: Use of a trialkylsilyl-protected alcohol during a Grignard reaction.

? Exercise 6.9.1

Propose a mechanism for the reaction of cyclohexyl TMS ether with LiF to deprotect the silyl ether.

Answer

S_N2 reaction of F^- on silicon with displacement of alkoxide ion.

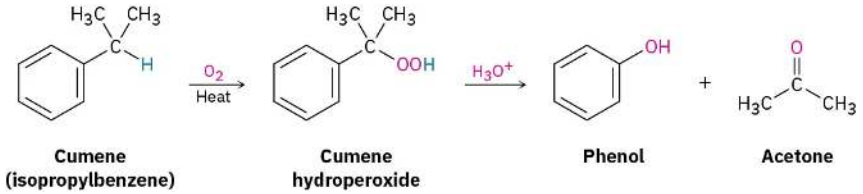
This page titled 6.9: Protection of Alcohols is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **17.8: Protection of Alcohols** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

6.10: Phenols and Their Uses

The outbreak of World War I provided a stimulus for the industrial preparation of large amounts of synthetic phenol, which was needed as a raw material to manufacture the explosive, picric acid (2,4,6-trinitrophenol). Today, approximately 132 million tons of phenol is manufactured worldwide each year for use in such products as Bakelite resin and adhesives for binding plywood.

Phenol was manufactured for many years by the Dow process, in which chlorobenzene reacts with NaOH at high temperature and pressure (Section 16.7). Now, however, an alternative synthesis uses isopropylbenzene, commonly called *cumene*. Cumene reacts with air at high temperature by benzylic oxidation through a radical mechanism to form cumene hydroperoxide, which is converted into phenol and acetone by treatment with acid. This is a particularly efficient process because two valuable chemicals are prepared at the same time.



Cumene (isopropylbenzene) **Cumene hydroperoxide** **Phenol** **Acetone**

As shown in Figure 6.10.1, the reaction occurs by protonation of oxygen followed by shift of the phenyl group from carbon to oxygen with simultaneous loss of water. Replacement of the water then yields an intermediate called a *hemiacetal*—a compound that contains one –OR group and one –OH group bonded to the same carbon atom—which breaks down to phenol and acetone.

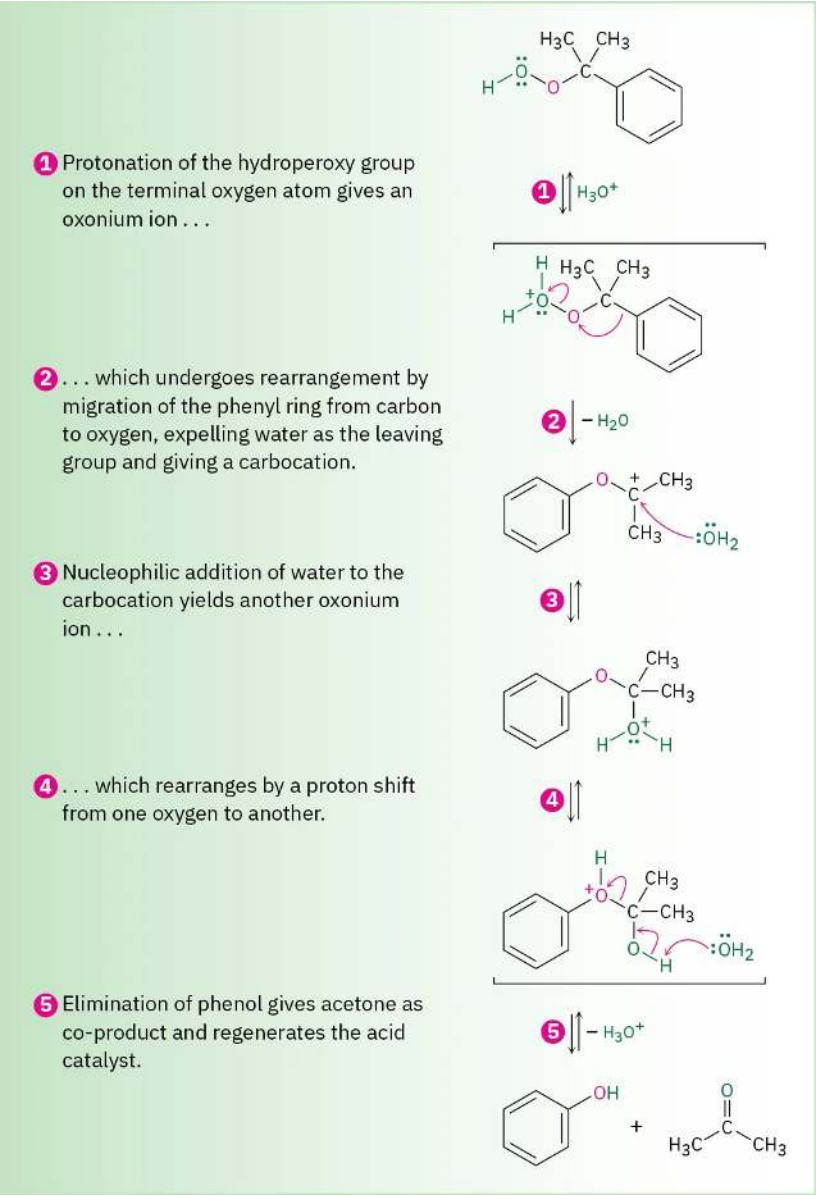
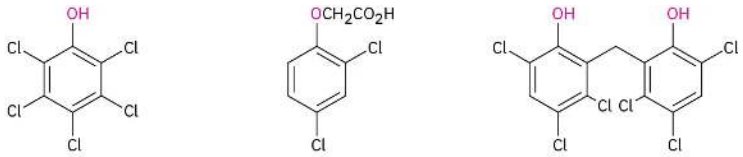


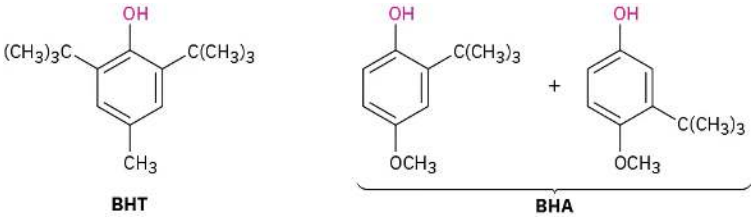
Figure 6.10.1: Mechanism for the formation of phenol by acid-catalyzed rearrangement of cumene hydroperoxide

In addition to its use in making resins and adhesives, phenol is also the starting material for the synthesis of chlorinated phenols and the food preservatives BHT (butylated hydroxytoluene) and BHA (butylated hydroxyanisole). Pentachlorophenol, a widely used wood preservative, is prepared by reaction of phenol with excess Cl_2. The herbicide 2,4-D (2,4-dichlorophenoxyacetic acid) is prepared from 2,4-dichlorophenol, and the hospital antiseptic agent hexachlorophene is prepared from 2,4,5-trichlorophenol.



Pentachlorophenol (wood preservative) | **2,4-Dichlorophenoxyacetic acid, 2,4-D (herbicide)** | **Hexachlorophene (antiseptic)**

The food preservative BHT is prepared by Friedel–Crafts alkylation of *p*-methylphenol (*p*-cresol) with 2-methylpropene in the presence of acid; BHA is prepared similarly by alkylation of *p*-methoxyphenol.



? Exercise 6.10.1

Show the mechanism for the reaction of *p*-methylphenol with 2-methylpropene and H_3PO_4 catalyst to yield the food additive BHT.

Answer

Protonation of 2-methylpropene gives the *tert*-butyl cation, which carries out an electrophilic aromatic substitution reaction.

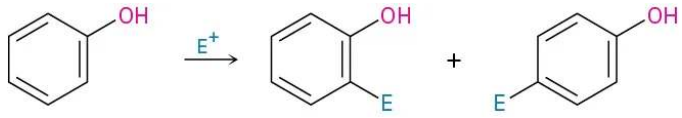
This page titled 6.10: Phenols and Their Uses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **17.9: Phenols and Their Uses** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

6.11: Reactions of Phenols

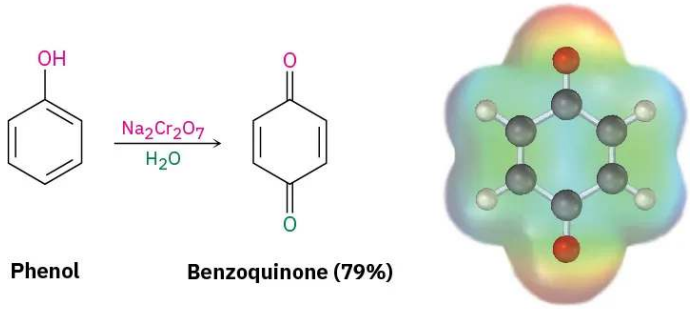
Electrophilic Aromatic Substitution Reactions

The hydroxyl group is a strongly activating, ortho- and para-directing substituent in electrophilic aromatic substitution reactions (Section 16.4). As a result, phenols are highly reactive substrates for electrophilic halogenation, nitration, sulfonation, and Friedel–Crafts reactions.



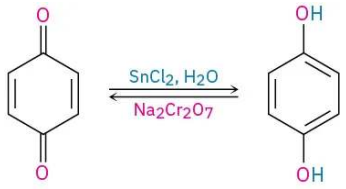
Oxidation of Phenols: Quinones

Phenols don't undergo oxidation in the same way as alcohols because they don't have a hydrogen atom on the hydroxyl-bearing carbon. Instead, oxidation of a phenol yields a 2,5-cyclohexadiene-1,4-dione, or quinone. Many different oxidizing agents will accomplish the transformation, but potassium nitrosodisulfonate [$(KSO_3)_2NO$], called Fremy's salt, is often used.



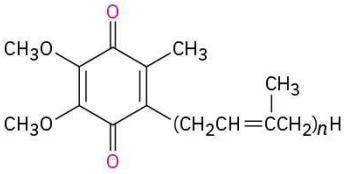
Phenol **Benzoquinone (79%)**

Quinones are a valuable class of compounds because of their oxidation–reduction, or *redox*, properties. They can be easily reduced to hydroquinones (*p*-dihydroxybenzenes) by reagents such as $NaBH_4$ and $SnCl_2$, and hydroquinones can be easily reoxidized back to quinones.



Benzoquinone **Hydroquinone**

The redox properties of quinones are crucial to the functioning of living cells, where compounds called *ubiquinones* act as biochemical oxidizing agents to mediate the electron-transfer processes involved in energy production. Ubiquinones, also called *coenzymes Q*, are components of the cells in all aerobic organisms, from the simplest bacterium to humans. They are so named because of their ubiquitous occurrence throughout nature.

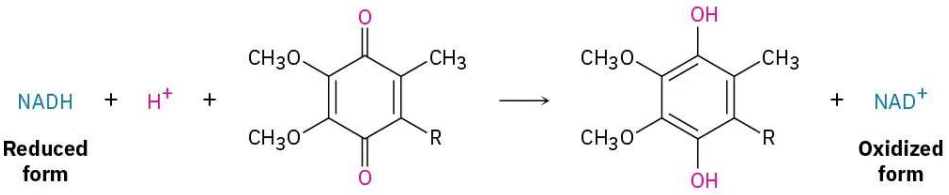


Ubiquinones (n = 1–10)

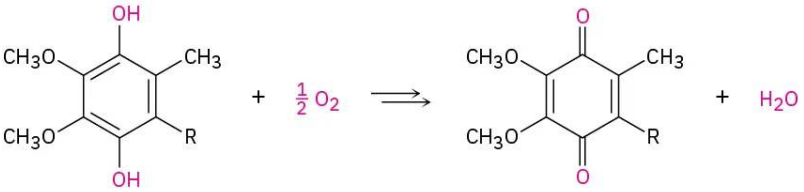
Ubiquinones function within the mitochondria of cells to mediate the respiration process in which electrons are transported from the biological reducing agent NADH to molecular oxygen. Through a complex series of steps, the ultimate result is a cycle

whereby NADH is oxidized to NAD^+, O_2 is reduced to water, and energy is produced. Ubiquinone acts only as an intermediary and is itself unchanged.

Step 1



Step 2



Net change: $NADH + \frac{1}{2}O_2 + H^+ \longrightarrow NAD^+ + H_2O$

This page titled 6.11: Reactions of Phenols is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **17.10: Reactions of Phenols** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

6.12: Spectroscopy of Alcohols and Phenols

Infrared Spectroscopy

Alcohols have a strong C–O stretching absorption near 1050 cm^{-1} and a characteristic O–H stretching absorption at 3300 to 3600 cm^{-1}. The exact position of the O–H stretch depends on the extent of hydrogen-bonding in the molecule. Unassociated alcohols show a fairly sharp absorption near 3600 cm^{-1}, whereas hydrogen-bonded alcohols show a broader absorption in the 3300 to 3400 cm^{-1} range. The hydrogen-bonded hydroxyl absorption appears at 3350 cm^{-1} in the IR spectrum of cyclohexanol (Figure 6.12.1).

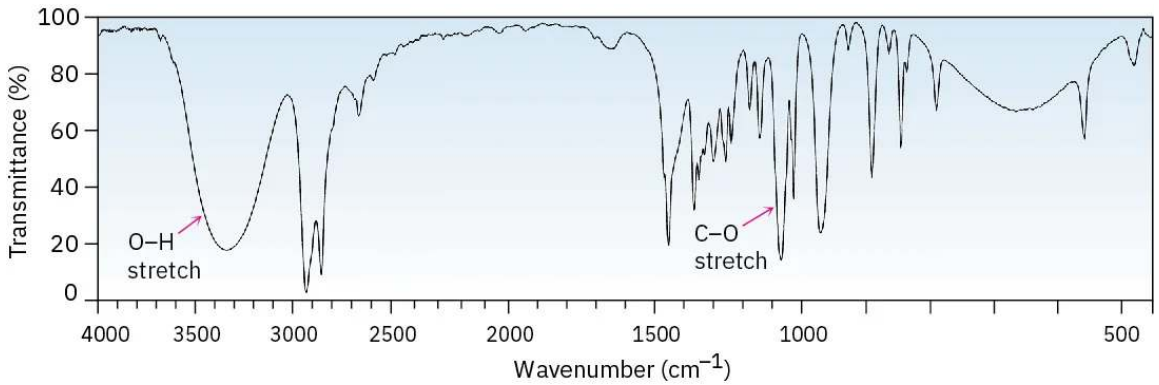


Figure 6.12.1: IR spectrum of cyclohexanol. Characteristic O–H and C–O stretching absorptions are indicated.

Phenols also show a characteristic broad IR absorption at 3500 cm^{-1} due to the –OH group, as well as the usual 1500 and 1600 cm^{-1} aromatic bands (Figure 6.12.2). In phenol itself, monosubstituted aromatic-ring peaks are visible at 690 and 760 cm^{-1}.

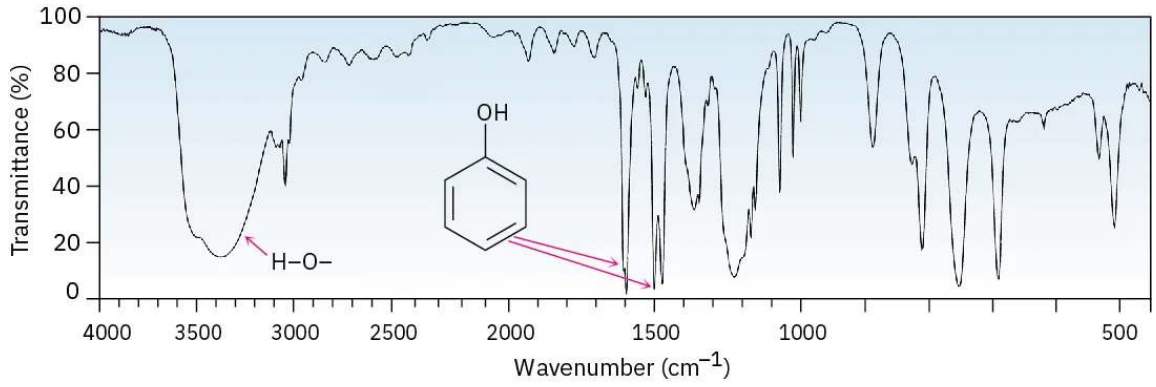
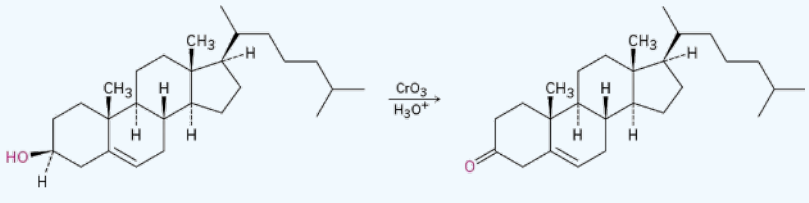


Figure 6.12.2: IR spectrum of phenol.

? Exercise 6.12.1

Assume that you need to prepare 5-cholesten-3-one from cholesterol. How could you use IR spectroscopy to tell whether the reaction was successful? What differences would you look for in the IR spectra of starting material and product?

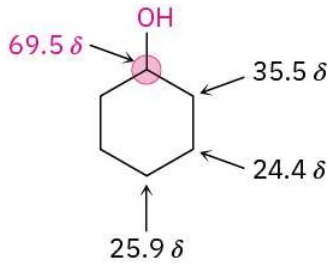


Cholesterol 5-Cholestene-3-one

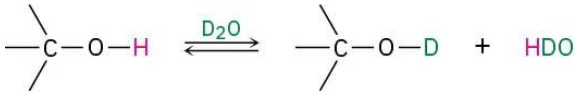
Answer

Disappearance of –OH absorption; appearance of C=O

Carbon atoms bonded to electron-withdrawing –OH groups are deshielded and absorb at a lower field in the ^{13}C NMR spectrum than do typical alkane carbons. Most alcohol carbon absorptions fall in the range 50 to 80 δ, as shown in the following drawing for cyclohexanol:



Alcohols also show characteristic absorptions in the ^1H NMR spectrum. Hydrogens on the oxygen-bearing carbon atom are deshielded by the electron-withdrawing effect of the nearby oxygen, and their absorptions occur in the range 3.4 to 4.5 δ. Spin–spin splitting, however, is not usually observed between the O–H proton of an alcohol and the neighboring protons on carbon. Most samples contain small amounts of acidic impurities, which catalyze an exchange of the O–H proton on a timescale so rapid that the effect of spin–spin splitting is removed. It's often possible to take advantage of this rapid proton exchange to identify the position of the O–H absorption. If a small amount of deuterated water, D_2O, is added to an NMR sample tube, the O–H proton is rapidly exchanged for deuterium and the hydroxyl absorption disappears from the spectrum.



Typical spin–spin splitting *is* observed between protons on the oxygen-bearing carbon and other neighbors. For example, the signal of the two $–CH_2O–$ protons in 1-propanol is split into a triplet by coupling with the neighboring $–CH_2–$ protons (Figure 6.12.3).

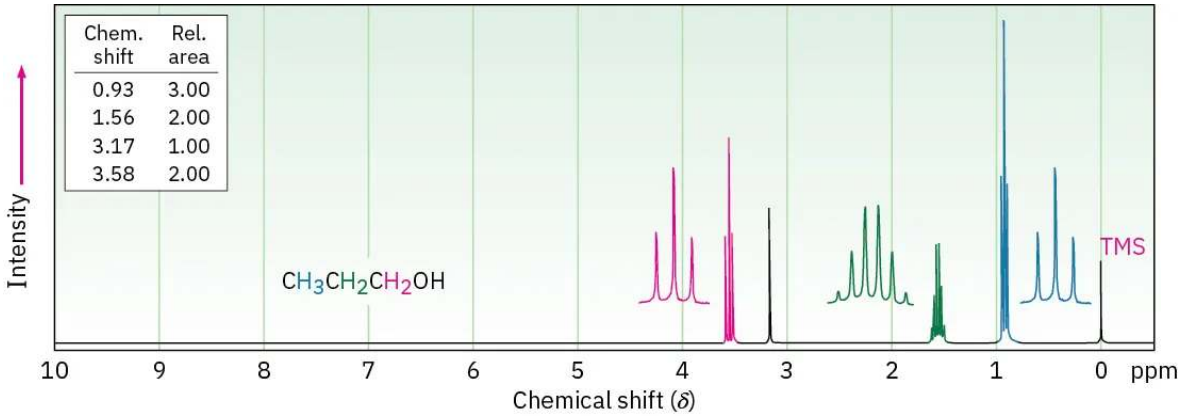


Figure 6.12.3: ^1H NMR spectrum of 1-propanol. The protons on the oxygen-bearing carbon are split into a triplet at 3.58 δ.

Phenols, like all aromatic compounds, show ^1H NMR absorptions near 7 to 8 δ, the expected position for aromatic-ring protons (Section 15.7). In addition, phenol O–H protons absorb at 3 to 8 δ. In neither case are these absorptions uniquely diagnostic for phenols, since other kinds of protons absorb in the same range.

? Exercise 6.12.2

When the ^1H NMR spectrum of an alcohol is run in dimethyl sulfoxide (DMSO) solvent rather than in chloroform, exchange of the O–H proton is slow and spin–spin splitting is seen between the O–H proton and C–H protons on the adjacent carbon. What spin multiplicities would you expect for the hydroxyl protons in the following alcohols?

a. 2-Methyl-2-propanol
b. Cyclohexanol
c. Ethanol

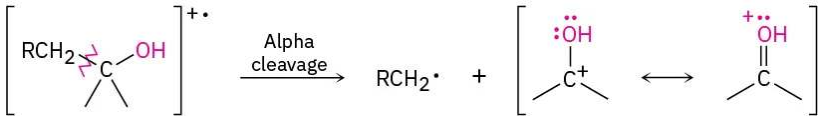
d. 2-Propanol
e. Cholesterol
f. 1-Methylcyclohexanol

Answer

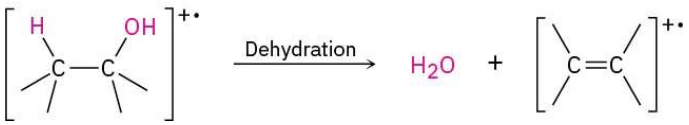
a. Singlet
b. Doublet
c. Triplet
d. Doublet
e. Doublet
f. Singlet

Mass Spectrometry

As noted in Section 12.3, alcohols undergo fragmentation in the mass spectrometer by two characteristic pathways, alpha cleavage and dehydration. In the alpha-cleavage pathway, a C–C bond nearest the hydroxyl group is broken, yielding a neutral radical plus a resonance-stabilized, oxygen-containing cation.



In the dehydration pathway, water is eliminated, yielding an alkene radical cation.



Both fragmentation modes are apparent in the mass spectrum of 1-butanol (Figure 6.12.4). The peak at *m/z* = 56 is due to loss of water from the molecular ion, and the peak at *m/z* = 31 is due to an alpha cleavage.

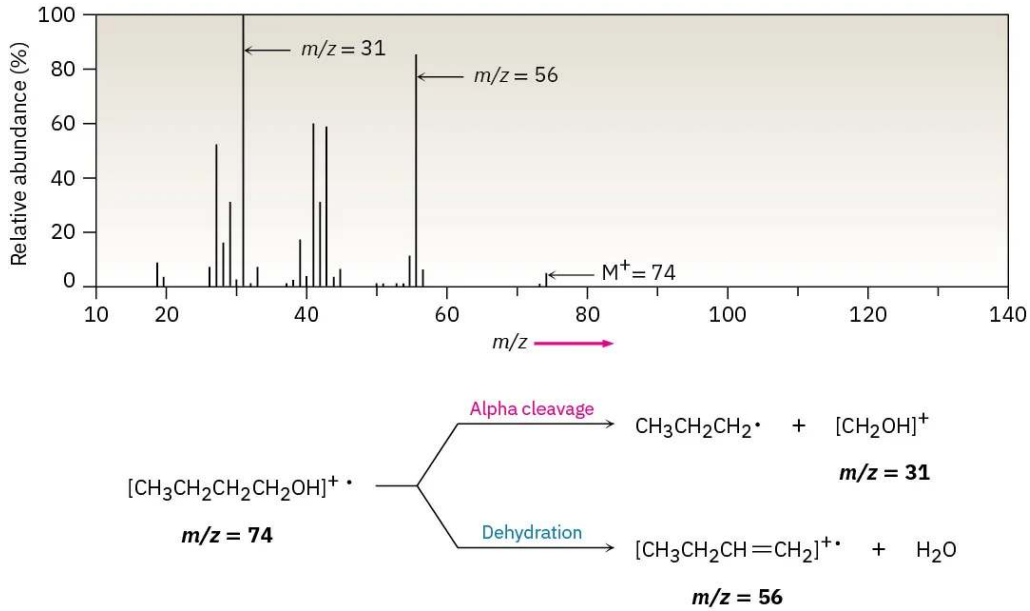


Figure 6.12.4: Mass spectrum of 1-butanol (M^+ = 74). Dehydration gives a peak at *m/z* = 56, and fragmentation by alpha cleavage gives a peak at *m/z* = 31.

This page titled 6.12: Spectroscopy of Alcohols and Phenols is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **17.11: Spectroscopy of Alcohols and Phenols** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

6.13: Chemistry Matters—Ethanol- Chemical, Drug, and Poison

The production of ethanol by fermentation of grains and sugars is one of the oldest known organic reactions, going back at least 8000 years in the Middle East and perhaps as many as 9000 years in China. Fermentation is carried out by adding yeast to an aqueous sugar solution, where enzymes break down carbohydrates into ethanol and CO_2. As noted in the chapter introduction, approximately 26 billion gallons of ethanol is produced each year by fermentation of corn and sugar, with essentially the entire amount used to make bus and automobile fuel.

$$\underset{\text{A carbohydrate}}{C_6H_{12}O_6} \xrightarrow{\text{Yeast}} 2\,CH_3CH_2OH + 2\,CO_2$$

Ethanol is classified medically as a central nervous system (CNS) depressant. Its effects—that is, being drunk—resemble the human response to anesthetics. There is an initial excitability and increase in sociable behavior, but this results from depression of inhibition rather than from stimulation. At a blood alcohol concentration of 0.1% to 0.3%, motor coordination is affected, accompanied by loss of balance, slurred speech, and amnesia. When blood alcohol concentration rises to between 0.3% and 0.4%, nausea and loss of consciousness occur. Above 0.6%, spontaneous respiration and cardiovascular regulation are affected, ultimately leading to death. The LD_{50} of ethanol is 10.6 g/kg (Chapter 1 *Chemistry Matters*).

The passage of ethanol through the body begins with its absorption in the stomach and small intestine, followed by rapid distribution to all body fluids and organs. In the pituitary gland, ethanol inhibits the production of a hormone that regulates urine flow, causing increased urine production and dehydration. In the stomach, ethanol stimulates production of acid. Throughout the body, ethanol causes blood vessels to dilate, resulting in flushing of the skin and a sensation of warmth as blood moves into capillaries beneath the surface. The result is not a warming of the body, but an increased loss of heat at the surface.

Figure 6.13.1: The Harger Drunkometer was the first breath analyzer, introduced in 1938 to help convict drunk drivers. (credit: "Unidentified police officer with a Harger "Drunkometer" breathalyzer" by Florida Memory, State Library and Archives of Florida/Wikimedia Commons, Public Doman)

Ethanol metabolism occurs mainly in the liver and proceeds by oxidation in two steps, first to acetaldehyde (CH_3CHO) and then to acetic acid (CH_3CO_2H). When continuously present in the body, ethanol and acetaldehyde are toxic, leading to the devastating physical and metabolic deterioration seen in people with chronic alcohol use disorder. The liver usually suffers the worst damage since it is the major site of alcohol metabolism.

Approximately 17,000 people are killed each year in the United States in alcohol-related automobile accidents. Thus, all 50 states have made it illegal to drive with a blood alcohol concentration (BAC) above 0.08%. Fortunately, simple tests have been devised for measuring blood alcohol concentration. The original breath analyzer test measured alcohol concentration in expired air by the color change occurring when the bright-orange oxidizing agent potassium dichromate ($K_2Cr_2O_7$) reduced to blue-green chromium(III). Current consumer devices use a conductivity sensor, and tests used by law-enforcement agencies use IR spectroscopy to measure blood-alcohol levels in expired air. Just breathe into the machine, and let the spectrum tell the tale.

This page titled 6.13: Chemistry Matters—Ethanol- Chemical, Drug, and Poison is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **17.12: Chemistry Matters—Ethanol- Chemical, Drug, and Poison** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

6.14: Key Terms

- alcohol
- alkoxide ion, RO^-
- hydroquinone
- phenol
- phenoxide ion ArO^-
- protecting group
- quinone

This page titled 6.14: Key Terms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **17.13: Key Terms** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

6.15: Summary

In previous chapters, we focused on developing general ideas of organic reactivity, looking at the chemistry of hydrocarbons and alkyl halides and seeing some of the tools used in structural studies. With that accomplished, we have now begun to study the oxygen-containing functional groups that lie at the heart of organic and biological chemistry.

Alcohols are among the most versatile of all organic compounds. They occur widely in nature, are important industrially, and have an unusually rich chemistry. The most widely used methods of alcohol synthesis start with carbonyl compounds. Aldehydes, esters, and carboxylic acids are reduced by reaction with $LiAlH_4$ to give primary alcohols (RCH_2OH); ketones are reduced to yield secondary alcohols (R_2CHOH).

Alcohols are also prepared by reaction of carbonyl compounds with Grignard reagents, RMgX. Addition of a Grignard reagent to formaldehyde yields a primary alcohol, addition to an aldehyde yields a secondary alcohol, and addition to a ketone or an ester yields a tertiary alcohol. The Grignard reaction is limited by the fact that Grignard reagents can't be prepared from alkyl halides that contain reactive functional groups in the same molecule. This problem can sometimes be avoided by **protecting** the interfering functional group. Alcohols are often protected by formation of trialkylsilyl ethers.

Alcohols undergo many reactions and can be converted into many other functional groups. They can be dehydrated to give alkenes by treatment with $POCl_3$ and can be transformed into alkyl halides by treatment with PBr_3 or $SOCl_2$. Furthermore, alcohols are weakly acidic ($pK_a \approx 16–18$) and react with strong bases and with alkali metals to form **alkoxide anions**, which are used frequently in organic synthesis. Perhaps the most important reaction of alcohols is their oxidation to carbonyl compounds. Primary alcohols yield either aldehydes or carboxylic acids, secondary alcohols yield ketones, but tertiary alcohols are not normally oxidized.

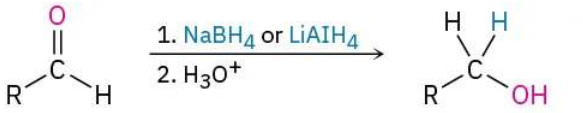
Phenols are aromatic counterparts of alcohols but are more acidic ($pK_a \approx 10$) because their corresponding **phenoxide anions** are resonance stabilized by delocalization of the negative charge into the aromatic ring. Substitution of the aromatic ring by an electron-withdrawing group increases phenol acidity, and substitution by an electron-donating group decreases acidity. Phenols can be oxidized to **quinones**, and quinones can be reduced back to **hydroquinones**.

This page titled 6.15: Summary is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **17.14: Summary** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

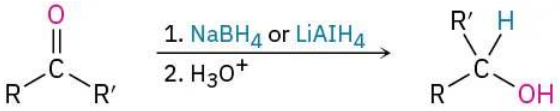
6.16: Summary of Reactions

1. Synthesis of alcohols
   a. Reduction of carbonyl compounds (Section 17.4)
      (1) Aldehydes



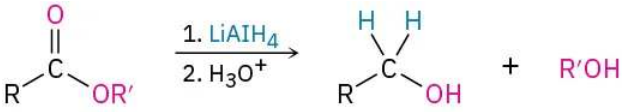
Primary alcohol

(2) Ketones



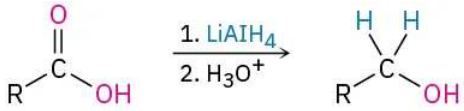
Secondary alcohol

(3) Esters



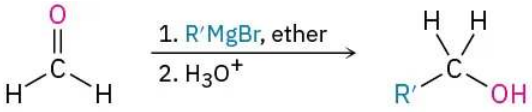
Primary alcohol

(4) Carboxylic acids



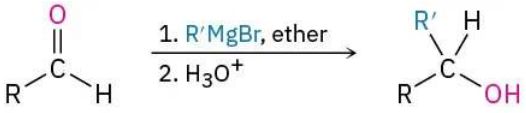
Primary alcohol

- Grignard addition to carbonyl compounds (Section 17.5)
  (1) Formaldehyde



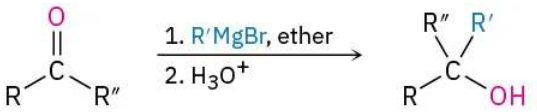
Primary alcohol

(2) Aldehydes



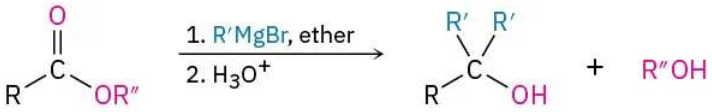
Secondary alcohol

(3) Ketones



Tertiary alcohol

(4) Esters

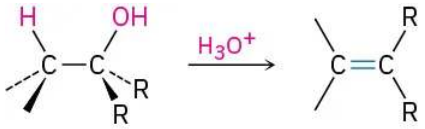


Tertiary alcohol

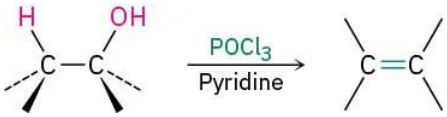
- Reactions of alcohols

a. Dehydration (Section 17.6)

(1) Tertiary alcohols

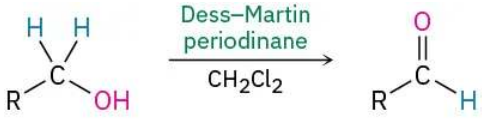


(2) Secondary and tertiary alcohols

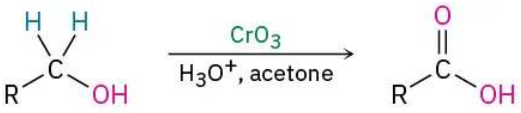


b. Oxidation (Section 17.7)

(1) Primary alcohols

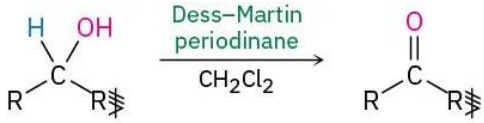


Aldehyde



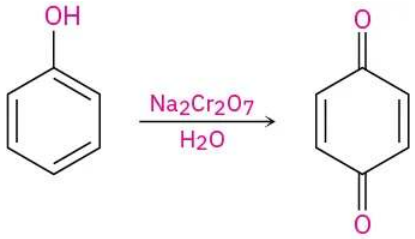
Carboxylic acid

(2) Secondary alcohols



Ketone

- Oxidation of phenols to quinones (Section 17.10)



This page titled 6.16: Summary of Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **17.15: Summary of Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

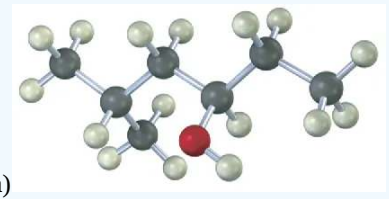
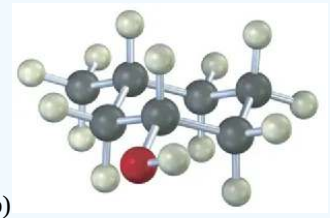
6.17: Additional Problems

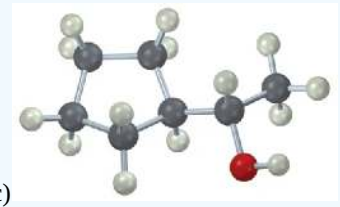
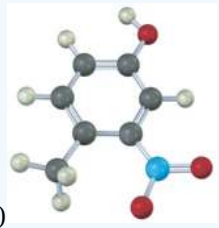
6.17.●

Visualizing Chemistry

Exercise 6.17.20

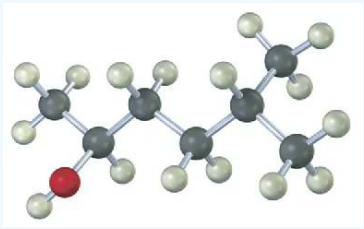
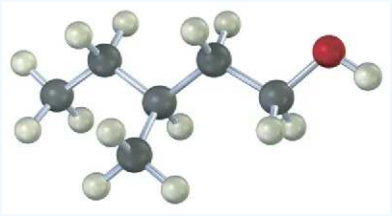
Give IUPAC names for the following compounds:

(a)  (b) 

(c)  (d) 

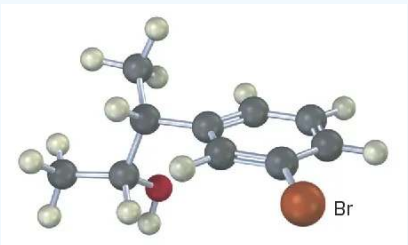
Exercise 6.17.21

Draw the structure of the carbonyl compound(s) from which each of the following alcohols might have been prepared, and show the products you would obtain by treatment of each alcohol with (1) Na metal, (2) $SOCl_2$, and (3) Dess–Martin periodinane. (a)

(a)  (b) 

Exercise 6.17.22

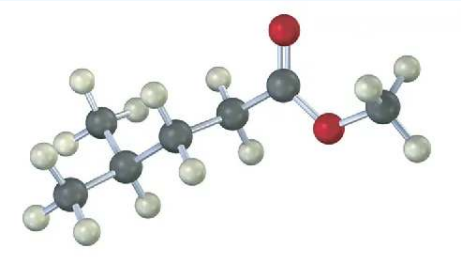
Predict the product from the reaction of the following substance (reddish brown = Br) with:



(a) PBr_3 (b) Aqueous H_2SO_4 (c) $SOCl_2$ (d) Dess–Martin periodinane (e) Br_2, $FeBr_3$

? Exercise 6.17.25

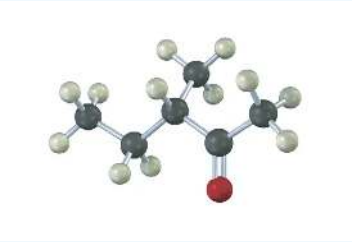
Predict the product from reaction of the following substance with:



(a) $NaBH_4$; then H_3O^+ (b) $LiAlH_4$; then H_3O^+ (c) 2 CH_3CH_2MgBr; then H_3O^+

? Exercise 6.17.24

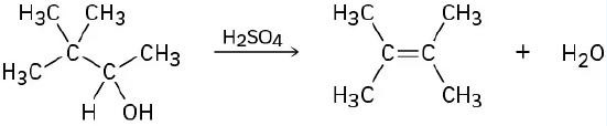
Name and assign *R* or *S* stereochemistry to the product(s) you would obtain by reaction of the following substance with ethylmagnesium bromide. Is the product chiral? Is it optically active? Explain.



Mechanism Problems

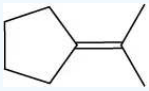
? Exercise 6.17.25

Evidence for the intermediate carbocations in the acid-catalyzed dehydration of alcohols comes from the observation that rearrangements sometimes occur. Propose a mechanism to account for the formation of 2,3-dimethyl-2-butene from 3,3-dimethyl-2-butanol.



? Exercise 6.17.26

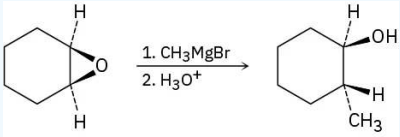
Acid-catalyzed dehydration of 2,2-dimethylcyclohexanol yields a mixture of 1,2-dimethylcyclohexene and isopropylidenecyclopentane. Propose a mechanism to account for the formation of both products.



Isopropylidenecyclopentane

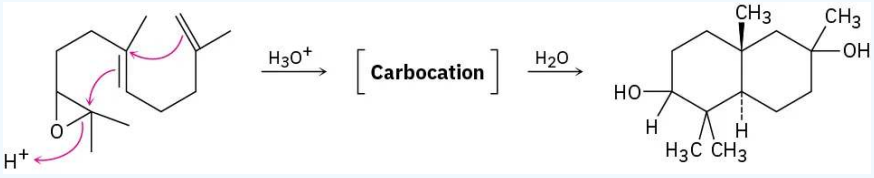
? Exercise 6.17.27

Epoxides react with Grignard reagents to yield alcohols. Propose a mechanism.



Exercise 6.17.28

Treatment of the following epoxide with aqueous acid produces a carbocation intermediate that reacts with water to give a diol product. Show the structure of the carbocation, and propose a mechanism for the second step.

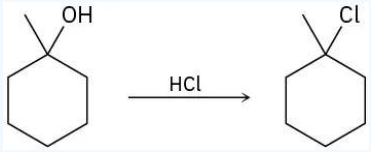


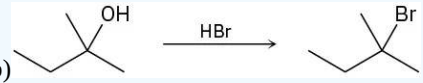
Exercise 6.17.29

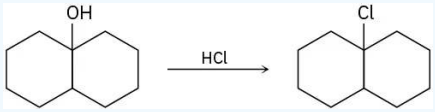
Reduction of 2-butanone with $NaBH_4$ yields 2-butanol. Is the product chiral? Is it optically active? Explain.

Exercise 6.17.30

The conversion of 3° alcohols into 3° alkyl halides under acidic conditions involves two cationic intermediates. For each reaction, draw the complete mechanism using curved arrows.

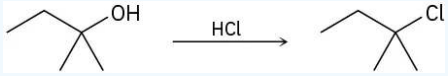
(a)


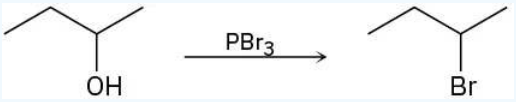
(b)


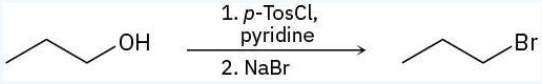
(c)


Exercise 6.17.31

Identify the type of substitution mechanism (S_N1, S_N2) involved in the conversion of the following alcohols into the corresponding alkyl halide.

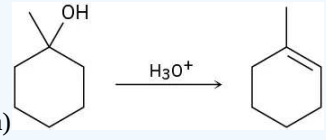
(a)


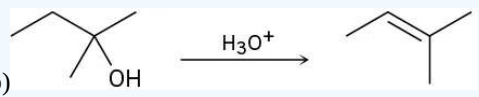
(b)


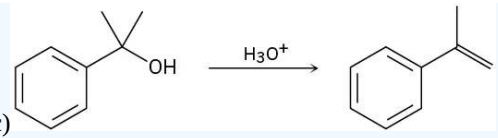
(c)


Exercise 6.17.32

The conversion of 3° alcohols into alkenes under acidic conditions involves two cationic intermediates. For each reaction, draw the complete mechanism using curved arrows.

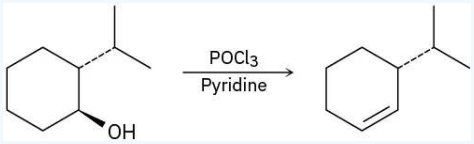
(a)


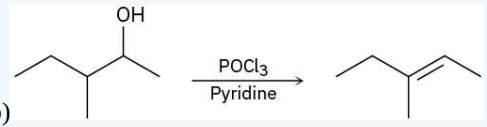
(b)


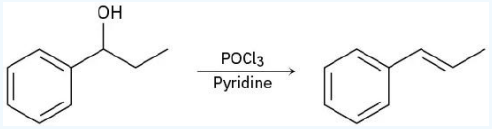
c) 

Exercise 6.17.33

For each reaction, draw the complete mechanism using curved arrows. For each reaction, write the mechanism using curved arrows for the conversion of the alcohol into the corresponding alkene with $POCl_3$. In each case, explain the regiochemistry of the elimination.

(a) 

(b) 

(c) 

Exercise 6.17.34

The trimethylsilyl (TMS) protecting group is one of several silicon-protecting groups for alcohols. For each reaction, draw the mechanism for the protection of (*R*)-3-bromo-1-butanol with the following silyl chlorides, using triethylamine as the base:

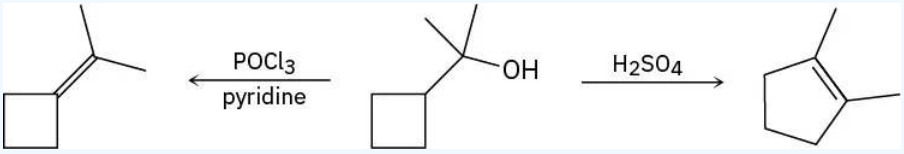
(a) *tert*-butyldimethylsilyl chloride (TBS-Cl)

(b) triisopropylsilyl chloride (TIPS-Cl)

(c) triethylsilyl chloride (TES-Cl)

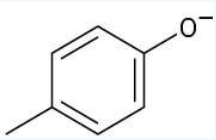
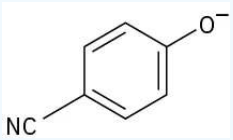
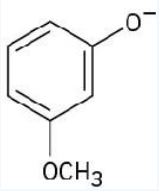
Exercise 6.17.35

When the following alcohol is treated with $POCl_3$ and pyridine, the expected elimination product is formed. However, when the same alcohol is treated with H_2SO_4, the elimination product is 1,2-dimethylcyclopentene. Propose a mechanism for each pathway to account for these differences.



Exercise 6.17.36

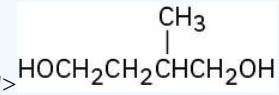
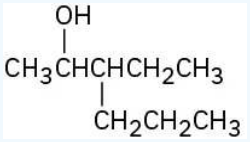
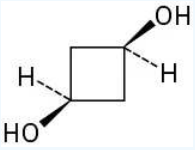
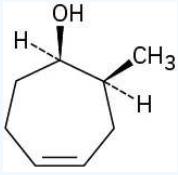
Phenols generally have lower pK_a's than alcohols because of resonance stabilization with the aromatic ring. Draw all of the resonance contributors for the following phenolate ions.

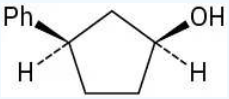
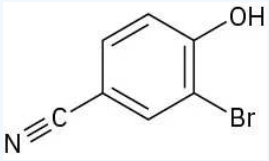
(a)  (b)  (c) 

Naming Alcohols

? Exercise 6.17.37

Give IUPAC names for the following compounds:

(a) <p">  (b)  (c)  (d) 

(e)  (f) 

? Exercise 6.17.38

Draw and name the eight isomeric alcohols with formula $C_5H_{12}O$.

? Exercise 6.17.39

Draw structures corresponding to the following IUPAC names:

(a) *Trans*-3-Chlorocycloheptanol

(b) 2-Ethyl-2-buten-1-ol

(c) *o*-(2-Hydroxyethyl)phenol

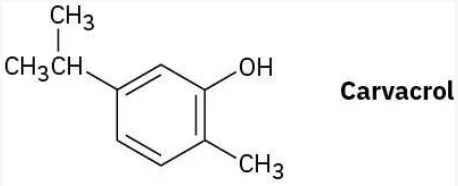
(d) 3-Methyl-1-phenyl-1-butanol

? Exercise 6.17.40

Bombykol, the sex pheromone secreted by the female silkworm moth has the formula $C_{16}H_{28}O$ and the systematic name (10*E*,12*Z*)-10,12-hexadecadien-1-ol. Draw bombykol, showing the correct geometry for the two double bonds.

? Exercise 6.17.41

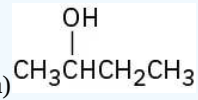
Carvacrol is a naturally occurring substance isolated from oregano, thyme, and marjoram. What is its IUPAC name?

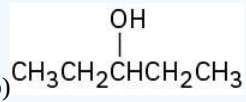


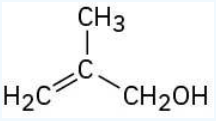
Carvacrol

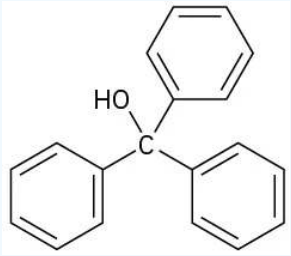
Exercise 6.17.42

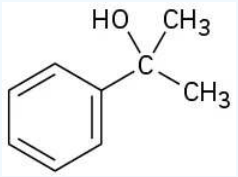
What Grignard reagent and what carbonyl compound might you start with to prepare the following alcohols:

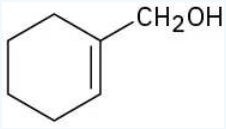
(a) 

(b) 

(c) 

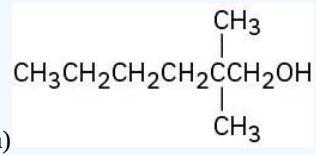
(d) 

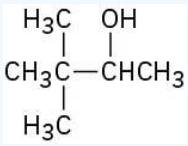
(e) 

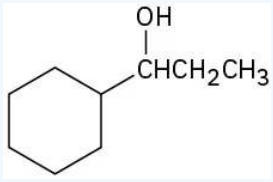
(f) 

Exercise 6.17.43

What carbonyl compounds would you reduce to prepare the following alcohols: List all possibilities.

(a) 

(b) 

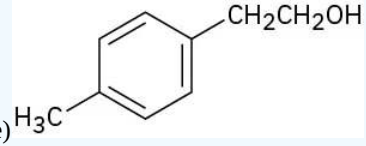
(c) 

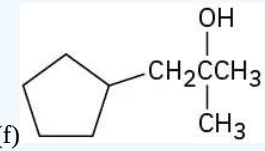
Exercise 6.17.44

What carbonyl compounds might you start with to prepare the following compounds by Grignard reaction? List all possibilities.

(a) 2-Methyl-2-propanol (b) 1-Ethylcyclohexanol

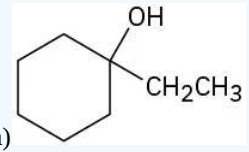
(c) 3-Phenyl-3-pentanol (d) 2-Phenyl-2-pentanol

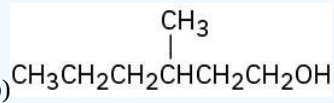
(e) 

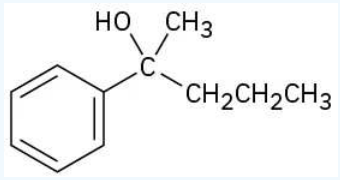
(f) 

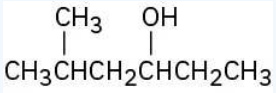
Exercise 6.17.45

How would you synthesize the following alcohols, starting with benzene and other alcohols of six or fewer carbons as your only organic reagents?

(a) 

(b) 

(c) 

(d) 

Reactions of Alcohols

Exercise 6.17.46

What products would you obtain from reaction of 1-pentanol with the following reagents:

(a) PBr_3 (b) $SOCl_2$ (c) Dess–Martin periodinane

Exercise 6.17.47

How would you prepare the following compounds from 2-phenylethanol: More than one step may be required.

(a) Styrene ($PhCH{=}CH_2$)(b) Phenylacetaldehyde ($PhCH_2CHO$) (c) Phenylacetic acid ($PhCH_2CO_2H$) (d) Benzoic acid (e) Ethylbenzene (f) Benzaldehyde (g) 1-Phenylethanol (h) 1-Bromo-2-phenylethane

Exercise 6.17.48

How would you prepare the following compounds from 1-phenylethanol: More than one step may be required.

(a) Acetophenone ($PhCOCH_3$) (b) Benzyl alcohol (c) *m*-Bromobenzoic acid (d) 2-Phenyl-2-propanol

Exercise 6.17.49

How would you prepare the following substances from cyclopentanol: More than one step may be required.

(a) Cyclopentanone (b) Cyclopentene (c) 1-Methylcyclopentanol (d) *trans*-2-Methylcyclopentanol

Exercise 6.17.50

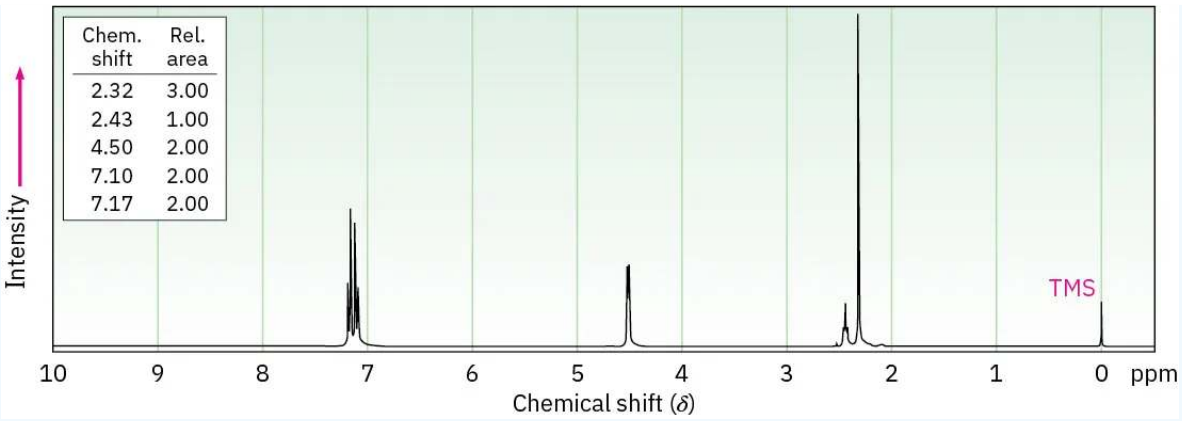
What products would you expect to obtain from the reaction of 1-methylcyclohexanol with the following reagents?

(a) HBr (b) NaH (c) H_2SO_4

Spectroscopy

Exercise 6.17.51

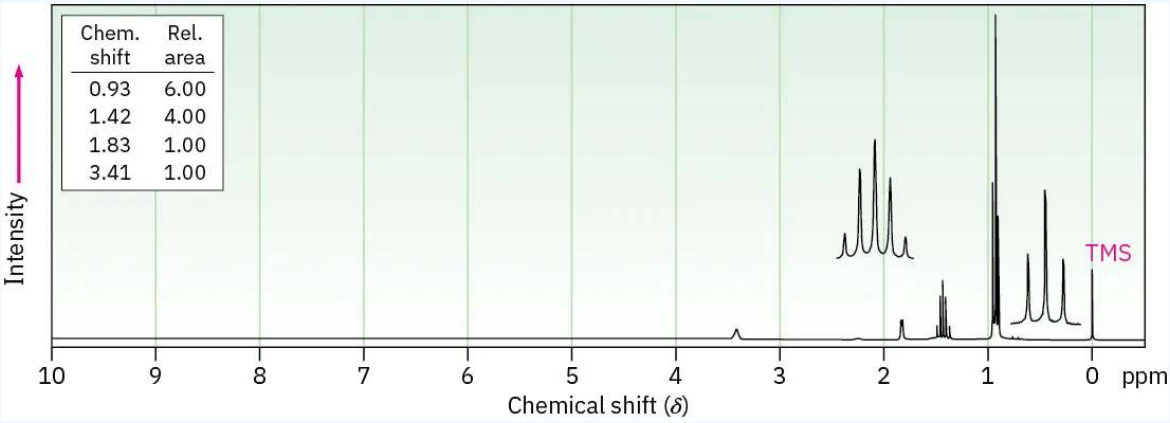
The following ^1H NMR spectrum is that of an alcohol, $C_8H_{10}O$. Propose a structure.



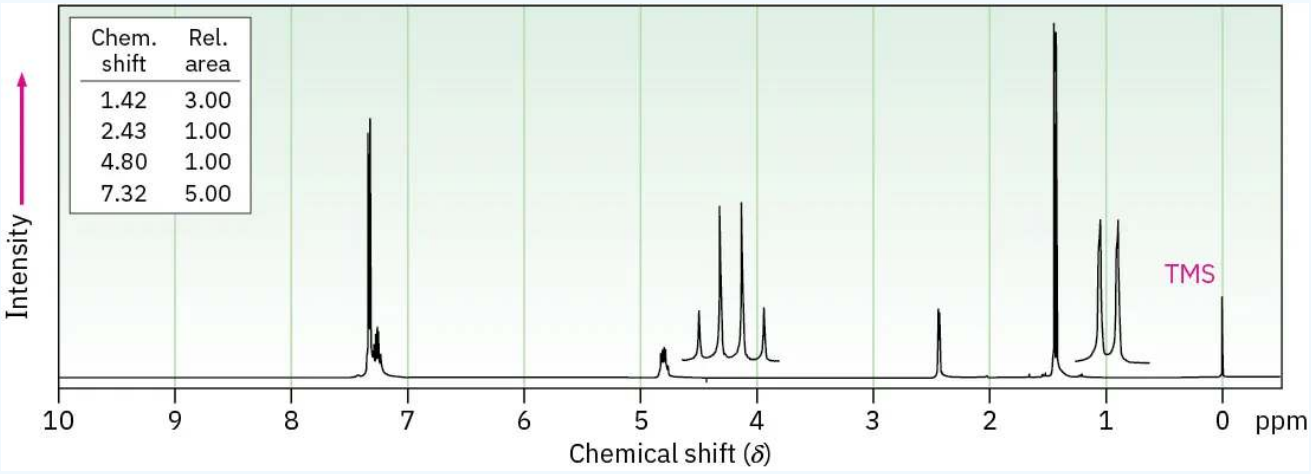
Exercise 6.17.52

1H NMR spectra:

(a) **$C_5H_{12}O$**



(b) $C_8H_{10}O$



Exercise 6.17.53

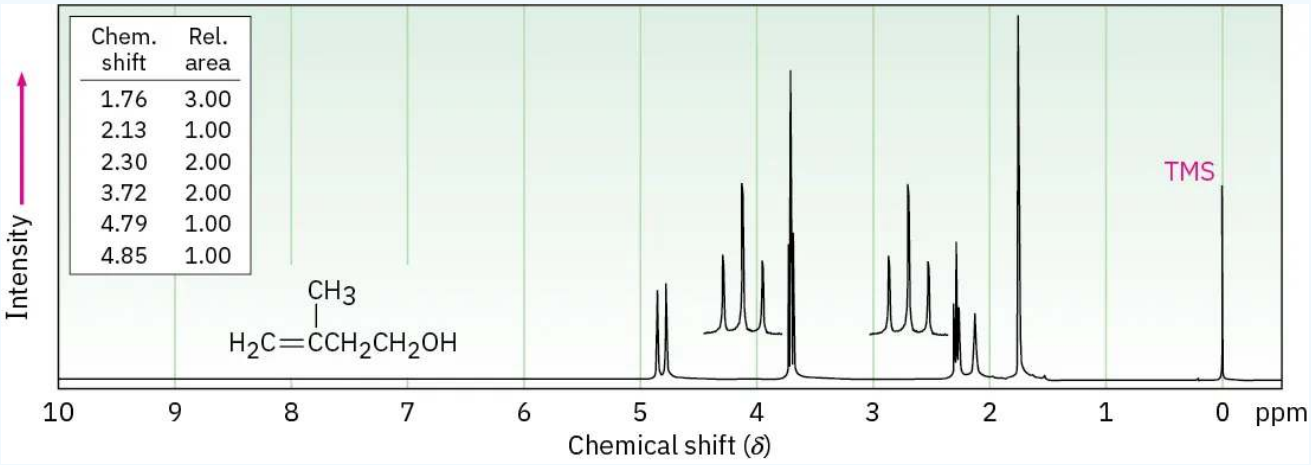
Propose a structure consistent with the following spectral data for a compound $C_8H_{18}O_2$:

IR: 3350 cm^{-1}

^1H NMR: 1.24 δ (12 H, singlet); 1.56 δ (4 H, singlet); 1.95 δ (2 H, singlet)

Exercise 6.17.54

The ^{1}H NMR spectrum shown is that of 3-methyl-3-buten-1-ol. Assign all the observed resonance peaks to specific protons, and account for the splitting patterns.



Exercise 6.17.55

A compound of unknown structure gave the following spectroscopic data:

Mass spectrum: $M^+ = 88.1$
IR: 3600 cm^{-1}
^{1}H NMR: 1.4 δ (2 H, quartet, J = 7 Hz); 1.2 δ (6 H, singlet); 1.0 δ (1 H, singlet); 0.9 δ (3 H, triplet, J = 7 Hz)
^{13}C NMR: 74, 35, 27, 25 δ

(a) Assuming that the compound contains C and H but may or may not contain O, give three possible molecular formulas.

(b) How many hydrogens does the compound contain?

(c) What functional group(s) does the compound contain?

(d) How many carbons does the compound contain?

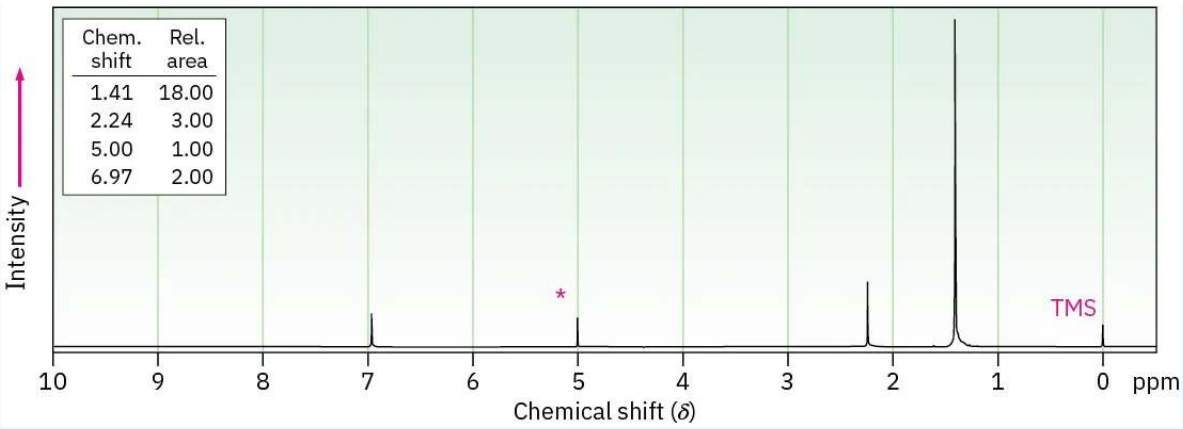
(e) What is the molecular formula of the compound?

(f) What is the structure of the compound?

(g) Assign peaks in the molecule's ^{1}H NMR spectrum corresponding to specific protons.

Exercise 6.17.56

Propose a structure for a compound $C_{15}H_{24}O$ that has the following ^{1}H NMR spectrum. The peak marked by an asterisk disappears when D_2O is added to the sample.



General Problems

? Exercise 6.17.57

How would you carry out the following transformations?

(a)

(b)

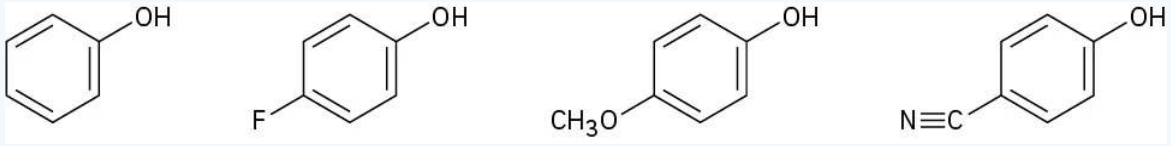
(c)

? Exercise 6.17.58

Benzoquinone is an excellent dienophile in the Diels–Alder reaction. What product would you expect from reaction of benzoquinone with 1 equivalent of 1,3-butadiene? From reaction with 2 equivalents of 1,3-butadiene?

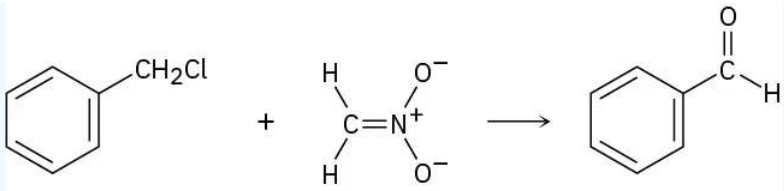
? Exercise 6.17.59

Rank the following substituted phenols in order of increasing acidity, and explain your answer:>



? Exercise 6.17.60

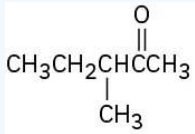
Benzyl chloride can be converted into benzaldehyde by treatment with nitromethane and base. The reaction involves initial conversion of nitromethane into its anion, followed by S_N2 reaction of the anion with benzyl chloride and subsequent E2 reaction. Write the mechanism in detail, using curved arrows to indicate the electron flow in each step.



Benzyl chloride **Nitromethane anion** **Benzaldehyde**

Exercise 6.17.61

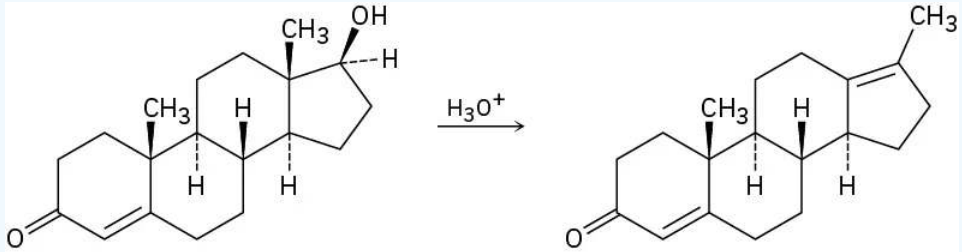
Reaction of (*S*)-3-methyl-2-pentanone with methylmagnesium bromide followed by acidification yields 2,3-dimethyl-2-pentanol. What is the stereochemistry of the product? Is the product optically active?



3-Methyl-2-pentanone

Exercise 6.17.62

Testosterone is one of the most important male steroid hormones. When testosterone is dehydrated by treatment with acid, rearrangement occurs to yield the product shown. Propose a mechanism to account for this reaction.

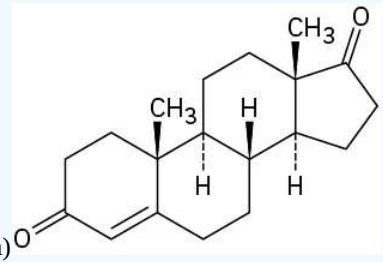


Testosterone

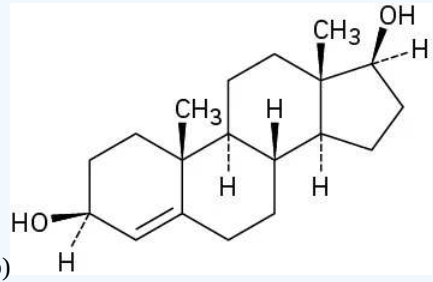
Exercise 6.17.63

Starting from testosterone (Problem 17-62), how would you prepare the following substances?

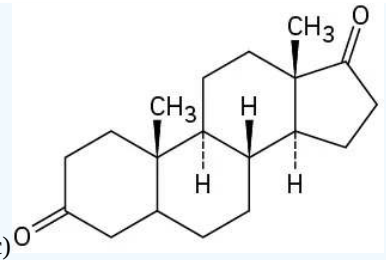
(a)



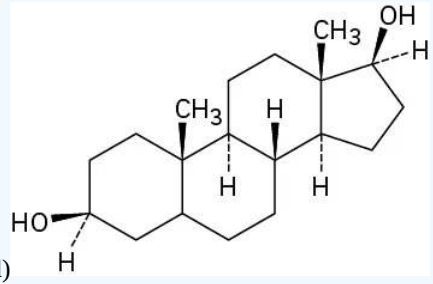
(b)



(c)

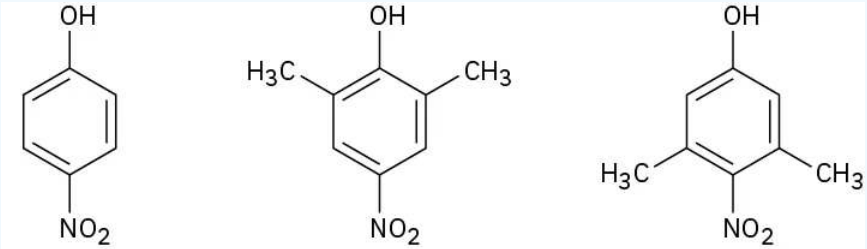


(d)



Exercise 6.17.64

p-Nitrophenol and 2,6-dimethyl-4-nitrophenol both have pK_a = 7.15, but 3,5-dimethyl-4-nitrophenol has pK_a = 8.25. Why is 3,5-dimethyl-4-nitrophenol so much less acidic?



Exercise 6.17.65

Compound **A**, $C_{10}H_{18}O$, undergoes reaction with dilute H_2SO_4 at 25 °C to yield a mixture of two alkenes, $C_{10}H_{16}$. The major alkene product, **B**, gives only cyclopentanone after ozone treatment followed by reduction with zinc in acetic acid. Write the reactions involved, and identify **A** and **B**.

Exercise 6.17.66

Compound **A**, $C_5H_{10}O$, is one of the basic building blocks of nature. All steroids and many other naturally occurring compounds are built from compound **A**. Spectroscopic analysis of **A** yields the following information:

IR: 3400 cm^{-1}; 1640 cm^{-1}

^{1}H NMR: 1.63 δ (3 H, singlet); 1.70 δ (3 H, singlet); 3.83 δ (1 H, broad singlet); 4.15 δ (2 H, doublet, J = 7 Hz); 5.70 δ (1 H, triplet, J = 7 Hz)

(a) How many double bonds and/or rings does **A** have?

(b) From the IR spectrum, what is the identity of the oxygen-containing functional group?

(c) What kinds of hydrogens are responsible for the NMR absorptions listed?

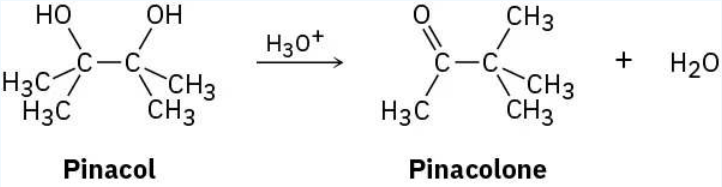
(d) Propose a structure for **A**.

Exercise 6.17.67

Dehydration of *trans*-2-methylcyclopentanol with $POCl_3$ in pyridine yields predominantly 3-methylcyclopentene. Is the stereochemistry of this dehydration syn or anti?

Exercise 6.17.68

2,3-Dimethyl-2,3-butanediol has the common name *pinacol*. On heating with aqueous acid, pinacol rearranges to *pinacolone*, 3,3-dimethyl-2-butanone. Suggest a mechanism for this reaction.



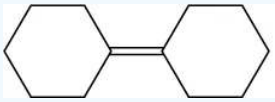
Pinacol **Pinacolone**

Exercise 6.17.69

As a rule, axial alcohols oxidize somewhat faster than equatorial alcohols. Which would you expect to oxidize faster, *cis*-4-*tert*-butylcyclohexanol or *trans*-4-*tert*-butylcyclohexanol? Draw the more stable chair conformation of each molecule.

Exercise 6.17.70

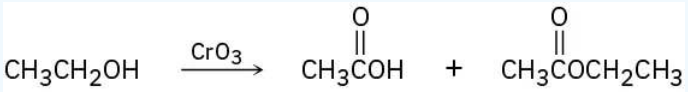
Propose a synthesis of bicyclohexylidene, starting from cyclohexanone as the only source of carbon.



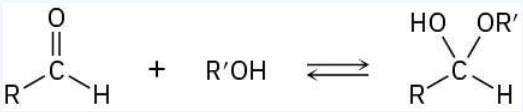
Bicyclohexylidene

Exercise 6.17.71

A problem often encountered in the oxidation of primary alcohols to carboxylic acids is that esters are sometimes produced as by-products. For example, oxidation of ethanol yields acetic acid and ethyl acetate:

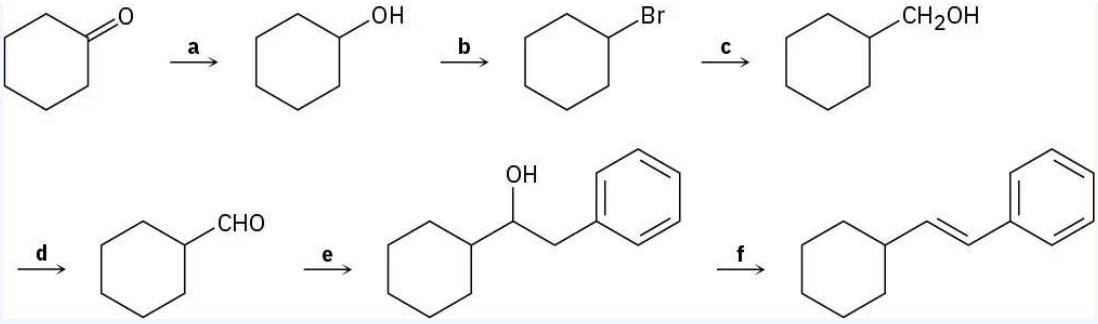


Propose a mechanism to account for the formation of ethyl acetate. Take into account the reversible reaction between aldehydes and alcohols:



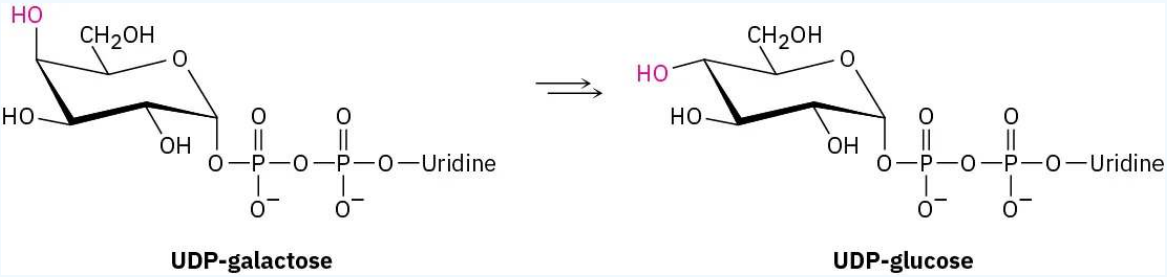
Exercise 6.17.72

Identify the reagents **a**–**f** in the following scheme:



Exercise 6.17.73

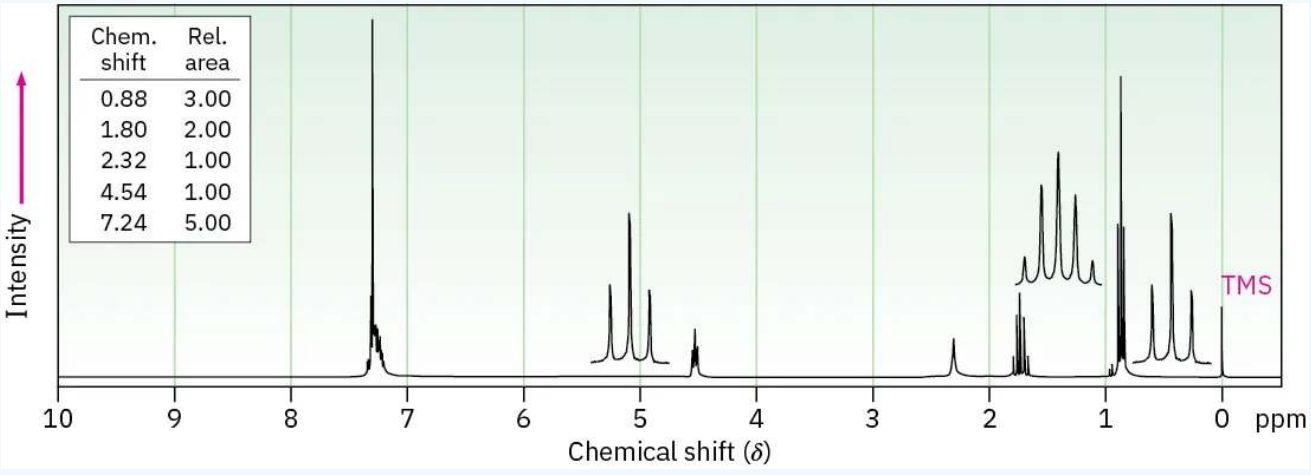
Galactose, a constituent of the disaccharide lactose found in dairy products, is metabolized by a pathway that includes the isomerization of UDP-galactose to UDP-glucose, where UDP = uridylyl diphosphate. The enzyme responsible for the transformation uses NAD^+ as cofactor. Propose a mechanism.



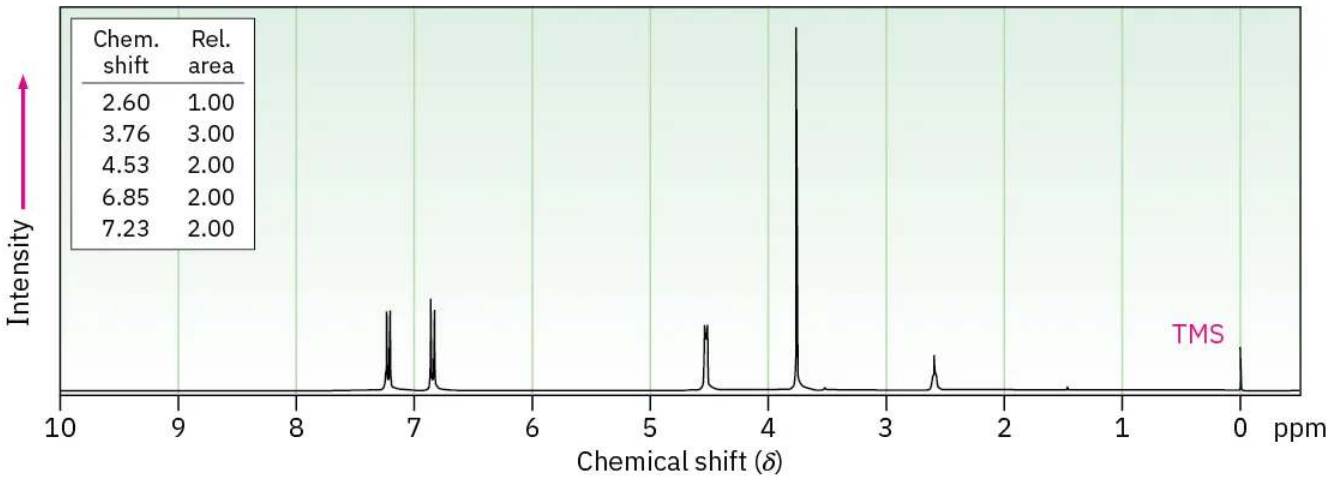
Exercise 6.17.74

Propose structures for alcohols that have the following <sup">1H NMR spectra:

(a) $C_9H_{12}O$

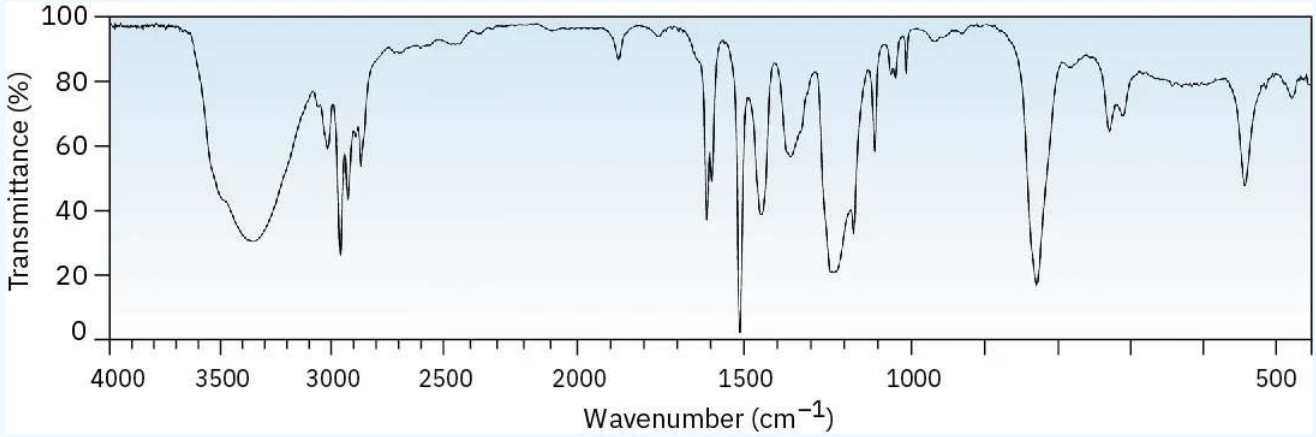


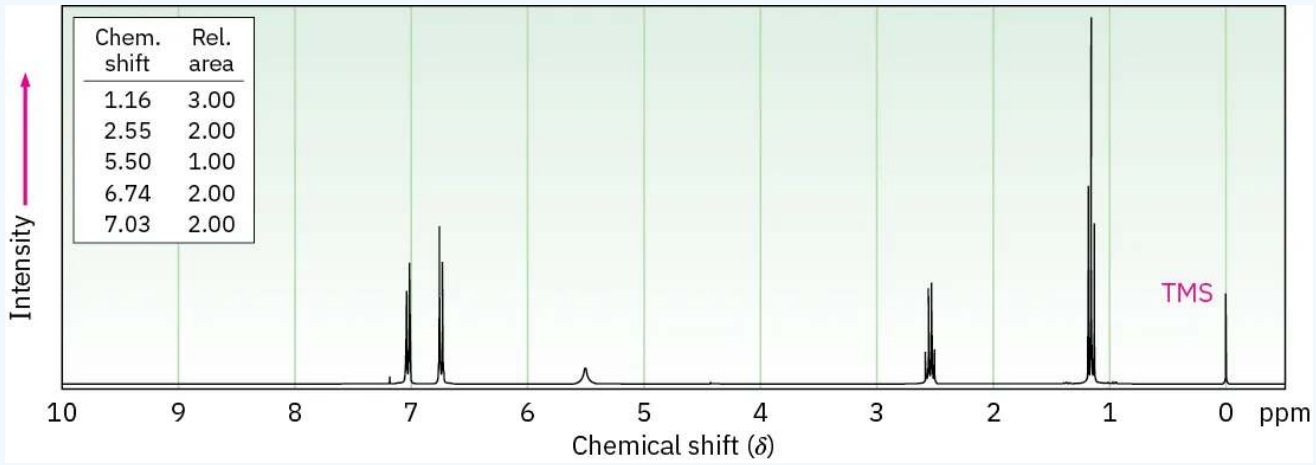
(b) $C_8H_{10}O_2$



Exercise 6.17.75

Compound **A**, $C_8H_{10}O$, has the IR and ^1H NMR spectra shown. Propose a structure consistent with the observed spectra, and label each peak in the NMR spectrum. Note that the absorption at 5.5 δ disappears when D_2O is added.





This page titled 6.17: Additional Problems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **17.16: Additional Problems** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

CHAPTER OVERVIEW

7: Ethers and Epoxides; Thiols and Sulfides

Learning Objectives

- fulfill all of the detailed objectives listed under each individual section.
- design a multi-step synthesis using one or more of the reactions introduced in this chapter, along with any number of the reactions you have studied to date.
- solve “road-map” problems that may require a knowledge of the chemistry of ethers, epoxides, thiols and sulfides, in addition to any of the material you have studied up to this point in organic chemistry.
- define, and use in context, the key terms introduced in this chapter.

We shall begin in a very traditional manner, with a discussion of the nomenclature of ethers. We will then describe how ethers may be prepared in the laboratory, and discuss the relative inertness of these compounds. A discussion of the chemistry of cyclic ethers follows, with particular emphasis on the preparation and reactions of epoxides (cyclic ethers containing a three-membered ring). We will then introduce crown ethers—compounds that consist of large rings containing several oxygen atoms and the spectroscopic properties of ethers. The unit will close with a description of the chemistry of thiols and sulfides, the sulfur-containing analogues of alcohols and ethers.

7.1: Why This Chapter?
7.2: Names and Properties of Ethers
7.3: Preparing Ethers
7.4: Reactions of Ethers - Acidic Cleavage
7.5: Cyclic Ethers - Epoxides
7.6: Reactions of Epoxides - Ring-opening
7.7: Crown Ethers
7.8: Thiols and Sulfides
7.9: Spectroscopy of Ethers
7.10: Chemistry Matters—Epoxy Resins and Adhesives
7.11: Key Terms
7.12: Summary
7.13: Summary of Reactions
7.14: Additional Problems
7.15: Preview of Carbonyl Chemistry

This page titled 7: Ethers and Epoxides; Thiols and Sulfides is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

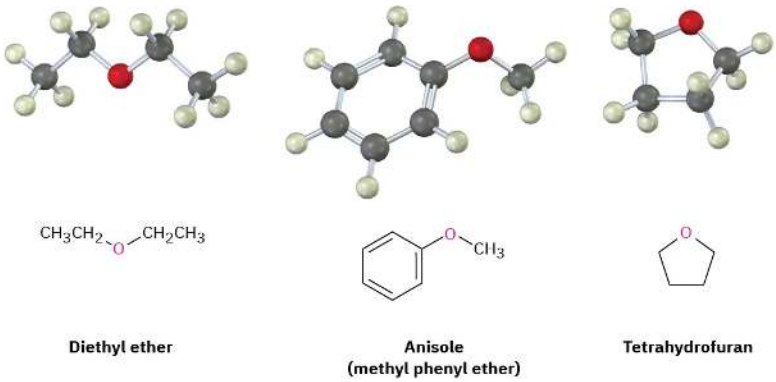
7.1: Why This Chapter?

This chapter finishes the coverage of functional groups with C–O and C–S single bonds that was begun in the chapter on Alcohols and Phenols. We'll focus primarily on ethers and take only a brief look at thiols and sulfides before going on to an extensive coverage of compounds with C=O double bonds in Chapters 19 through 23.

Figure 7.1.1: The appalling and unforgettable odor of skunks is due to a mixture of several simple thiols. (credit: modification of work "Striped Skunk" by Tom Friedel/Wikimedia Commons, CC BY 3.0)

Ethers (R–O–R′), like the alcohols we saw in the preceding chapter, are organic derivatives of water, but they have two organic groups bonded to the same oxygen atom rather than one. The organic groups might be alkyl, aryl, or vinylic, and the oxygen atom might be in an open chain or a ring.

Perhaps the most well-known ether is diethyl ether, which has a long history of medicinal use as an anesthetic and industrial use as a solvent. Other useful ethers include anisole, a pleasant-smelling aromatic ether used in perfumery, and tetrahydrofuran (THF), a cyclic ether often used as a solvent.



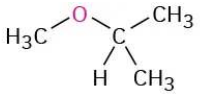
Thiols (R–S–H) and sulfides (R–S–R′) are sulfur analogs of alcohols and ethers, respectively. Both functional groups are found in various biomolecules, although not as commonly as their oxygen-containing relatives.

This page titled 7.1: Why This Chapter? is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

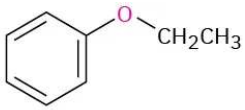
- **18.0: Why This Chapter?** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

7.2: Names and Properties of Ethers

Simple ethers with no other functional groups are named by identifying the two organic substituents and adding the word *ether*.

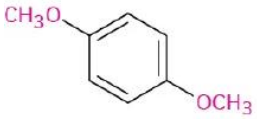


Isopropyl methyl ether

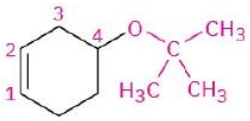


Ethyl phenyl ether

If other functional groups are present, the ether part is considered an *alkoxy* substituent. For example:



***p*-Dimethoxybenzene**

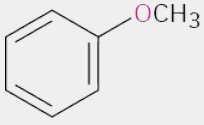
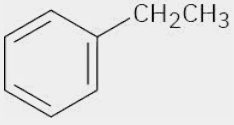


4-*tert*-Butoxy-1-cyclohexene

Like alcohols, ethers have nearly the same geometry as water. The R–O–R bonds have an approximately tetrahedral bond angle (112° in dimethyl ether), and the oxygen atom is sp^3-hybridized.

The electronegative oxygen atom gives ethers a slight dipole moment, and the boiling points of ethers are often slightly higher than the boiling points of comparable alkanes. Table 7.2.1 compares the boiling points of some common ethers and their corresponding hydrocarbons.

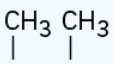
Table 7.2.1: Comparison of Boiling Points of Ethers and Hydrocarbons

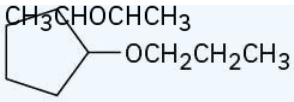
Ether	Boiling point °C	Hydrocarbon	Boiling point °C
CH_3OCH_3	–25	$CH_3CH_2CH_3$	–45
$CH_3CH_2OCH_2CH_3$	34.6	$CH_3CH_2CH_2CH_2CH_3$	36
	65		49
	158		136

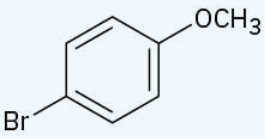
Ethers are relatively stable and unreactive in many respects, but some ethers react slowly with the oxygen in air to give *peroxides*, compounds that contain an O–O bond. The peroxides from low-molecular-weight ethers such as diisopropyl ether and tetrahydrofuran are explosive and extremely dangerous, even in small amounts. Ethers are very useful as solvents in the laboratory, but they must always be used cautiously and should not be stored for long periods of time.

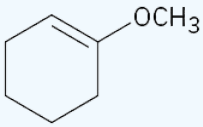
? Exercise 7.2.1

Name the following ethers:

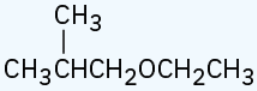


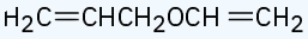
a. 

b. 

c. 

d.

e. 

f. 

Answer

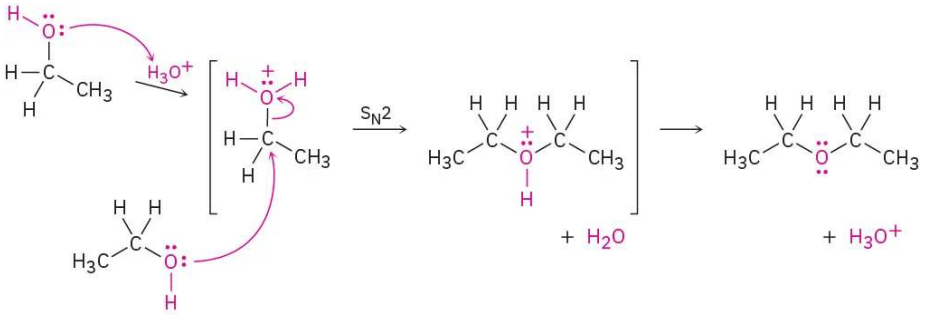
a. Diisopropyl ether
b. Cyclopentyl propyl ether
c. *p*-Bromoanisole or 4-bromo-1-methoxybenzene
d. 1-Methoxycyclohexene
e. Ethyl isobutyl ether
f. Allyl vinyl ether

This page titled 7.2: Names and Properties of Ethers is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **18.1: Names and Properties of Ethers** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

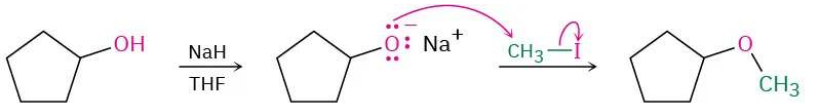
7.3: Preparing Ethers

Diethyl ether and other simple symmetrical ethers are prepared industrially by the sulfuric-acid-catalyzed reaction of alcohols. The reaction occurs by S_N2 displacement of water from a protonated ethanol molecule by the oxygen atom of a second ethanol. Unfortunately, this method is limited to use with primary alcohols because secondary and tertiary alcohols dehydrate by an E1 mechanism to yield alkenes (Section 17.6).



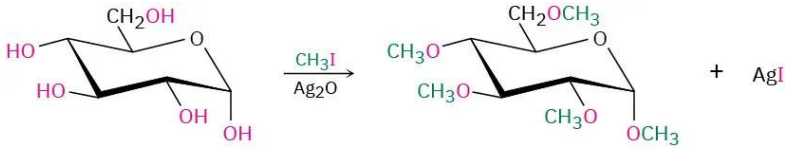
The Williamson Ether Synthesis

The most generally useful method of preparing ethers is the Williamson ether synthesis, in which an alkoxide ion reacts with a primary alkyl halide or tosylate in an S_N2 reaction. As we saw in Section 17.2, the alkoxide ion is normally prepared by reaction of an alcohol with a strong base such as sodium hydride, NaH.



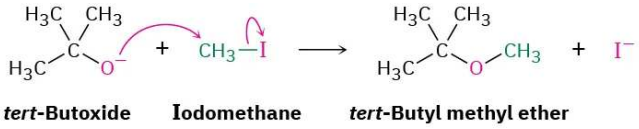
Cyclopentanol **Alkoxide ion** **Cyclopentyl methyl ether (74%)**

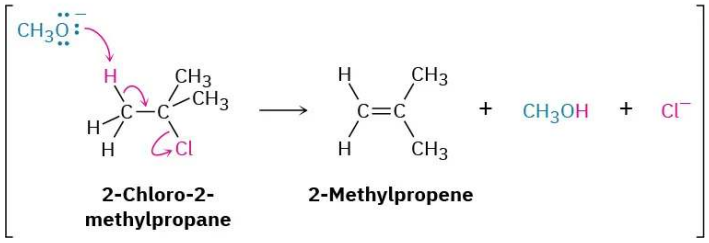
A useful variation of the Williamson synthesis involves silver oxide, Ag_2O, as a mild base rather than NaH. Under these conditions, the free alcohol reacts directly with the alkyl halide, so there is no need to preform the metal alkoxide intermediate. Sugars react particularly well; glucose, for example, reacts with excess iodomethane in the presence of Ag_2O to generate a pentaether in 85% yield.



α-D-Glucose **α-D-Glucose pentamethyl ether (85%)**

Because the Williamson synthesis is an S_N2 reaction, it is subject to all the usual constraints, as discussed in Section 11.3. Primary halides and tosylates work best because competitive E2 elimination can occur with more hindered substrates. Unsymmetrical ethers should therefore be synthesized by reaction between the more hindered alkoxide partner and less hindered halide partner rather than vice versa. For example, *tert*-butyl methyl ether, a substance used in the 1990s as an octane booster in gasoline, is best prepared by reaction of *tert*-butoxide ion with iodomethane rather than by reaction of methoxide ion with 2-chloro-2-methylpropane.





? Exercise 7.3.1

Why do you suppose only symmetrical ethers are prepared by the sulfuric-acid-catalyzed dehydration procedure? What product(s) would you expect if ethanol and 1-propanol were allowed to react together? In what ratio would the products be formed if the two alcohols were of equal reactivity?

Answer

A mixture of diethyl ether, dipropyl ether, and ethyl propyl ether is formed in a 1 : 1 : 2 ratio.

? Exercise 7.3.2

How would you prepare the following ethers using a Williamson synthesis?

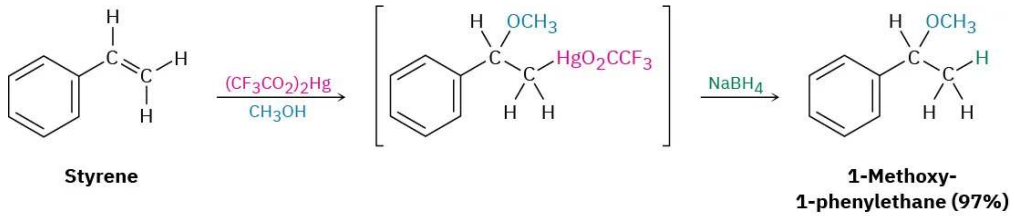
a. Methyl propyl ether
b. Anisole (methyl phenyl ether)
c. Benzyl isopropyl ether
d. Ethyl 2,2-dimethylpropyl ether

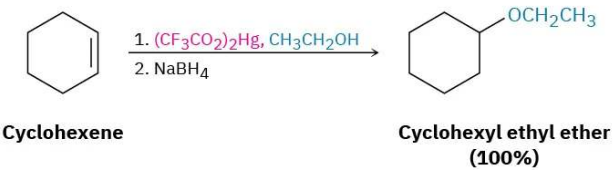
Answer

a. $CH_3CH_2CH_2O^- + CH_3Br$
b. $PhO^- + CH_3Br$
c. $(CH_3)_2CHO^- + PhCH_2Br$
d. $(CH_3)_3CCH_2O^- + CH_3CH_2Br$

Alkoxymercuration of Alkenes

We saw in Section 8.4 that alkenes react with water in the presence of mercuric acetate to yield a hydroxymercuration product. Subsequent treatment with $NaBH_4$ breaks the C–Hg bond and yields the alcohol. A similar alkoxymercuration reaction occurs when an alkene is treated with an alcohol in the presence of mercuric acetate or, even better, mercuric trifluoroacetate, $(CF_3CO_2)_2Hg$. Demercuration by reaction with $NaBH_4$ then yields an ether. The net result is Markovnikov addition of the alcohol to the alkene.





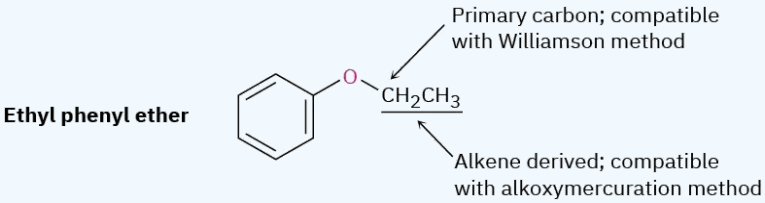
The mechanism of the alkoxymercuration reaction is similar to that described in Section 8.4 for hydroxymercuration. The reaction is initiated by electrophilic addition of Hg^{2+} to the alkene, followed by reaction of the intermediate cation with alcohol and reduction of the C–Hg bond by $NaBH_4$. A variety of alcohols and alkenes can be used in alkoxymercuration. Primary, secondary, and even tertiary alcohols react well, but ditertiary ethers can't be prepared because of steric hindrance.

Worked Example 7.3.1: Synthesizing an Ether

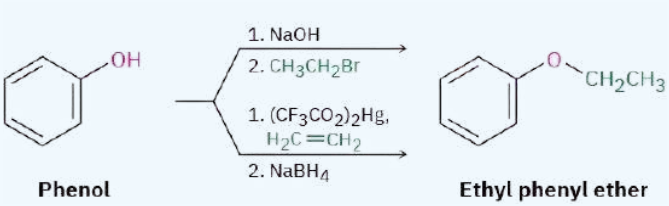
How would you prepare ethyl phenyl ether? Use whichever method you think is more appropriate, Williamson synthesis or the alkoxymercuration reaction.

Strategy

Draw the target ether, identify the two groups attached to oxygen, and recall the limitations of the two methods for preparing ethers. Williamson synthesis uses an S_N2 reaction and requires that one of the two groups attached to oxygen be either secondary or (preferably) primary. The alkoxymercuration reaction requires that one of the two groups come from an alkene precursor. Ethyl phenyl ether could be made by either method.



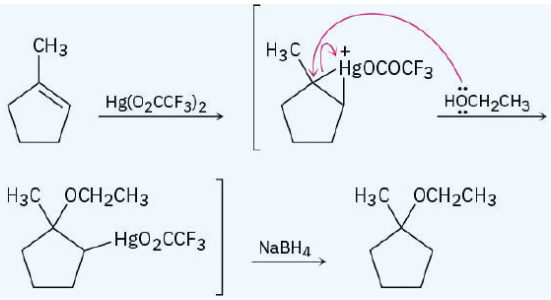
Solution



Exercise 7.3.3

Review the mechanism of oxymercuration shown in Figure in Chapter 8, and then write the mechanism of the alkoxymercuration reaction of 1-methylcyclopentene with ethanol. Use curved arrows to show the electron flow in each step.

Answer



? Exercise 7.3.4

How would you prepare the following ethers? Use whichever method you think is more appropriate, Williamson synthesis or the alkoxymercuration reaction.

a. Butyl cyclohexyl ether
b. Benzyl ethyl ether ($C_6H_5CH_2OCH_2CH_3$)
c. *sec*-Butyl *tert*-butyl ether
d. Tetrahydrofuran.

Answer

a. Either method
b. Williamson
c. Alkoxymercuration
d. Williamson

? Exercise 7.3.5

Rank the following halides in order of their reactivity in the Williamson synthesis:

a. Bromoethane, 2-bromopropane, bromobenzene
b. Chloroethane, bromoethane, 1-Iodopropene

Answer

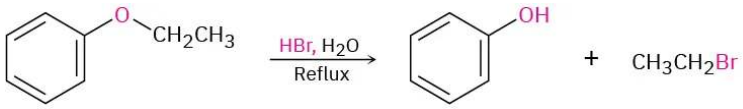
a. Bromoethane > 2-Bromopropane > Bromobenzene
b. Bromoethane > Chloroethane > 1-Iodopropene

This page titled 7.3: Preparing Ethers is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **18.2: Preparing Ethers** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

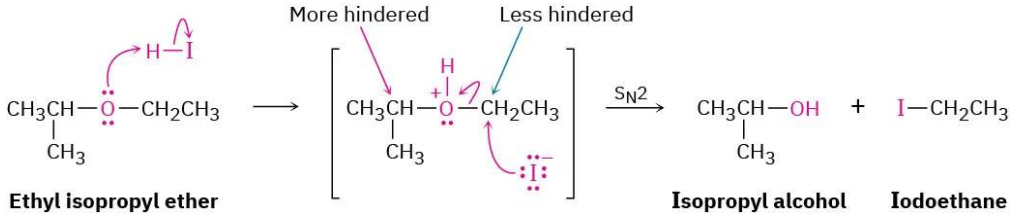
7.4: Reactions of Ethers - Acidic Cleavage

Ethers are unreactive to many reagents used in organic chemistry, a property that accounts for their wide use as reaction solvents. Halogens, dilute acids, bases, and nucleophiles have no effect on most ethers. In fact, ethers undergo only one truly general reaction —they are cleaved by strong acids. Aqueous HBr and HI both work well, but HCl does not cleave ethers.



Ethyl phenyl ether **Phenol** **Bromoethane**

Acidic ether cleavages are typical nucleophilic substitution reactions and take place by either S_N1 or S_N2 mechanisms, depending on the structure of the substrate. Ethers with only primary and secondary alkyl groups react by an S_N2 mechanism, in which I^- or Br^- reacts with the protonated ether at the less hindered site. This usually results in a selective cleavage into a single alcohol and a single alkyl halide. For example, ethyl isopropyl ether exclusively yields isopropyl alcohol and iodoethane on cleavage by HI because nucleophilic attack by iodide ion occurs at the less hindered primary site rather than at the more hindered secondary site.



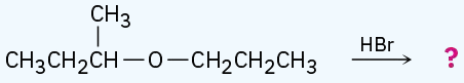
Ethyl isopropyl ether **Isopropyl alcohol** **Iodoethane**

Ethers with a tertiary, benzylic, or allylic group cleave by either an S_N1 or E1 mechanism because these substrates can produce stable intermediate carbocations. These reactions are often fast and take place at moderate temperatures. *tert*-Butyl ethers, for example, react by an E1 mechanism on treatment with trifluoroacetic acid at 0 °C. We'll see in **Section 26.7** that this reaction is often used in the laboratory synthesis of peptides.

***tert*-Butyl cyclohexyl ether** **Cyclohexanol (90%)** **2-Methylpropene**

Worked Example 7.4.1: Predicting the Product of an Ether Cleavage Reaction

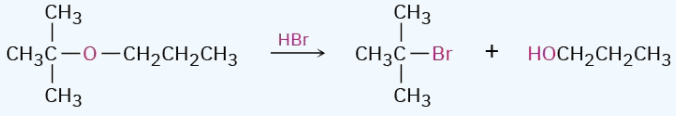
Predict the products of the following reaction:



Strategy

Identify the substitution pattern of the two groups attached to oxygen—in this case a tertiary alkyl group and a primary alkyl group. Then recall the guidelines for ether cleavages. An ether with only primary and secondary alkyl groups usually undergoes cleavage by S_N2 attack of a nucleophile on the less hindered alkyl group, but an ether with a tertiary alkyl group usually undergoes cleavage by an S_N1 mechanism. In this case, an S_N1 cleavage of the tertiary C–O bond will occur, giving 1-propanol and a tertiary alkyl bromide. In addition, a competitive E1 reaction leading to alkene might occur.

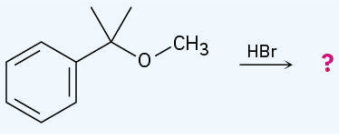
Solution

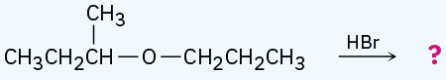


***tert*-Butyl propyl ether** **2-Bromo-2-methylpropane** **1-Propanol**

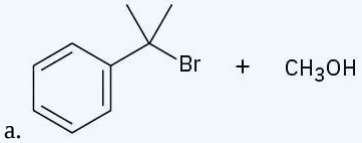
Exercise 7.4.1

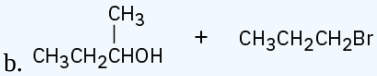
Predict the products of the following reactions:

a. 

b. 

Answer

a. 

b. 

Exercise 7.4.2

Write the mechanism of the acid-induced cleavage of *tert*-butyl cyclohexyl ether to yield cyclohexanol and 2-methylpropene.

Answer

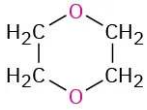
Protonation of the oxygen atom, followed by E1 reaction.

This page titled 7.4: Reactions of Ethers - Acidic Cleavage is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

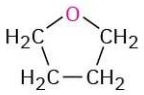
- **18.3: Reactions of Ethers - Acidic Cleavage** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

7.5: Cyclic Ethers - Epoxides

For the most part, cyclic ethers behave like acyclic ethers. The chemistry of the ether functional group is the same, whether it's in an open chain or in a ring. Common cyclic ethers such as tetrahydrofuran and dioxane are often used as solvents because of their inertness, yet they can be cleaved by strong acids.



1,4-Dioxane

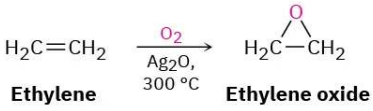


Tetrahydrofuran

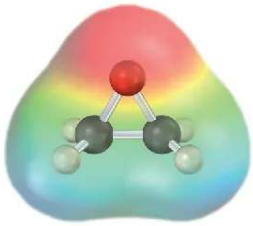
The one group of cyclic ethers that behaves differently from open-chain ethers are the three-membered-ring compounds called *epoxides*, or *oxiranes*, which we saw in Section 8.7. The strain of the three-membered ring gives epoxides unique chemical reactivity.

Ethylene oxide, the simplest epoxide, is an intermediate in the manufacture of both ethylene glycol, used for automobile antifreeze, and polyester polymers. Approximately 37 million tons of ethylene oxide is produced worldwide each year, most of it by air oxidation of ethylene over a silver oxide catalyst at 300 °C. This process is not useful for other epoxides, however, and is of little value in the laboratory.

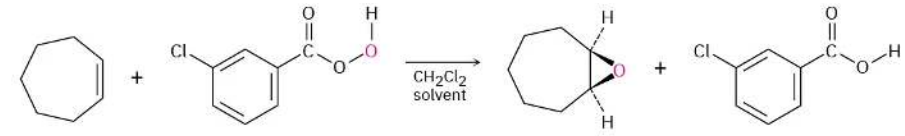
Note that the name *ethylene oxide* is not a systematic one because the *-ene* ending implies the presence of a double bond in the molecule. The name is frequently used, however, because ethylene oxide is derived *from* ethylene by addition of an oxygen atom. Other simple epoxides are named similarly. The systematic name for ethylene oxide is 1,2-epoxyethane.



Ethylene **Ethylene oxide**

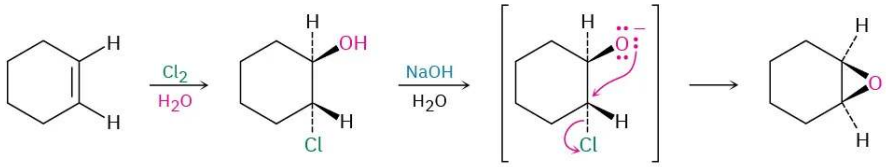


In the laboratory, as we saw in Section 8.7, epoxides are usually prepared by treatment of an alkene with a peroxyacid (RCO_3H), typically *m*-chloroperoxybenzoic acid.



Cycloheptene ***meta*-Chloroperoxy-benzoic acid** **1,2-Epoxy-cycloheptane** ***meta*-Chloro-benzoic acid**

Epoxides can also be prepared from halohydrins, themselves produced by electrophilic addition of Cl_2 or Br2 to an alkene in the presence of water (Section 8.3). When a halohydrin is treated with base, HX is eliminated and an epoxide is produced by an intramolecular Williamson ether synthesis. That is, the nucleophilic alkoxide ion and the electrophilic alkyl halide are in the same molecule.

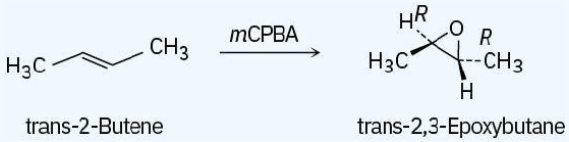


Cyclohexene ***trans*-2-Chloro-cyclohexanol** **1,2-Epoxy-cyclohexane**

Exercise 7.5.1

What product would you expect from reaction of *trans*-2-butene with *m*-chloroperoxybenzoic acid? Show the stereochemistry.

Answer



trans-2-Butene trans-2,3-Epoxybutane

Exercise 7.5.2

Reaction of *cis*-2-butene with *m*-chloroperoxybenzoic acid yields an epoxide different from that obtained by reaction of the trans isomer. Explain.

Answer

Epoxidation of *cis*-2-butene yields *cis*-2,3-epoxybutane, while epoxidation of *trans*-2-butene yields *trans*-2,3-epoxybutane.

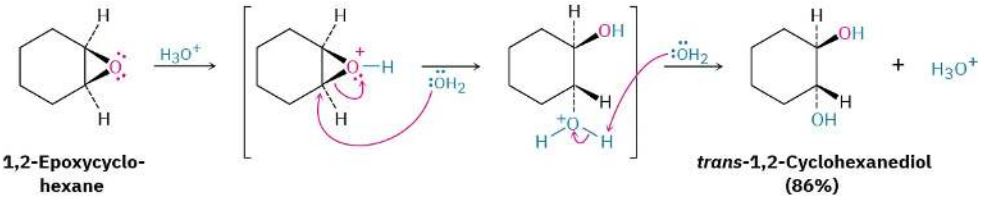
This page titled 7.5: Cyclic Ethers - Epoxides is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **18.4: Cyclic Ethers - Epoxides** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

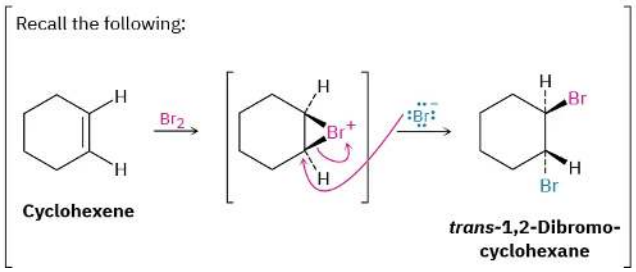
7.6: Reactions of Epoxides - Ring-opening

Acid-Catalyzed Epoxide Opening

Epoxides are cleaved by treatment with acid just as other ethers are, but under much milder conditions because of ring strain. As we saw in Section 8.7, dilute aqueous acid at room temperature is sufficient for facilitating the hydrolysis of epoxides to give 1,2-diols, also called *vicinal glycols.* (The word *vicinal* means "adjacent," and a *glycol* is a diol.) The epoxide cleavage takes place by S_N2-like backside attack of a nucleophile on the protonated epoxide, giving a trans-1,2-diol as product.

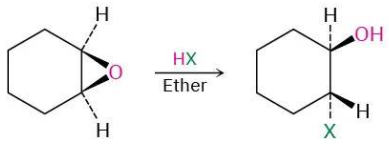


1,2-Epoxycyclohexane → ***trans*-1,2-Cyclohexanediol (86%)**



Cyclohexene → ***trans*-1,2-Dibromocyclohexane**

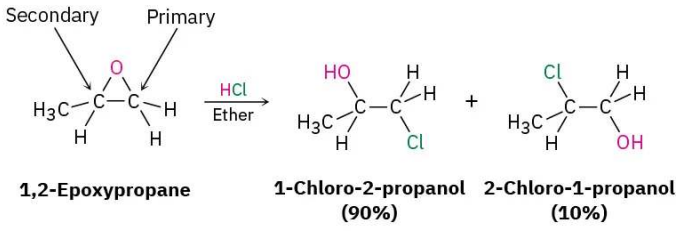
Epoxides can also be opened by reaction with acids other than H_3O^+. If anhydrous HX is used, for instance, an epoxide is converted into a trans halohydrin.



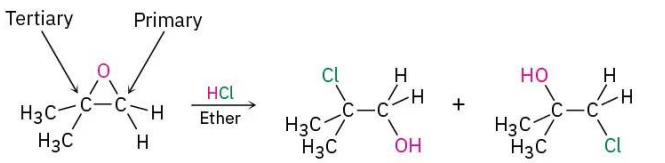
A trans 2-halocyclohexanol

where X = F, Br, Cl, or I

The regiochemistry of acid-catalyzed ring-opening depends on the epoxide's structure, and a mixture of products is often formed. When both epoxide carbon atoms are either primary or secondary, attack of the nucleophile occurs primarily at the less highly substituted site: an S_N2-like result. When one of the epoxide carbon atoms is tertiary, however, nucleophilic attack occurs primarily at the *more* highly substituted site—an S_N1-like result. Thus, 1,2-epoxypropane reacts with HCl to give primarily 1-chloro-2-propanol, but 2-methyl-1,2-epoxypropane gives 2-chloro-2-methyl-1- propanol as the major product.



1,2-Epoxypropane → **1-Chloro-2-propanol (90%)** + **2-Chloro-1-propanol (10%)**



2-Methyl-1,2-epoxypropane → **2-Chloro-2-methyl-1-propanol (60%)** + **1-Chloro-2-methyl-2-propanol (40%)**

The mechanisms of these acid-catalyzed epoxide openings are more complex than they initially appear. They seem to be neither purely S_N1 nor S_N2 but instead to be midway between the two extremes and to have characteristics of both. For instance, take the reaction of 1,2-epoxy-1-methylcyclohexane with HBr, shown in Figure 7.6.1. The reaction yields only a single stereoisomer of 2-bromo-2-methylcyclohexanol in which the –Br and –OH groups are trans, an S_N2-like result caused by backside displacement of the epoxide oxygen. But the fact that Br^- attacks the more hindered tertiary side of the epoxide rather than the less hindered secondary side is an S_N1-like result in which the more stable, tertiary carbocation is involved.

Evidently, the transition state for acid-catalyzed epoxide opening has an S_N2-like geometry but also has a high degree of S_N1-like carbocationic character. Because the positive charge in the protonated epoxide is shared by the more highly substituted carbon atom, backside attack of Br^- occurs at the more highly substituted site.

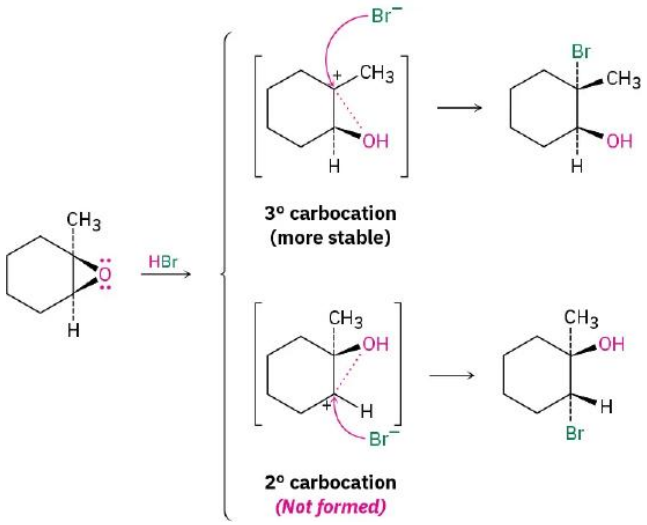
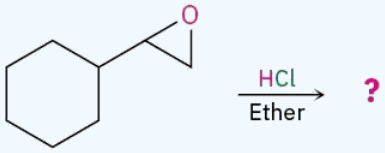


Figure 7.6.1: Ring-opening of 1,2-epoxy-1-methylcyclohexane with HBr. There is a high degree of S_N1-like carbocation character in the transition state, which leads to backside attack of the nucleophile at the tertiary center and to formation of a product isomer that has –Br and –OH groups trans.

✔ Worked Example 7.6.1: Predicting the Product of Epoxide Ring-Opening

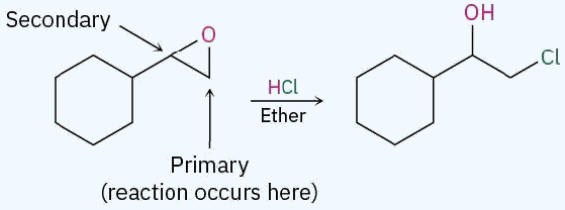
Predict the major product of the following reaction:



Strategy

Identify the substitution pattern of the two epoxide carbon atoms. In this case, one carbon is secondary and one is primary. Then recall the guidelines for epoxide cleavages. An epoxide with only primary and secondary carbons usually undergoes cleavage by S_N2-like attack of a nucleophile on the less hindered carbon, but an epoxide with a tertiary carbon atom usually undergoes cleavage by backside attack on the more hindered carbon. In this case, an S_N2 cleavage of the primary C–O epoxide bond will occur.

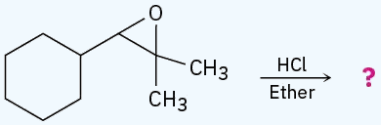
Solution

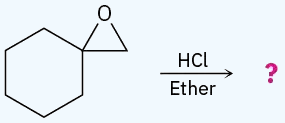


https://chem.libretexts.org/@go/page/564228

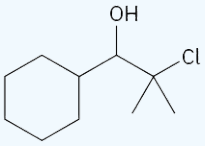
Exercise 7.6.1

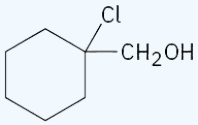
Predict the major product of each of the following reactions:

a. 

b. 

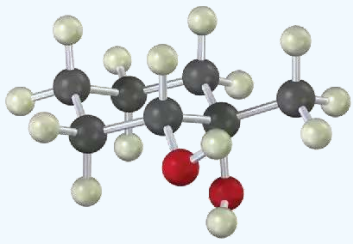
Answer

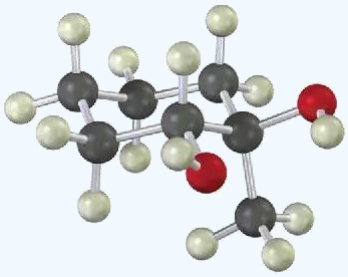
a. 

b. 

Exercise 7.6.2

How would you prepare the following diols?

a. 

b. 

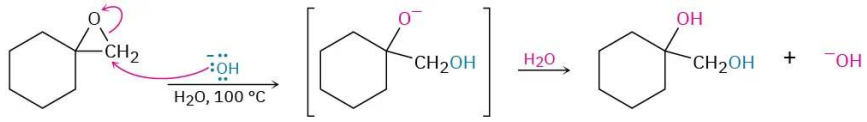
Answer

a. 1-Methylcyclohexene + OsO_4; then $NaHSO_3$

b. 1-Methylcyclohexene + *m*-chloroperoxybenzoic acid, then H_3O^+

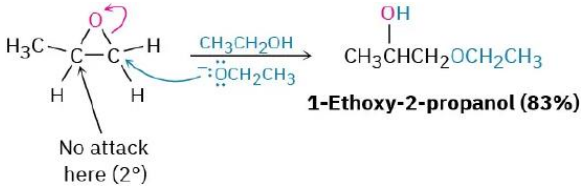
Base-Catalyzed Epoxide Opening

Unlike other ethers, epoxide rings can be cleaved by bases and nucleophiles as well as by acid. Although an ether oxygen is normally a poor leaving group in an S_N2 reaction (Section 11.3), the strain of the three-membered ring causes epoxides to react with hydroxide ion at elevated temperatures.



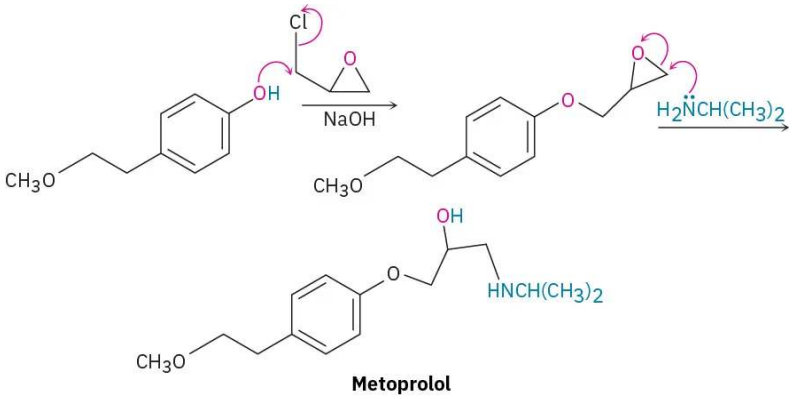
Methylenecyclohexane oxide **1-Hydroxymethyl-cyclohexanol (70%)**

Base-catalyzed epoxide opening is a typical S_N2 reaction in which attack of the nucleophile takes place at the less hindered epoxide carbon. For example, 1,2-epoxypropane reacts with ethoxide ion exclusively at the less highly substituted, primary carbon to give 1-ethoxy-2-propanol.



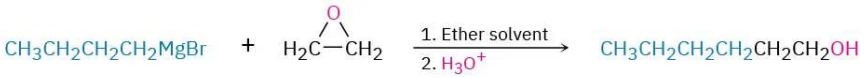
1-Ethoxy-2-propanol (83%)

Many different nucleophiles can be used for epoxide opening, including amines (RNH_2 or R_2NH) and Grignard reagents (RMgX). An example of an amine reacting with an epoxide occurs in the commercial synthesis of metoprolol, a so-called β-blocker that is used for treatment of cardiac arrhythmias, hypertension, and heart attacks. β-Blockers are among the most widely prescribed drugs in the world.



Metoprolol

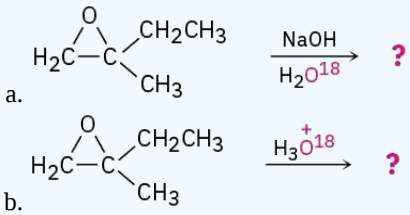
A similar nucleophilic ring-opening occurs when epoxides are treated with Grignard reagents. Ethylene oxide is frequently used, thereby allowing the conversion of a Grignard reagent into a primary alcohol having two more carbons than the starting alkyl halide. 1-Bromobutane, for example, is converted into 1-hexanol by reaction of its Grignard reagent with ethylene oxide.

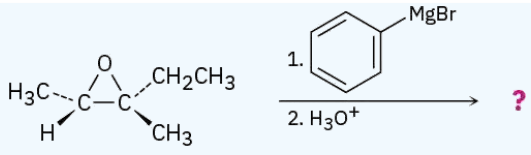


Butylmagnesium bromide **Ethylene oxide** **1-Hexanol (62%)**

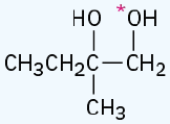
? Exercise 7.6.3

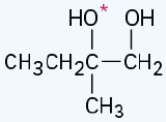
Predict the major product of the following reactions:

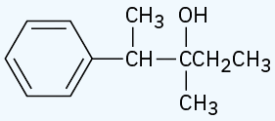


c. 

Answer

a. 

b. 

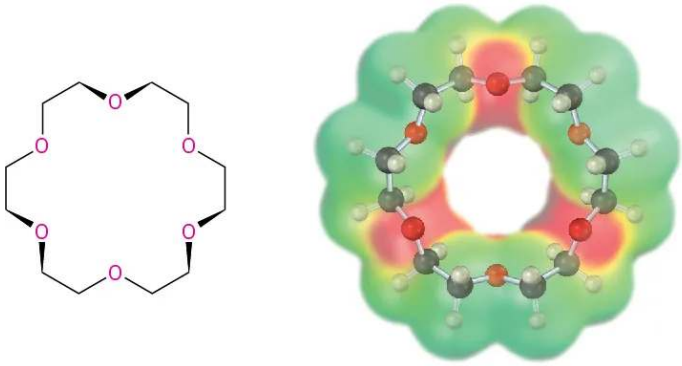
c. 

This page titled 7.6: Reactions of Epoxides - Ring-opening is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **18.5: Reactions of Epoxides - Ring-opening** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

7.7: Crown Ethers

Crown ethers, discovered in the early 1960s by Charles Pedersen at the DuPont Company, are a relatively recent addition to the ether family. They are named according to the general format *x*-crown-*y*, where *x* is the total number of atoms in the ring and *y* is the number of oxygen atoms. Thus, 18-crown-6 ether is an 18-membered ring containing 6 ether oxygen atoms. Note the size and negative (red) character of the crown ether cavity in the following electrostatic potential map.

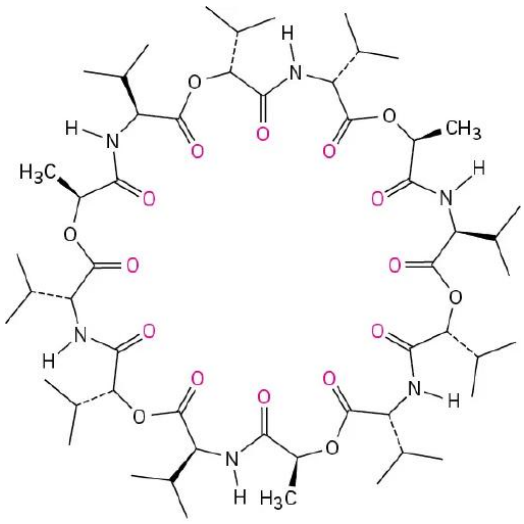


18-Crown-6 ether

The importance of crown ethers stems from their ability to sequester specific metal cations in the center of the polyether cavity. 18-Crown-6, for example, binds strongly with potassium ion. As a result, a solution of 18-crown-6 in a nonpolar organic solvent will dissolve many potassium salts. Potassium permanganate, $KMnO_4$, dissolves in toluene in the presence of 18-crown-6, for instance, and the resulting solution is a valuable reagent for oxidizing alkenes.

The effect of using a crown ether to dissolve an inorganic salt in a hydrocarbon or ether solvent is similar to the effect of dissolving the salt in a polar aprotic solvent such as DMSO, DMF, or HMPA (Section 11.3). In both cases, the metal cation is strongly solvated, leaving the anion bare. Thus, the S_N2 reactivity of an anion is tremendously enhanced in the presence of a crown ether.

Although crown ethers do not occur naturally, a group of compounds called **ionophores** have similar ion-binding properties. Produced by various microorganisms, ionophores are fat-soluble molecules that bind to specific ions and facilitate transport of the ions through biological membranes. The antibiotic valinomycin, for instance, binds specifically to K^+ ions with a ten-thousandfold selectivity over Na^+.

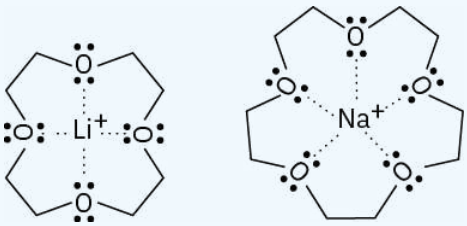


Valinomycin

Exercise 7.7.1

15-Crown-5 and 12-crown-4 ethers complex Na^+ and Li^+, respectively. Make models of these crown ethers, and compare the sizes of the cavities.

Answer



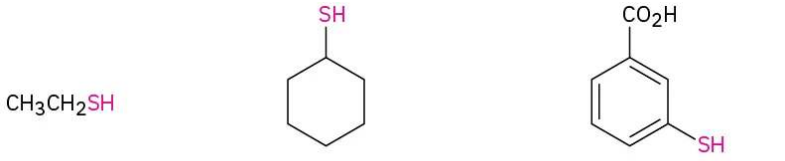
This page titled 7.7: Crown Ethers is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **18.6: Crown Ethers** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

7.8: Thiols and Sulfides

Thiols

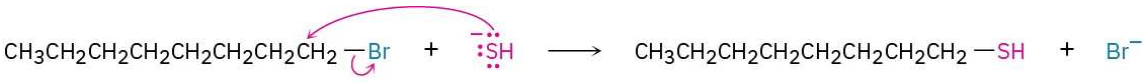
Thiols, also called **mercaptans**, are sulfur analogs of alcohols. They are named by the same system used for alcohols, with the suffix *-thiol* used in place of *-ol*. The –SH group itself is referred to as a mercapto group. Like alcohols, thiols are weakly acidic; the pK_a of CH_3SH, for instance, is 10.3. Unlike alcohols, however, thiols don't typically form hydrogen bonds because the sulfur atom is not sufficiently electronegative.



Ethanethiol **Cyclohexanethiol** ***m*-Mercaptobenzoic acid**

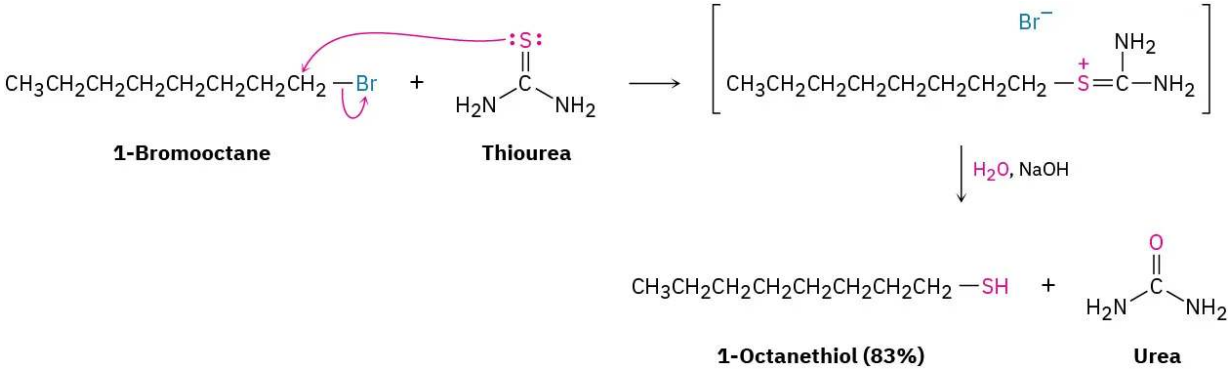
The most striking characteristic of thiols is their appalling odor. Skunk scent, for instance, is caused primarily by the simple thiols 3-methyl-1-butanethiol and 2-butene-1-thiol. Volatile thiols such as ethanethiol are also added to natural gas and liquefied propane to serve as an easily detectable warning in case of leaks.

Thiols are usually prepared from alkyl halides by S_N2 displacement with a sulfur nucleophile such as hydrosulfide anion, ^-SH.



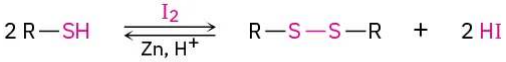
1-Bromooctane **1-Octanethiol (83%)**

The reaction often works poorly unless an excess of the nucleophile is used because the product thiol can undergo a second S_N2 reaction with alkyl halide to give a sulfide **(R–S–R′)** as by-product. To circumvent this problem, thiourea, $(NH_2)_2C{=}S$, is often used as the nucleophile in the preparation of a thiol from an alkyl halide. The reaction occurs by displacement of the halide ion to yield an intermediate alkyl isothiourea salt, which is hydrolyzed by subsequent reaction with aqueous base.



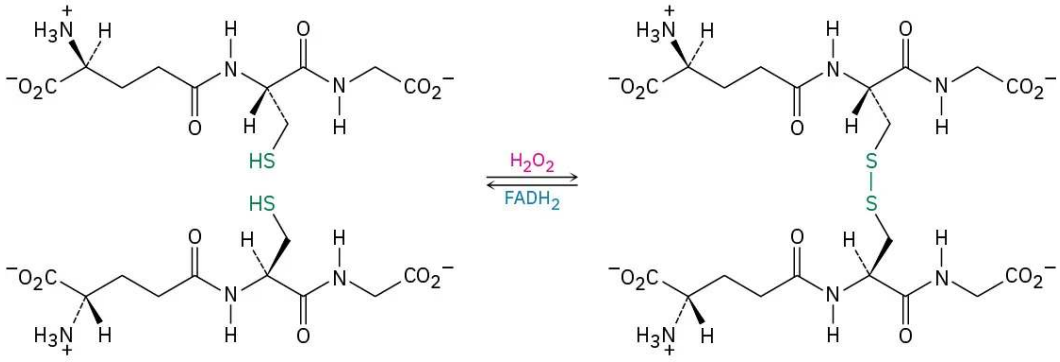
1-Bromooctane **Thiourea** **1-Octanethiol (83%)** **Urea**

Thiols can be oxidized by Br_2 or I_2 to yield disulfides (R–S–S–R′). The reaction is easily reversed, and a disulfide can be reduced back to a thiol by treatment with zinc and acid.



A thiol **A disulfide**

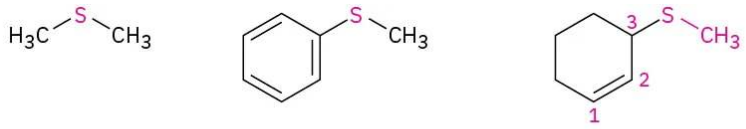
This thiol–disulfide interconversion is a key part of numerous biological processes. We'll see in Chapter 26, for instance, that disulfide formation is involved in defining the structure and three-dimensional conformations of proteins, where disulfide "bridges" often form cross-links between cysteine amino-acid units in the protein chains. Disulfide formation is also involved in the process by which cells protect themselves from oxidative degradation. A cellular component called **glutathione** removes potentially harmful oxidants and is itself oxidized to glutathione disulfide in the process. Reduction back to the thiol requires the coenzyme reduced flavin adenine dinucleotide, abbreviated $FADH_2$.



Glutathione (GSH) **Glutathione disulfide (GSSG)**

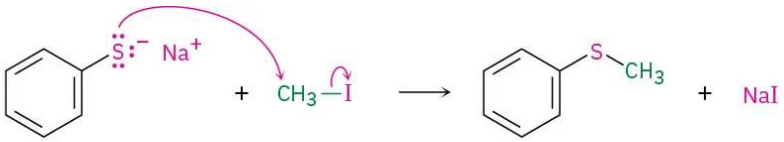
Sulfides

Sulfides are the sulfur analogs of ethers just as thiols are the sulfur analogs of alcohols. Sulfides are named by following the same rules used for ethers, with *sulfide* used in place of *ether* for simple compounds and *alkylthio* used in place of *alkoxy* for more complex substances.



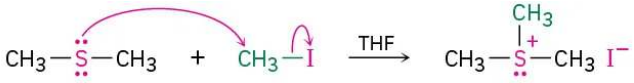
Dimethyl sulfide **Methyl phenyl sulfide** **3-(Methylthio)cyclohexene**

Treatment of a thiol with a base, such as NaH, gives the corresponding thiolate ion (RS^-), which undergoes reaction with a primary or secondary alkyl halide to give a sulfide. The reaction occurs by an S_N2 mechanism, analogous to the Williamson synthesis of ethers (Section 18.2).



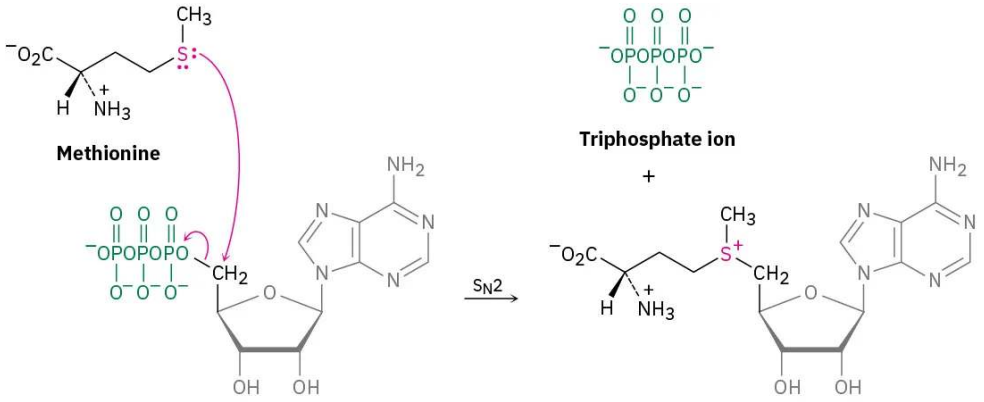
Sodium benzenethiolate **Methyl phenyl sulfide (96%)**

Despite their close structural similarity, sulfides and ethers differ substantially in their chemistry. Because the valence electrons on sulfur are farther from the nucleus and are less tightly held than those on oxygen (3*p* electrons versus 2*p* electrons), sulfur compounds are more nucleophilic than their oxygen analogs. Unlike dialkyl ethers, dialkyl sulfides react rapidly with primary alkyl halides by an S_N2 mechanism to give sulfonium ions (R_3S^+).



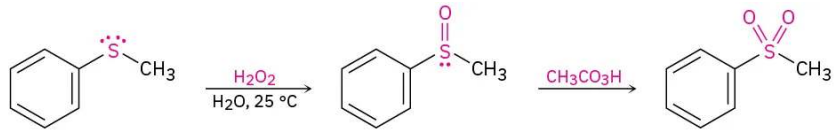
Dimethyl sulfide **Iodomethane** **Trimethylsulfonium iodide**

The most common example of this process in living organisms is the reaction of the amino acid methionine with adenosine triphosphate (ATP; Section 6.8) to give *S*-adenosylmethionine. The reaction is somewhat unusual in that the biological leaving group in this S_N2 process is the *triphosphate* ion rather than the more frequently seen diphosphate ion (Section 11.6).

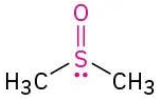


Sulfonium ions are themselves useful alkylating agents because a nucleophile can attack one of the groups bonded to the positively charged sulfur, displacing a neutral sulfide as leaving group. We saw an example of this in Section 11.6, in which *S*-adenosylmethionine transferred a methyl group to norepinephrine to give adrenaline.

Another difference between sulfides and ethers is that sulfides are easily oxidized. Treatment of a sulfide with hydrogen peroxide, H_2O_2, at room temperature yields the corresponding sulfoxide (R_2SO), and further oxidation of the sulfoxide with a peroxyacid yields a sulfone (R_2SO_2).



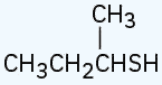
Dimethyl sulfoxide (DMSO) is a particularly well-known sulfoxide that is often used as a polar aprotic solvent. It must be handled with care, however, because it has a remarkable ability to penetrate the skin, carrying along whatever is dissolved in it.

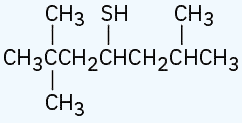


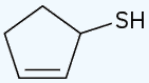
Dimethyl sulfoxide
(a polar aprotic solvent)

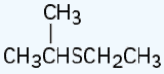
? Exercise 7.8.1

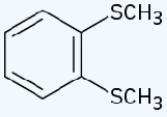
Name the following compounds:

a. 

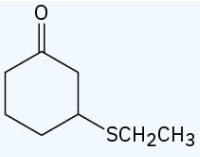
b. 

c. 

d. 

e. 

https://chem.libretexts.org/@go/page/564230

f. 

Answer

a. 2-Butanethiol
b. 2,2,6-Trimethyl-4-heptanethiol
c. 2-Cyclopentene-1-thiol
d. Ethyl isopropyl sulfide
e. o-Di(methylthio)benzene
f. 3-(Ethylthio)cyclohexanone

Exercise 7.8.2

2-Butene-1-thiol is one component of skunk spray.

a. How would you synthesize this substance (either cis or trans) from methyl 2-butenoate?
b. From 1,3-butadiene?

Methyl 2-butenoate **2-Butene-1-thiol**

Answer

(a) 1. $LiAlH_4$; 2. PBr_3; 3. (H2N)2C=S; 4. H_2O, NaOH

(b) 1. HBr; 2. (H2N)2C=S; 3. H_2O, NaOH

This page titled 7.8: Thiols and Sulfides is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **18.7: Thiols and Sulfides** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

7.9: Spectroscopy of Ethers

Infrared Spectroscopy

Ethers are difficult to identify by IR spectroscopy. Although they show an absorption due to C–O single-bond stretching in the range 1050 to 1150 cm^{-1}, many other kinds of absorptions occur in the same range. Figure 7.9.1 shows the IR spectrum of diethyl ether and identifies the C–O stretch. Phenyl alkyl ethers show two strong absorbances for C–O stretching at 1050 and 1250 cm^{-1}. Figure 7.9.2 shows the IR spectrum of anisole.

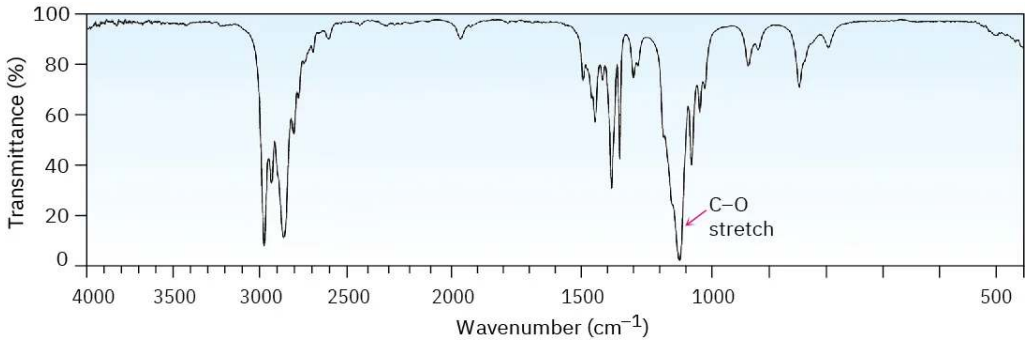


Figure 7.9.1: The infrared spectrum of diethyl ether, $CH_3CH_2OCH_2CH_3$.

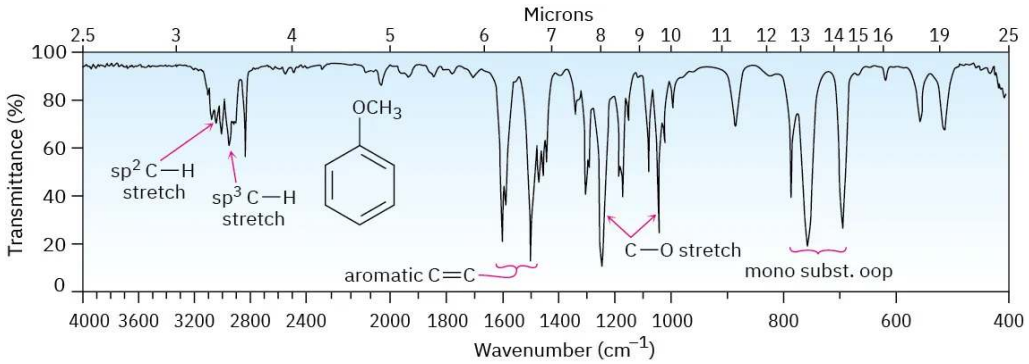


Figure 7.9.2: The infrared spectrum of anisole.

Nuclear Magnetic Resonance Spectroscopy

Hydrogens on carbon next to an ether oxygen are shifted downfield from the normal alkane resonance and show ^1H NMR absorptions in the region 3.4 to 4.5 δ. This downfield shift is clearly seen in the spectrum of dipropyl ether shown in Figure 7.9.3.

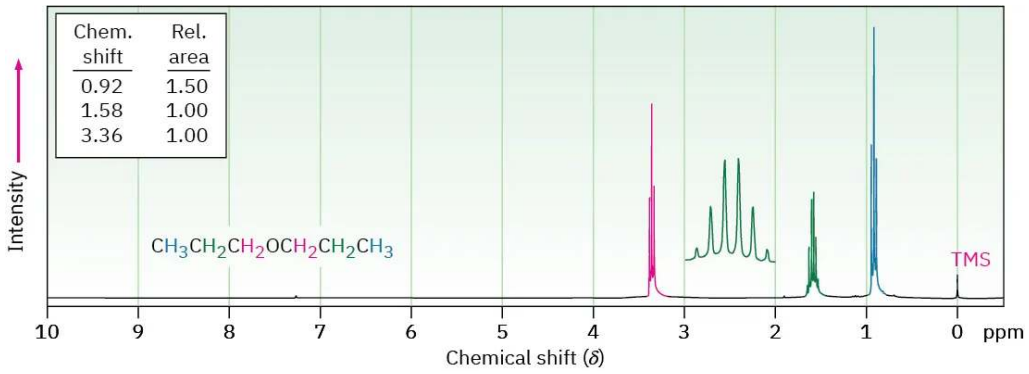


Figure 7.9.3: The ^1H NMR spectrum of dipropyl ether. Protons on carbon next to oxygen are shifted downfield to 3.4 δ.

Epoxides absorb at a slightly higher field than other ethers and show characteristic resonances at 2.5 to 3.5 δ in their ^1H NMR spectra, as indicated for 1,2-epoxypropane in Figure 7.9.4. The methylene protons of this epoxide are diastereotopic, and display complex splitting (see Section 13.7 and Section 13.8).

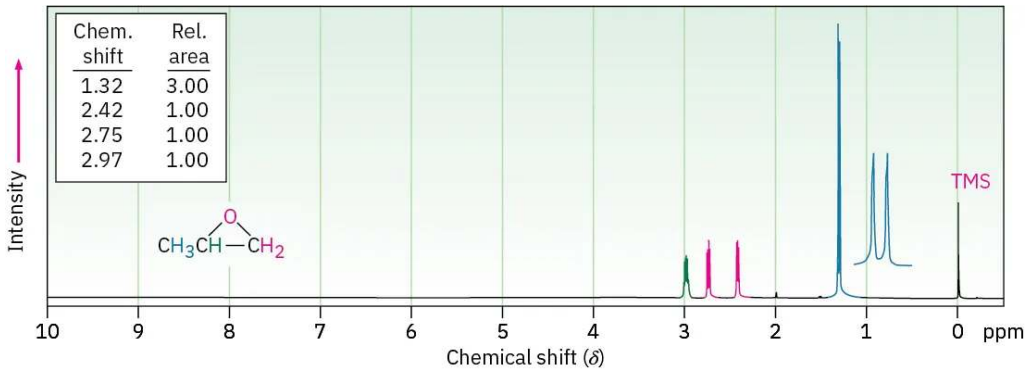
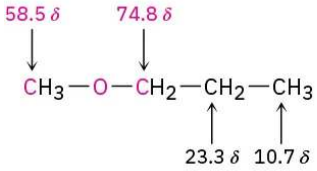
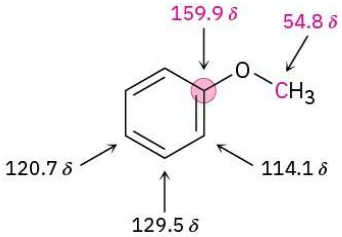


Figure 7.9.4: The ^{1}H NMR spectrum of 1,2-epoxypropane.

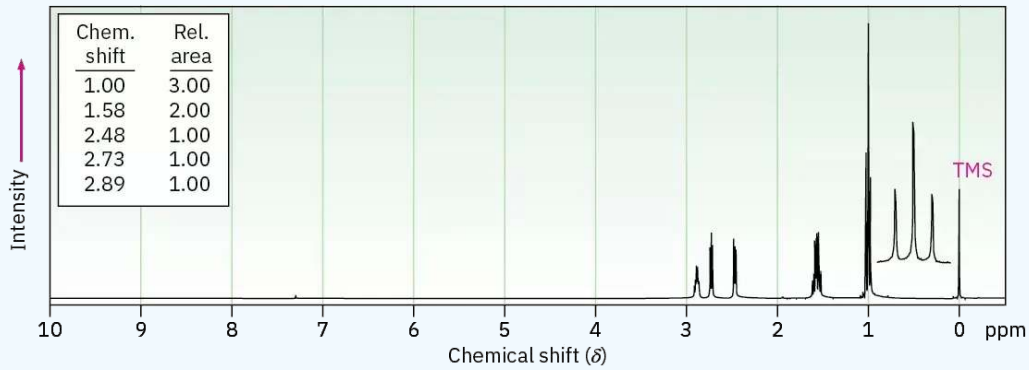
Ether carbon atoms also exhibit a downfield shift in the ^{13}C NMR spectrum, where they usually absorb in the 50 to 80 δ range. For example, the carbon atoms next to oxygen in methyl propyl ether absorb at 58.5 and 74.8 δ. Similarly, the methyl carbon in anisole absorbs at 54.8 δ.





Exercise 7.9.1

The ^{1}H NMR spectrum shown is that of a cyclic ether with the formula C_4H_8O. Propose a structure.



Answer

1,2-Epoxybutane

This page titled 7.9: Spectroscopy of Ethers is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **18.8: Spectroscopy of Ethers** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

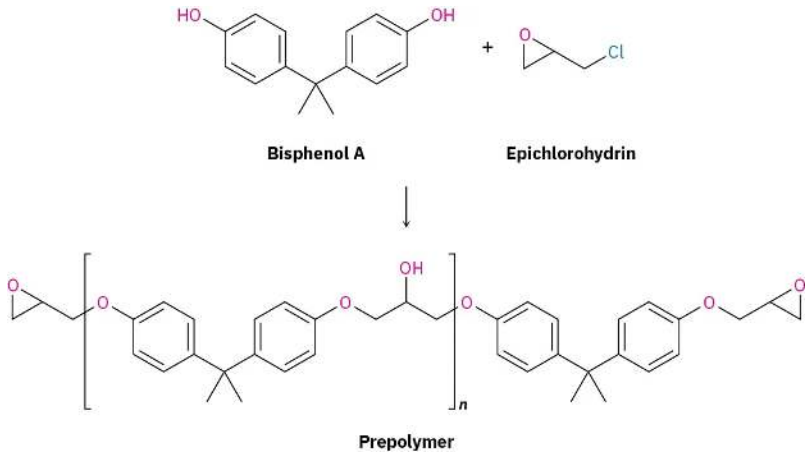
7.10: Chemistry Matters—Epoxy Resins and Adhesives

Few nonchemists know exactly what an epoxide is, but practically everyone has used an “epoxy glue” for household repairs or an epoxy resin for a protective coating. Worldwide, approximately 14 billion dollars’ worth of epoxy resins and adhesives are used annually for a vast number of applications, including many in the aerospace industry. Much of the Boeing 787 Dreamliner, for instance, is held together with epoxy-based adhesives.

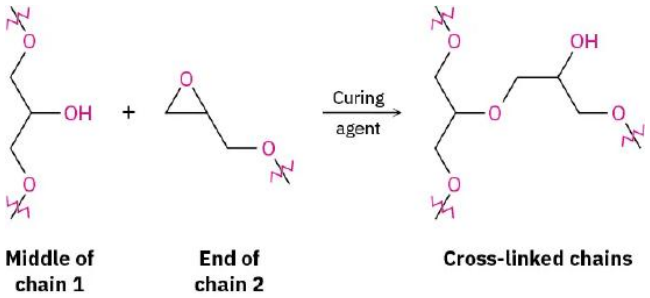
Epoxy resins and adhesives generally consist of two components that are mixed just prior to use. One component is a liquid “prepolymer,” and the second is a “curing agent” that reacts with the prepolymer and causes it to solidify.

Figure 7.10.1 Kayaks are often made of a high-strength polymer coated with epoxy resin. (credit: “Potomac River Festival Virginia 2017 Great Falls Kayak Race” by Watts/Flickr, CC BY 2.0)

The most widely used epoxy resins and adhesives are based on a prepolymer made from bisphenol A and epichlorohydrin. On treatment with base, bisphenol A is converted into its anion, which acts as a nucleophile in an S_N2 reaction with epichlorohydrin. Each epichlorohydrin molecule can react with two molecules of bisphenol A, once by S_N2 displacement of chloride ion and once by nucleophilic opening of the epoxide ring. At the same time, each bisphenol A molecule can react with two epichlorohydrins, leading to a long polymer chain. Each end of a prepolymer chain has an unreacted epoxy group, and each chain has numerous secondary alcohol groups spaced regularly along its midsection.



When an epoxide is to be used, a basic curing agent such as a tertiary amine, R_3N, is added to cause the individual prepolymer chains to link together. This cross-linking of chains is simply a base-catalyzed, S_N2 epoxide ring-opening of an –OH group in the middle of one chain with an epoxide group on the end of another chain. The result of such cross-linking is formation of a vast, three-dimensional tangle that has enormous strength and chemical resistance.



This page titled 7.10: Chemistry Matters—Epoxy Resins and Adhesives is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **18.9: Chemistry Matters—Epoxy Resins and Adhesives** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

7.11: Key Terms

- alkoxymercuration
- crown ether
- disulfide (R–S–S–R′)
- ether (R–O–R′)
- mercapto group
- sulfide (R–S–R′)
- sulfone
- sulfonium ion
- sulfoxide
- thiol
- thiolate ion (RS^-)
- Williamson ether synthesis

This page titled 7.11: Key Terms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **18.10: Key Terms** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

7.12: Summary

This chapter has finished the coverage of functional groups with C–O and C–S single bonds, focusing primarily on ethers, epoxides, thiols, and sulfides. **Ethers** are compounds that have two organic groups bonded to the same oxygen atom, ROR′. The organic groups can be alkyl, vinylic, or aryl, and the oxygen atom can be in a ring or in an open chain. Ethers are prepared by either Williamson ether synthesis, which involves S_N2 reaction of an alkoxide ion with a primary alkyl halide, or the **alkoxymercuration** reaction, which involves Markovnikov addition of an alcohol to an alkene.

Ethers are inert to most reagents but react with strong acids to give cleavage products. Both HI and HBr are often used. The cleavage reaction takes place by an S_N2 mechanism at the less highly substituted site if only primary and secondary alkyl groups are bonded to the ether oxygen, but by an S_N1 or E1 mechanism if one of the alkyl groups bonded to oxygen is tertiary.

Epoxides are cyclic ethers with a three-membered, oxygen-containing ring. Because of the strain in the ring, epoxides undergo a cleavage reaction with both acids and bases. Acid-catalyzed ring-opening occurs with a regiochemistry that depends on the structure of the epoxide. Cleavage of the C–O bond at the less highly substituted site occurs if both epoxide carbons are primary or secondary, but cleavage of the C–O bond to the more highly substituted site occurs if one of the epoxide carbons is tertiary. Base-catalyzed epoxide ring-opening occurs by S_N2 reaction of a nucleophile at the less hindered epoxide carbon.

Thiols, the sulfur analogs of alcohols, are usually prepared by S_N2 reaction of an alkyl halide with thiourea. Mild oxidation of a thiol yields a **disulfide**, and mild reduction of a disulfide returns the thiol. **Sulfides**, the sulfur analogs of ethers, are prepared by an S_N2 reaction between a thiolate anion and a primary or secondary alkyl halide. Sulfides are more nucleophilic than ethers and can be alkylated by reaction with a primary alkyl halide to yield a **sulfonium ion**. Sulfides can also be oxidized to **sulfoxides** and to **sulfones**.

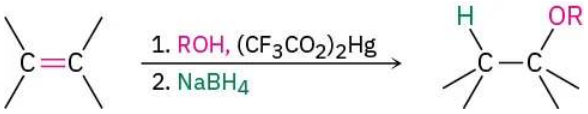
This page titled 7.12: Summary is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **18.11: Summary** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

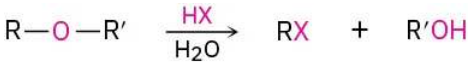
7.13: Summary of Reactions

1. Synthesis of ethers (Section 18.2)
   a. Williamson ether synthesis

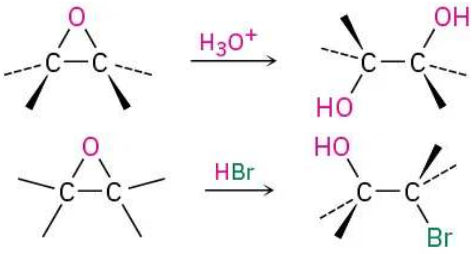
- Alkoxymercuration/demercuration



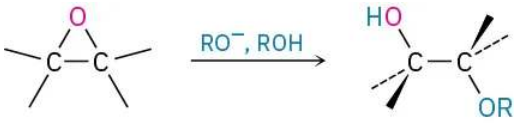
- Reactions of ethers
   a. Cleavage by HBr or HI (Section 18.3)

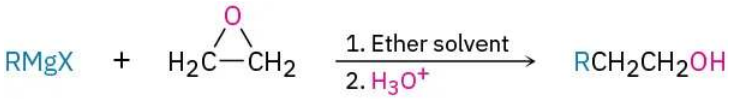


- Acid-catalyzed epoxide opening (Section 18.5)

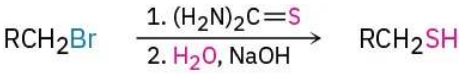


- Base-catalyzed epoxide opening (Section 18.5)

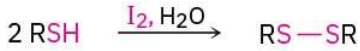




- Synthesis of thiols (Section 18.7)

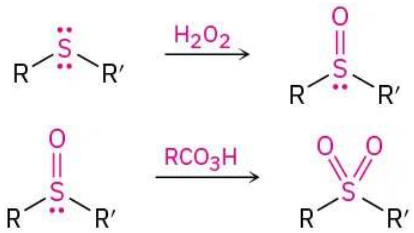


- Oxidation of thiols to disulfides (Section 18.7)



- Synthesis of sulfides (Section 18.7)

- Oxidation of sulfides to sulfoxides and sulfones (Section 18.7)



This page titled 7.13: Summary of Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

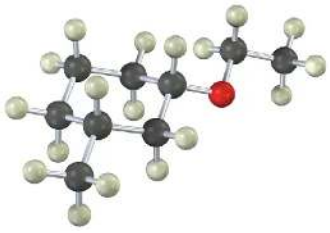
- **18.12: Summary of Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

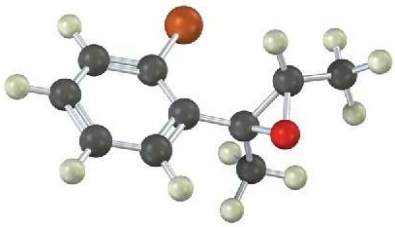
7.14: Additional Problems

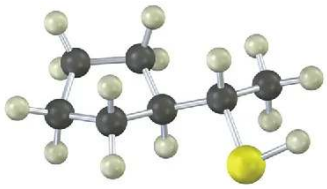
18 • Additional Problems

Visualizing Chemistry

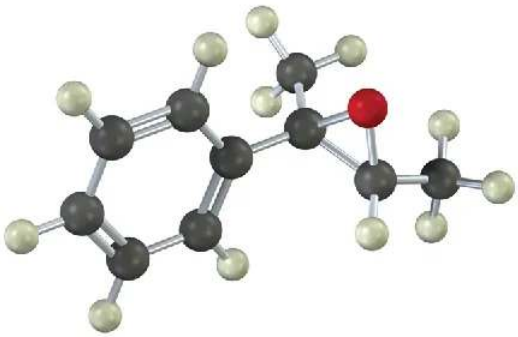
PROBLEM 18-19 Give IUPAC names for the following compounds (red = O; reddish brown = Br; yellow = S):

(a) 

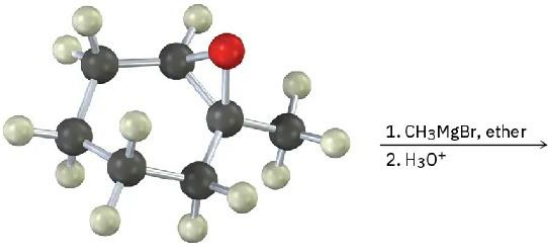
(b) 

(c) 

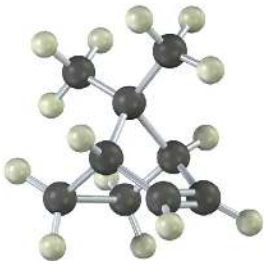
PROBLEM 18-20 Show the product, including stereochemistry, that would result from reaction of the following epoxide with HBr:



PROBLEM 18-21 Show the product, including stereochemistry, of the following reaction:

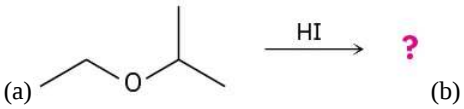


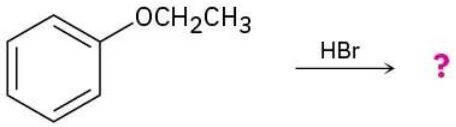
PROBLEM 18-22 Treatment of the following alkene with a peroxyacid yields an epoxide different from that obtained by reaction with aqueous Br_2 followed by base treatment. Propose structures for the two epoxides, and explain the result.



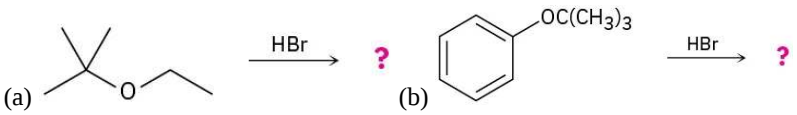
Mechanism Problems

PROBLEM 18-23 Predict the product(s) and provide the mechanism for each of the following reactions.

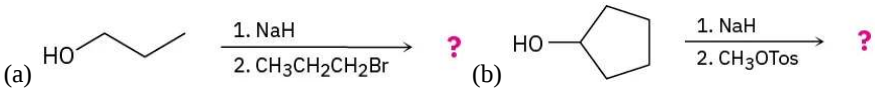




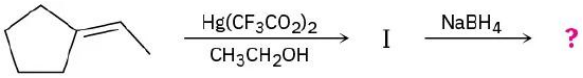
Problem 18-24 Predict the product(s) and provide the mechanism for each of the following reactions.



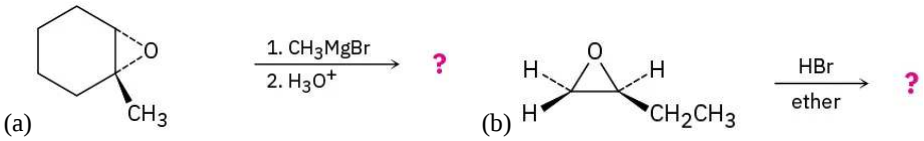
Problem 18-25 Predict the product(s) and provide the mechanism for each of the following two-step processes.



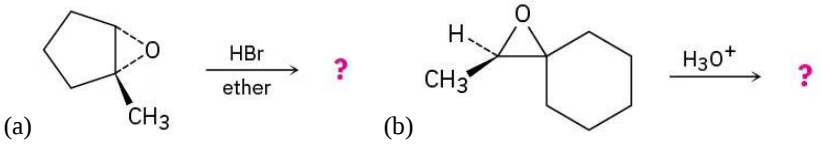
Problem 18-26 The alkoxymercuration of alkenes involves the formation of an organomercury intermediate (I), which is reduced with $NaBH_4$ to give an ether product. Predict the ether product and provide the mechanism for the following reaction.



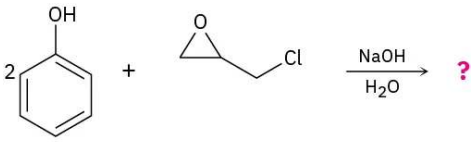
PROBLEM 18-27 Predict the product(s) and provide the mechanism for the following reactions:



Problem 18-28 Predict the product(s) and provide the mechanism for each of the following reactions.

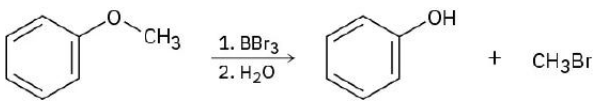


Problem 18-29 In the formation of the prepolymer used to make epoxy resins, a bisphenol reacts with epichlorohydrin in the presence of a base. Show the product and mechanism when two moles of phenol react with epichlorohydrin.

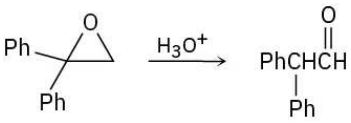


Epichlorohydrin

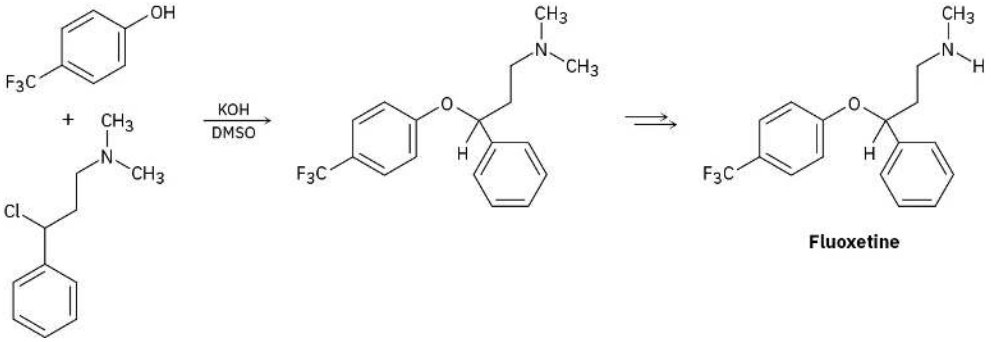
PROBLEM 18-30 Ethers undergo an acid-catalyzed cleavage reaction when treated with the Lewis acid BBr_3 at room temperature. Propose a mechanism for the reaction.



PROBLEM 18-31 Treatment of 1,1-diphenyl-1,2-epoxyethane with aqueous acid yields diphenyl acetaldehyde as the major product. Propose a mechanism for the reaction.



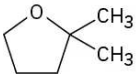
PROBLEM 18-32 Fluoxetine, a heavily prescribed antidepressant marketed under the name Prozac, can be prepared by a route that begins with reaction between a phenol and an alkyl chloride.



Fluoxetine

- (a) The rate of the reaction depends on both phenol and alkyl halide. Is this an S_N1 or an S_N2 reaction? Show the mechanism.
- (b) The physiologically active enantiomer of fluoxetine has (*S*) stereochemistry. Based on your answer in part **(a)**, draw the structure of the alkyl chloride you would need, showing the correct stereochemistry.

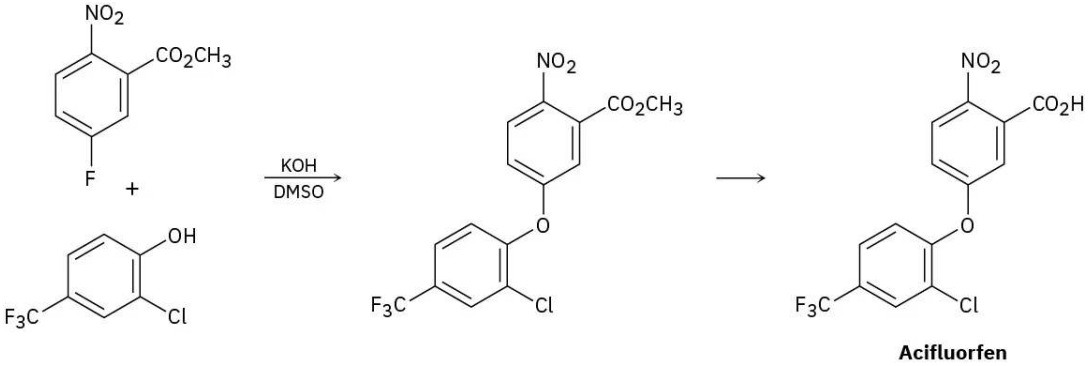
PROBLEM 18-33 When 2-methyl-2,5-pentanediol is treated with sulfuric acid, dehydration occurs and 2,2-dimethyltetrahydrofuran is formed. Suggest a mechanism for this reaction. Which of the two oxygen atoms is most likely to be eliminated, and why?



2,2-Dimethyltetrahydrofuran

PROBLEM 18-34 Methyl aryl ethers, such as anisole, are cleaved to iodomethane and a phenoxide ion by treatment with LiI in hot DMF. Propose a mechanism for this reaction.

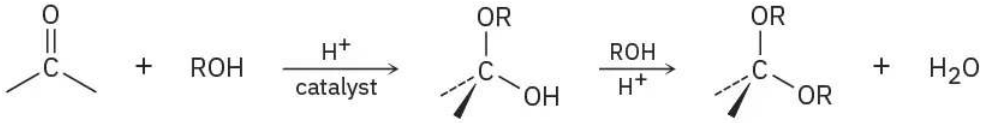
PROBLEM 18-35 The herbicide acifluorfen can be prepared by a route that begins with reaction between a phenol and an aryl fluoride. Propose a mechanism.



Acifluorfen

PROBLEM 18-36 Aldehydes and ketones undergo acid-catalyzed reaction with alcohols to yield *hemiacetals*, from aldehydes or ketals with ketones compounds that have one alcohol-like oxygen and one ether-like oxygen bonded to the same carbon. Further

reaction of a hemiacetal with alcohol then yields an *acetal*, a compound that has two ether-like oxygens bonded to the same carbon.

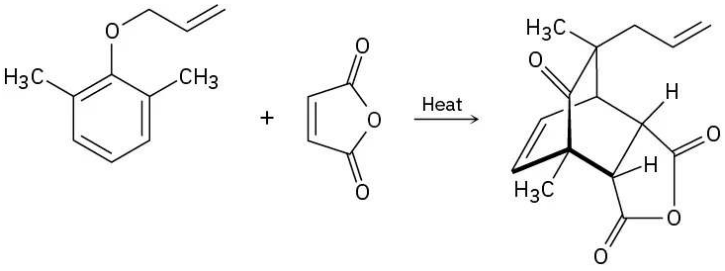


A ketone **A hemiketal** **A ketal**

(a) Show the structures of the hemiketal and ketal you would obtain by reaction of cyclohexanone with ethanol.

(b) Propose a mechanism for the conversion of a hemiacetal into a ketal.

PROBLEM 18-37 Propose a mechanism to account for the following transformation. What two kinds of reactions are occurring?



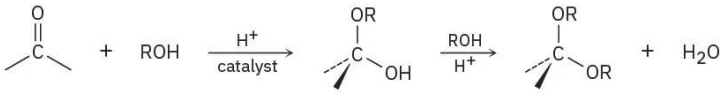
Naming Ethers

PROBLEM 18-38 Draw structures corresponding to the following IUPAC names:

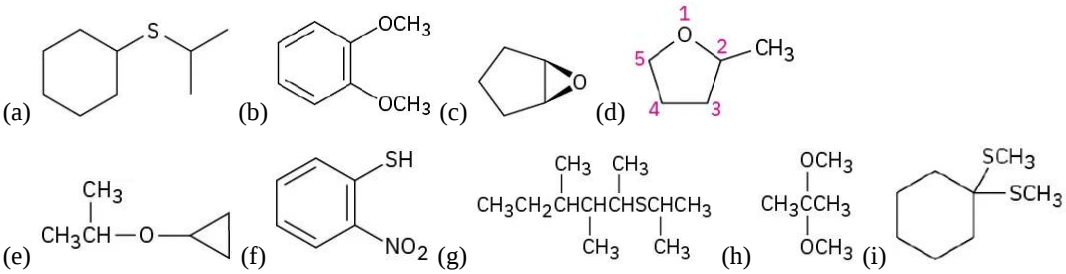
(a) Ethyl 1-ethylpropyl ether (b) Di(*p*-chlorophenyl) ether (c) 3,4-Dimethoxybenzoic acid

(d) Cyclopentyloxycyclohexane (e) 4-Allyl-2-methoxyphenol (eugenol; from oil of cloves)

PROBLEM 18-39 Give IUPAC names for the following structures:

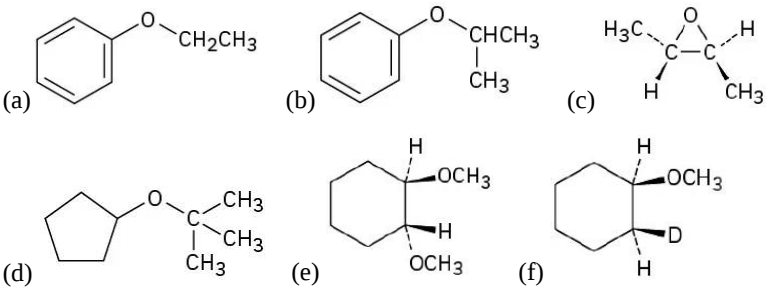


A ketone **A hemiketal** **A ketal**



Synthesizing Ethers

PROBLEM 18-40 How would you prepare the following ethers?



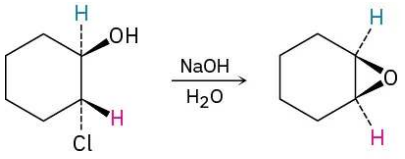
Problem 18-41 How would you prepare the following compounds from 1-phenylethanol?

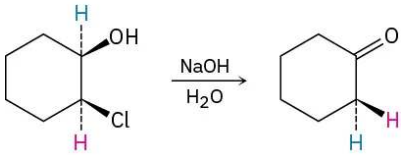
(a) Methyl 1-phenylethyl ether (b) Phenylepoxyethane

(c) *tert*-Butyl 1-phenylethyl ether (d) 1-Phenylethanethiol

PROBLEM 18-42 *tert*-Butyl ethers can be prepared by the reaction of an alcohol with 2-methylpropene in the presence of an acid catalyst. Propose a mechanism for this reaction.

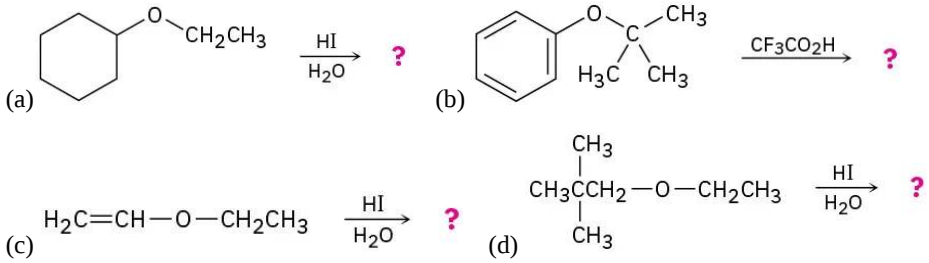
PROBLEM 18-43 Treatment of *trans*-2-chlorocyclohexanol with NaOH yields 1,2-epoxycyclohexane, but reaction of the cis isomer under the same conditions yields cyclohexanone. Propose mechanisms for both reactions, and explain why the different results are obtained.



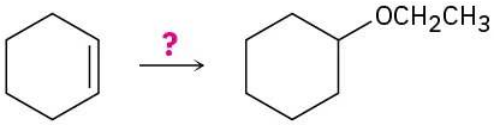


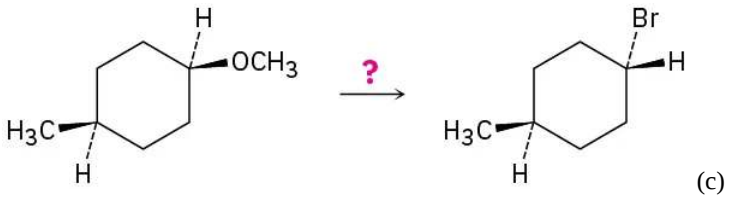
Reactions of Ethers and Epoxides

PROBLEM 18-44 Predict the products of the following ether cleavage reactions:

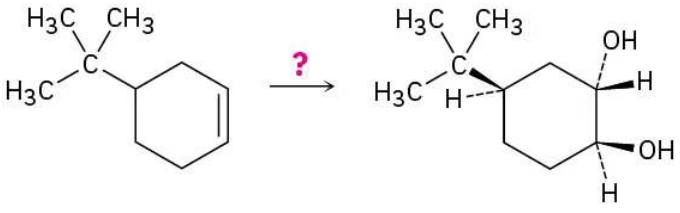


PROBLEM 18-1



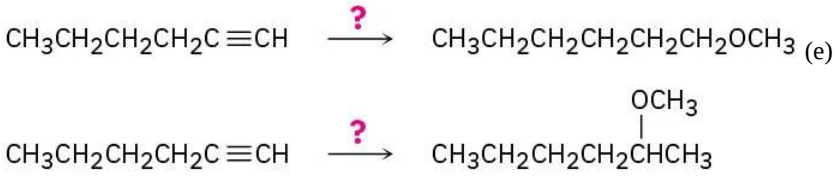


(c)



(d)

https://chem.libretexts.org/@go/page/564236



Problem 18-46

What product would you expect from cleavage of tetrahydrofuran with HI?

PROBLEM 18-1

Write the mechanism of the hydrolysis of *cis*-5,6-epoxydecane by reaction with aqueous acid. What is the stereochemistry of the product, assuming normal backside S_N2 attack?

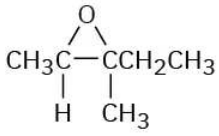
PROBLEM 18-1

What is the stereochemistry of the product from acid-catalyzed hydrolysis of *trans*-5,6-epoxydecane? How does the product differ from that formed in Problem 18-47?

PROBLEM 18-1

Acid-catalyzed hydrolysis of a 1,2-epoxycyclohexane produces a trans-diaxial 1,2-diol. What product would you expect to obtain from acidic hydrolysis of *cis*-3-*tert*-butyl-1,2-epoxycyclohexane? (Recall that the bulky *tert*-butyl group locks the cyclohexane ring into a specific conformation.)

PROBLEM 18-1



2,3-Epoxy-3-methylpentane
(no stereochemistry implied)

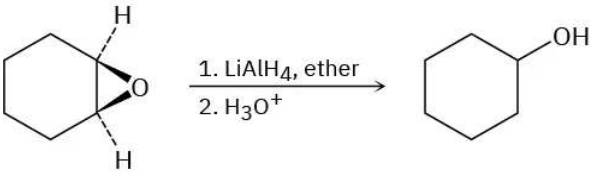
Draw the epoxide, showing stereochemistry.

(b)

Draw and name the product, showing stereochemistry. (c) Is the product chiral? Explain. (d) Is the product optically active? Explain.

PROBLEM 18-1

Epoxides are reduced by treatment with lithium aluminum hydride to yield alcohols. Propose a mechanism for this reaction.



PROBLEM 18-1

Show the structure and stereochemistry of the alcohol that would result if 1,2-epoxycyclohexane were reduced with lithium aluminum deuteride, $LiAlD_4$ (Problem 18-51).

Spectroscopy

PROBLEM 18-1

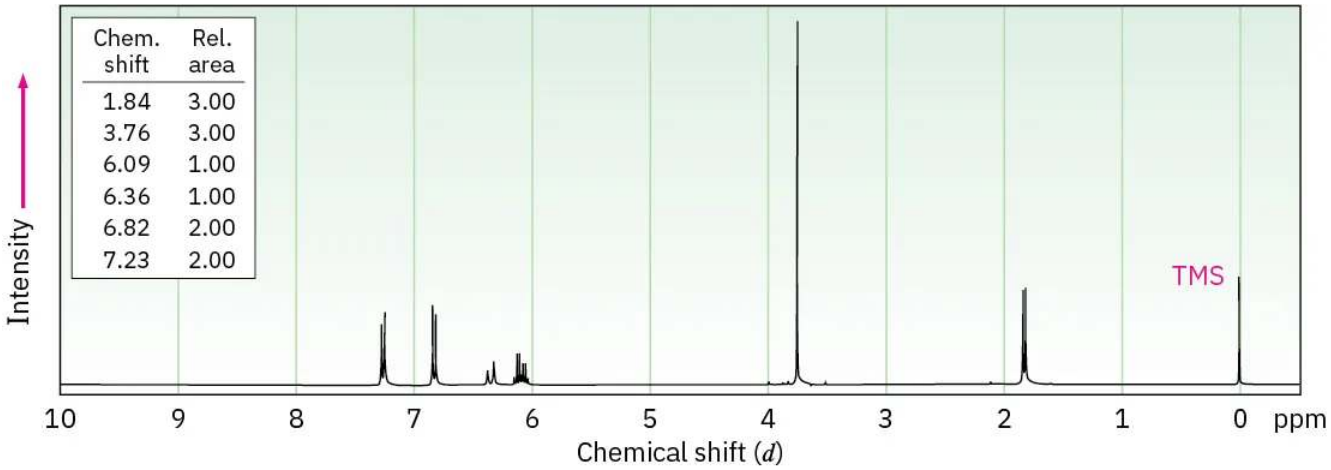
https://chem.libretexts.org/@go/page/564236

The red fox *(Vulpes vulpes)* uses a chemical communication system based on scent marks in urine. One component of fox urine is a sulfide whose mass spectrum has M^+ = 116. IR spectroscopy shows an intense band at 890 cm^{-1}, and ^1H NMR spectroscopy reveals the following peaks:

Propose a structure consistent with these data. [Note: $(CH_3)_2S$ absorbs at 2.1 δ].

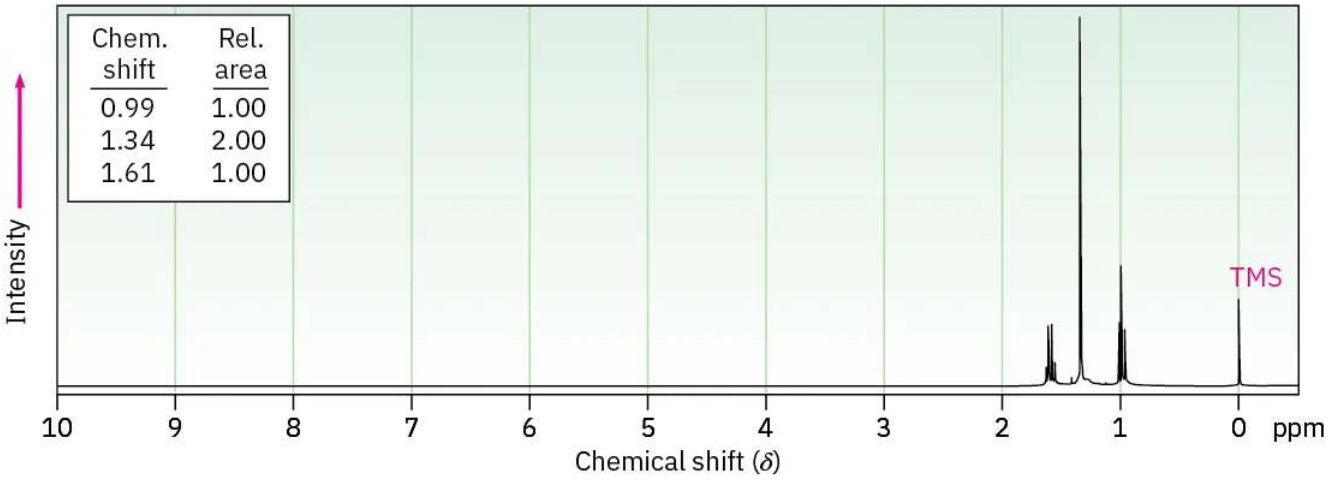
PROBLEM 18-1

Anethole, $C_{10}H_{12}O$, a major constituent of the oil of anise, has the ^1H NMR spectrum shown. On careful oxidation with $Na_2Cr_2O_7$, anethole yields *p*-methoxybenzoic acid. What is the structure of anethole? Assign all peaks in the NMR spectrum, and account for the observed splitting patterns.



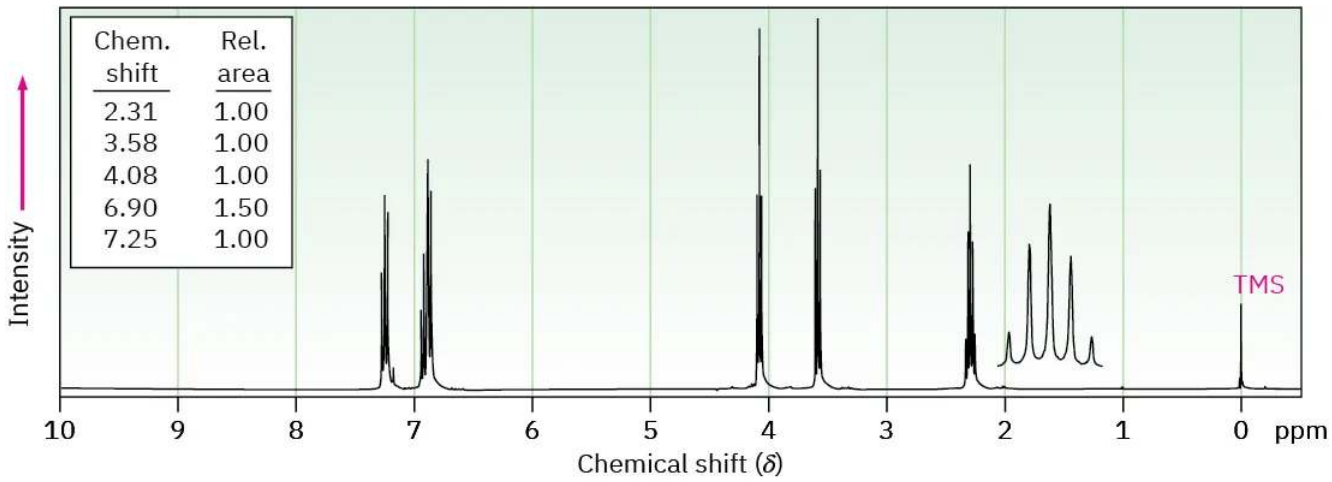
PROBLEM 18-1

$C_5H_{12}S$ (An –SH proton absorbs near 1.6 δ.)



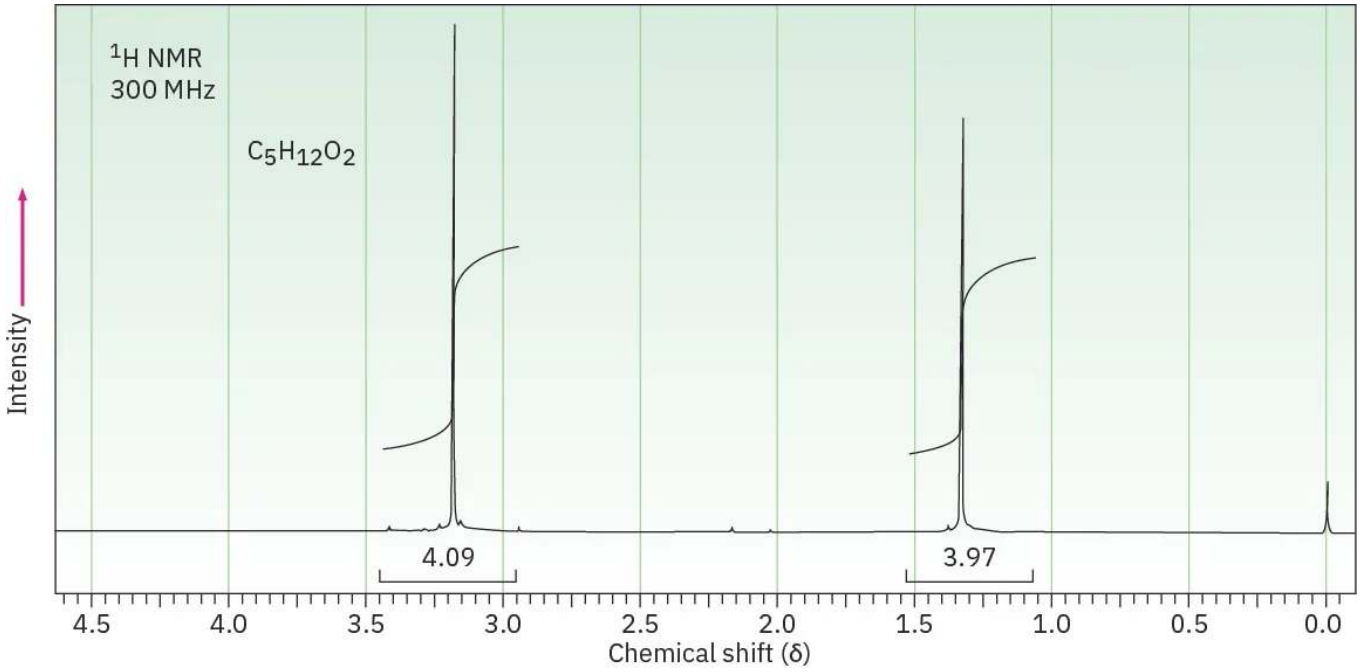
(b)

$C_9H_{11}BrO$



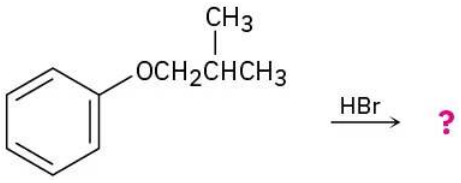
(c)

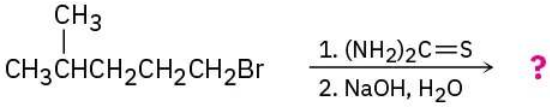
$C_5H_{12}O_2$



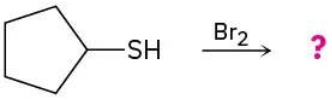
General Problems

PROBLEM 18-1

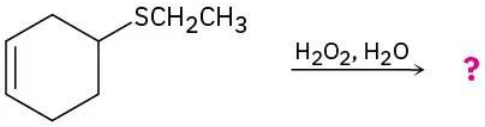




(c)



(d)



PROBLEM 18-1

How would you synthesize anethole (Problem 18-54) from phenol?

PROBLEM 18-1

How could you prepare benzyl phenyl ether from benzene and phenol? More than one step is required.

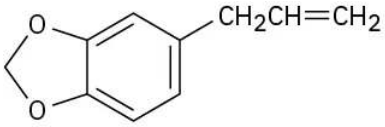
PROBLEM 18-1

Meerwein's reagent, triethyloxonium tetrafluoroborate, is a powerful ethylating agent that converts alcohols into ethyl ethers at neutral pH. Show the reaction of Meerwein's reagent with cyclohexanol, and account for the fact that trialkyloxonium salts are much more reactive alkylating agents than alkyl iodides.

$(CH_3CH_2)_3O^+\ BF_4^-$ **Meerwein's reagent**

PROBLEM 18-1

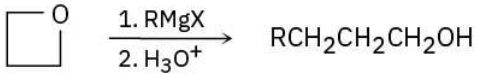
Safrole, a substance isolated from oil of sassafras, is used as a perfumery agent. Propose a synthesis of safrole from catechol (1,2-benzenediol).



Safrole

PROBLEM 18-1

Grignard reagents react with oxetane, a four-membered cyclic ether, to yield primary alcohols, but the reaction is much slower than the corresponding reaction with ethylene oxide. Suggest a reason for the difference in reactivity between oxetane and ethylene oxide.



Oxetane

PROBLEM 18-1

The *Zeisel method* is an old analytical procedure for determining the number of methoxyl groups in a compound. A weighed amount of the compound is heated with concentrated HI, ether cleavage occurs, and the iodomethane product is distilled off and passed into an alcohol solution of $AgNO_3$, where it reacts to form a precipitate of silver iodide. The AgI is then collected and weighed, and the percentage of methoxyl groups in the sample is thereby determined. For example, 1.06 g of vanillin, the material responsible for the characteristic odor of vanilla, yields 1.60 g of AgI. If vanillin has a molecular weight of 152, how many methoxyl groups does it contain?

PROBLEM 18-1

Disparlure, $C_{19}H_{38}O$, is a sex attractant released by the female spongy moth, *Lymantria dispar*. The ^1H NMR spectrum of disparlure shows a large absorption in the alkane region, 1 to 2 δ, and a triplet at 2.8 δ. Treatment of disparlure, first with aqueous acid and then with $KMnO_4$, yields two carboxylic acids identified as undecanoic acid and 6-methylheptanoic acid. ($KMnO_4$ cleaves

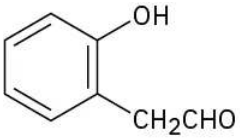
1,2-diols to yield carboxylic acids.) Neglecting stereochemistry, propose a structure for disparlure. The actual compound is a chiral molecule with 7*R*,8*S* stereochemistry. Draw disparlure, showing the correct stereochemistry.

PROBLEM 18-1

How would you synthesize racemic disparlure (Problem 18-63) from compounds having ten or fewer carbons?

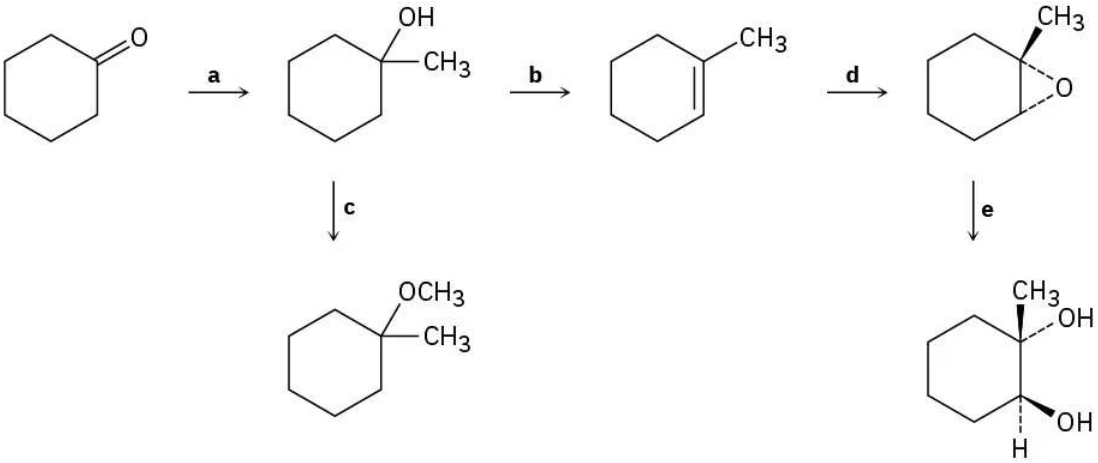
PROBLEM 18-1

How would you prepare *o*-hydroxyphenylacetaldehyde from phenol? More than one step is required.



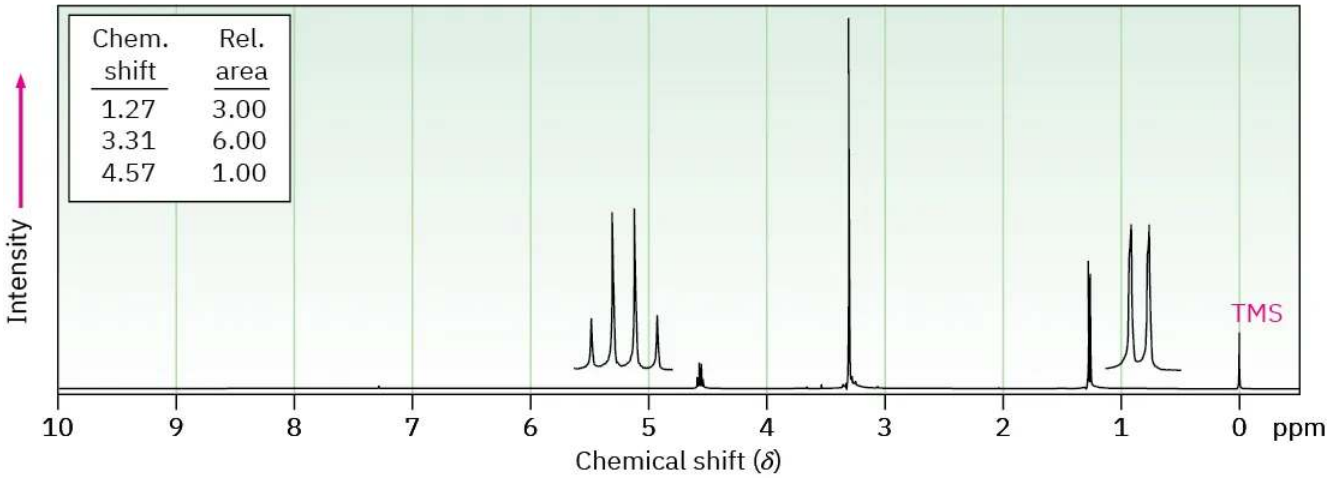
***o*-Hydroxyphenylacetaldehyde**

PROBLEM 18-66 Identify the reagents **a**–**e** in the following scheme:



PROBLEM 18-67 Propose structures for compounds that have the following <sup">1H NMR spectra: (a)

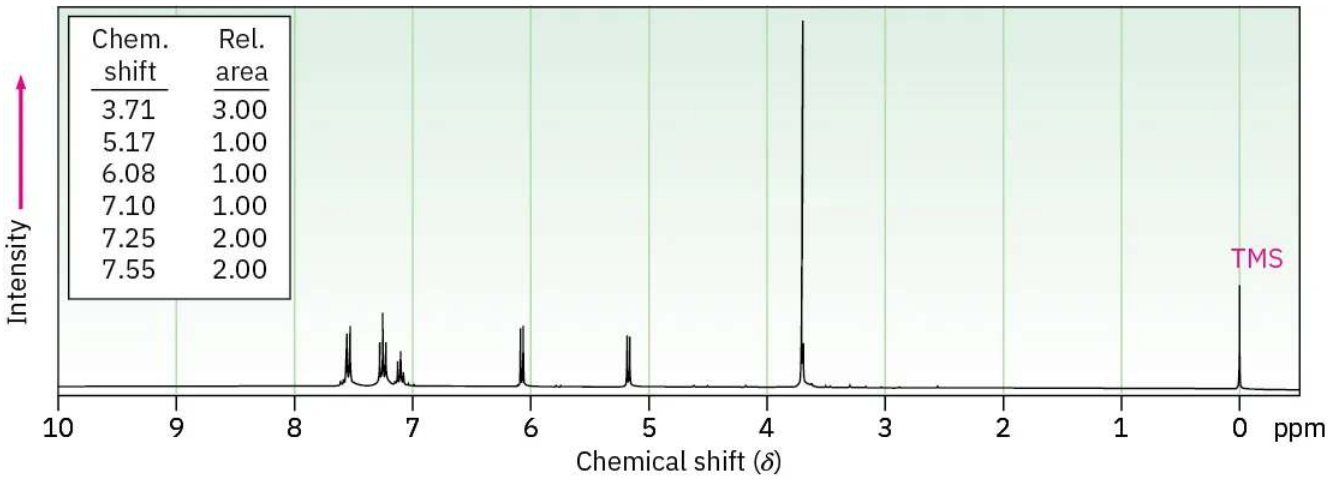
$C_4H_{10}O_2$



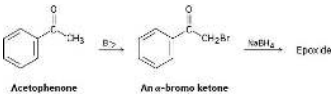
(b)

$C_9H_{10}O$

https://chem.libretexts.org/@go/page/564236



PROBLEM 18-68 We saw in **Section 17.4** that ketones react with $NaBH_4$ to yield alcohols. We'll also see in **Section 22.3** that ketones react with Br_2 to yield α-bromo ketones. Perhaps surprisingly, treatment with $NaBH_4$ of the α-bromo ketone from acetophenone yields an epoxide rather than a bromo alcohol. Show the structure of the epoxide, and explain its formation.

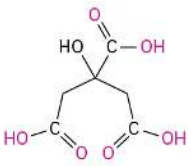


This page titled 7.14: Additional Problems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

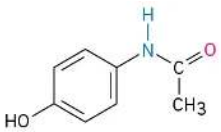
- **18.13: Additional Problems** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

7.15: Preview of Carbonyl Chemistry

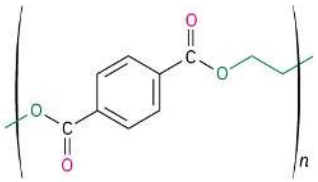
Carbonyl compounds are everywhere. Most biological molecules contain carbonyl groups, as do most pharmaceutical agents and many of the synthetic chemicals that affect our everyday lives. Citric acid, found in lemons and oranges; acetaminophen, the active ingredient in many over-the-counter headache remedies; and Dacron, the polyester material used in clothing, all contain different kinds of carbonyl groups.



Citric acid
(a carboxylic acid)



Acetaminophen
(an amide)



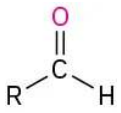
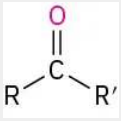
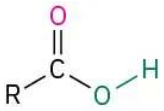
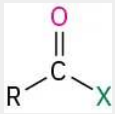
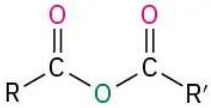
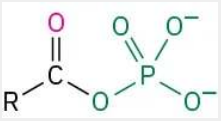
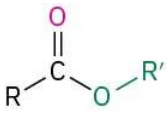
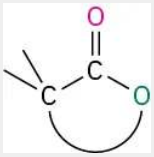
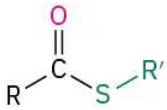
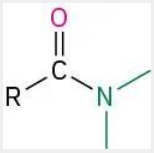
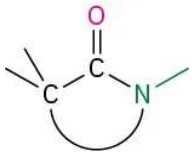
Dacron
(a polyester)

To a great extent, the chemistry of living organisms is the chemistry of carbonyl compounds. Thus, we'll spend the next five chapters discussing the chemistry of the **carbonyl group,** C=O (pronounced car-bo-**neel**). There are many different kinds of carbonyl compounds and many different reactions, but there are only a few fundamental principles that tie the entire field together. The purpose of this brief preview is not to show details of specific reactions but rather to provide a framework for learning carbonyl-group chemistry. Read through this preview now, and return to it on occasion to remind yourself of the larger picture.

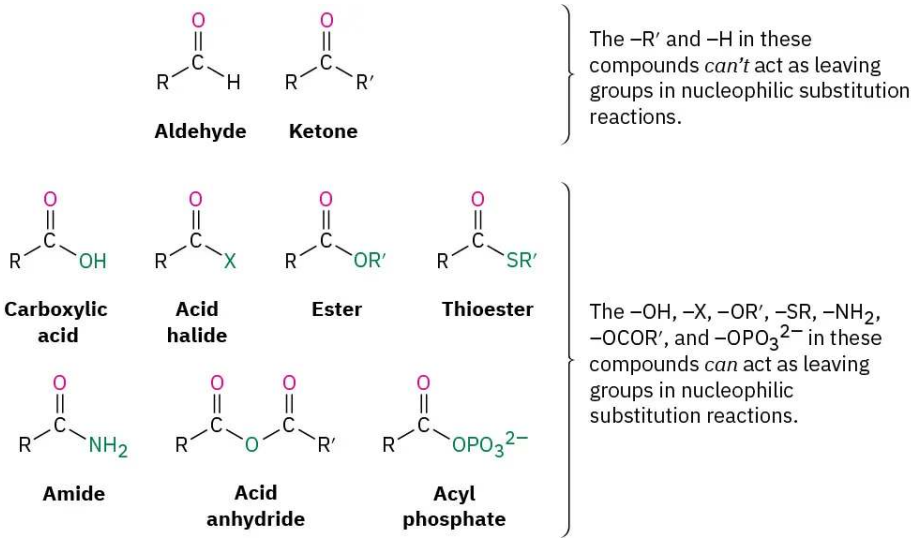
I Kinds of Carbonyl Compounds

Table 7.15.1shows some of the many different kinds of carbonyl compounds. All contain an **acyl group** (R–C=O) bonded to another substituent. The R part of the acyl group can be practically any organic part/structure, and the other substituent to which the acyl group is bonded might be a carbon, hydrogen, oxygen, halogen, nitrogen, or sulfur.

Table 7.15.1: Some Types of Carbonyl Compounds

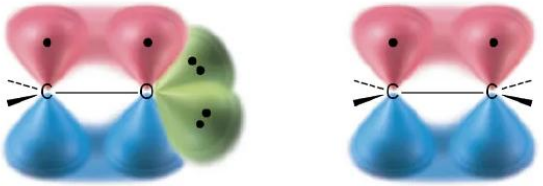
Name	General formula	Name ending
Aldehyde		*-al*
Ketone		*-one*
Carboxylic acid		*-oic acid*
Acid halide		*-yl or -oyl halide*
Acid anhydride		*-oic anhydride*
Acyl phosphate		*-yl phosphate*
Ester		*-oate*
Lactone (cyclic ester)		None
Thioester		*-thioate*
Amide		*-amide*
Lactam (cyclic amide)		None

It's useful to classify carbonyl compounds into two categories based on the kinds of chemistry they undergo. In one category are aldehydes and ketones; in the other are carboxylic acids and their derivatives. The acyl group in an aldehyde or ketone is bonded to an atom (H or C, respectively) that can't stabilize a negative charge and therefore can't act as a leaving group in a nucleophilic substitution reaction. The acyl group in a carboxylic acid or its derivative, however, is bonded to an atom (oxygen, halogen, sulfur, nitrogen) that *can* stabilize a negative charge and therefore *can* act as a leaving group in a nucleophilic substitution reaction.



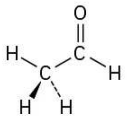
II Nature of the Carbonyl Group

The carbon–oxygen double bond of a carbonyl group is similar in many respects to the carbon–carbon double bond of an alkene. The carbonyl carbon atom is sp^2-hybridized and forms three σ bonds. The fourth valence electron remains in a carbon p orbital and forms a π bond to oxygen by overlapping with an oxygen p orbital. The oxygen atom also has two nonbonding pairs of electrons, which occupy its remaining two orbitals.



Like alkenes, carbonyl compounds are planar about the double bond and have bond angles of approximately 120°. Figure 7.15.1 shows the structure of acetaldehyde and indicates its bond lengths and angles. As you might expect, the carbon–oxygen double bond is both shorter (122 pm versus 143 pm) and stronger [732 kJ/mol (175 kcal/mol) versus 385 kJ/mol (92 kcal/mol)] than a C–O single bond.

Bond angle	(°)	Bond length	(pm)
H—C—C	118	C=O	122
C—C=O	121	C—C	150
H—C=O	121	OC—H	109



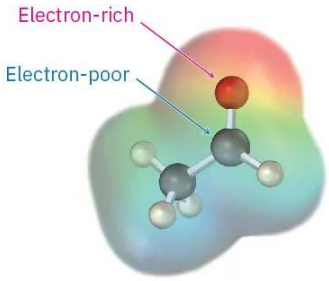


Figure 7.15.1: Structure of acetaldehyde.

As indicated by the electrostatic potential map in Figure 7.15.1, the carbon–oxygen double bond is strongly polarized because of the high electronegativity of oxygen relative to carbon. Thus, the carbonyl carbon atom carries a partial positive charge, is an

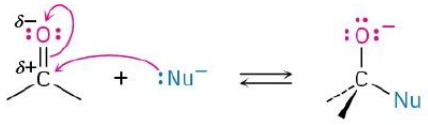
electrophilic (Lewis acidic) site, and reacts with nucleophiles. Conversely, the carbonyl oxygen atom carries a partial negative charge, is a nucleophilic (Lewis basic) site, and reacts with electrophiles. We'll see in the next five chapters that the majority of carbonyl-group reactions can be rationalized by simple polarity arguments.

III General Reactions of Carbonyl Compounds

Both in the laboratory and in living organisms, most reactions of carbonyl compounds take place by one of four general mechanisms: *nucleophilic addition*, *nucleophilic acyl substitution*, *alpha substitution*, and *carbonyl condensation*. These mechanisms have many variations, just as alkene electrophilic addition reactions and S_N2 reactions do, but the variations are much easier to learn when the fundamental features of the mechanisms are made clear. Let's see what the four mechanisms are and what kinds of chemistry carbonyl compounds undergo.

Nucleophilic Addition Reactions of Aldehydes and Ketones (Chapter 19)

The most common reaction of aldehydes and ketones is the **nucleophilic addition reaction**, in which a nucleophile, **:**Nu^-, adds to the electrophilic carbon of the carbonyl group. Because the nucleophile uses an electron pair to form a new bond to carbon, two electrons from the carbon–oxygen double bond must move toward the electronegative oxygen atom to give an alkoxide anion. The carbonyl carbon rehybridizes from sp^2 to sp^3 during the reaction, and the alkoxide ion product therefore has tetrahedral geometry.



A carbonyl compound (sp^2-hybridized carbon) **A tetrahedral intermediate (sp^3-hybridized carbon)**

Once formed, and depending on the nature of the nucleophile, the tetrahedral alkoxide intermediate can undergo one of two further reactions, as shown in Figure 7.15.2. Often, the tetrahedral alkoxide intermediate is simply protonated by water or acid to form an alcohol product. Alternatively, the tetrahedral intermediate can be protonated and expel the oxygen to form a new double bond between the carbonyl carbon and the nucleophile. We'll study both processes in detail in Chapter 19.

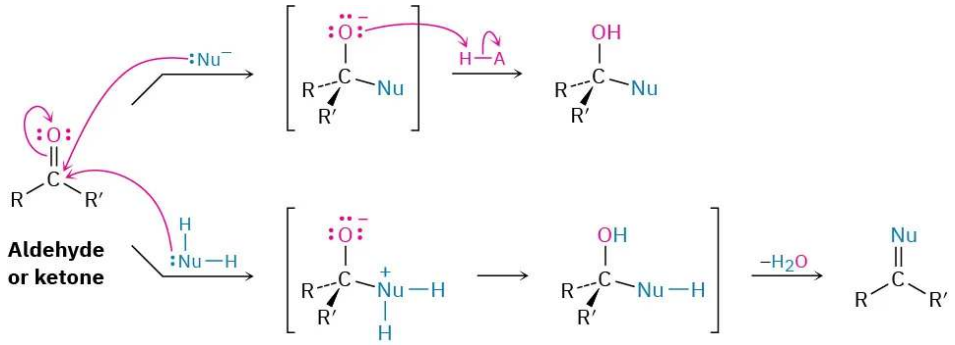
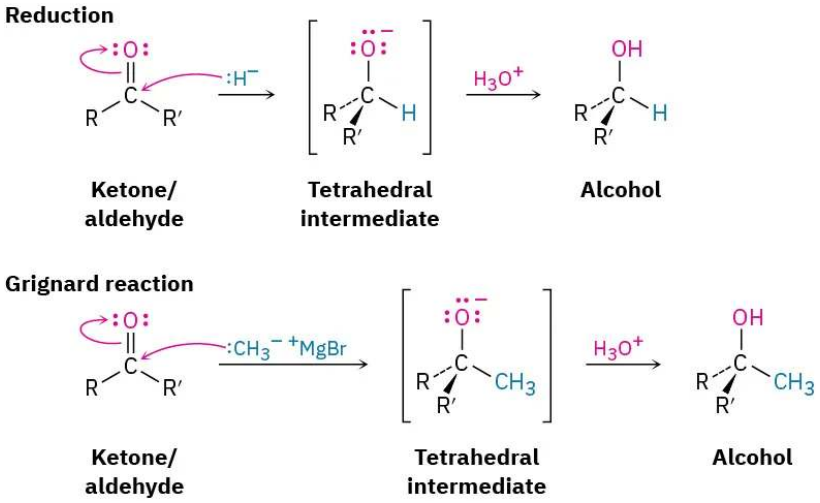


Figure 7.15.2: The addition reaction of an aldehyde or a ketone with a nucleophile. Depending on the nucleophile, either an alcohol or a compound with a C═ double bond is formed.

FORMATION OF AN ALCOHOL

The simplest reaction of a tetrahedral alkoxide intermediate is protonation to yield an alcohol. We've already seen two examples of this kind of process during reduction of aldehydes and ketones with hydride reagents such as $NaBH_4$ and $LiAlH_4$ (Section 17.4) and during Grignard reactions (Section 17.5). During a reduction, the nucleophile that adds to the carbonyl group is a hydride ion, $H:^-$, while during a Grignard reaction, the nucleophile is a carbanion, $R_3C:^-$.



FORMATION OF C=Nu

The second mode of nucleophilic addition, which often occurs with amine nucleophiles, involves elimination of oxygen and formation of a C=Nu double bond. For example, aldehydes and ketones react with primary amines, RNH_2, to form imines, $R_2C{=}NR'$. These reactions use the same kind of tetrahedral intermediate as that formed during hydride reduction and Grignard reaction, but the initially formed alkoxide ion is not isolated. Instead, it is protonated and then loses water to form an imine, as shown in Figure 7.15.3.

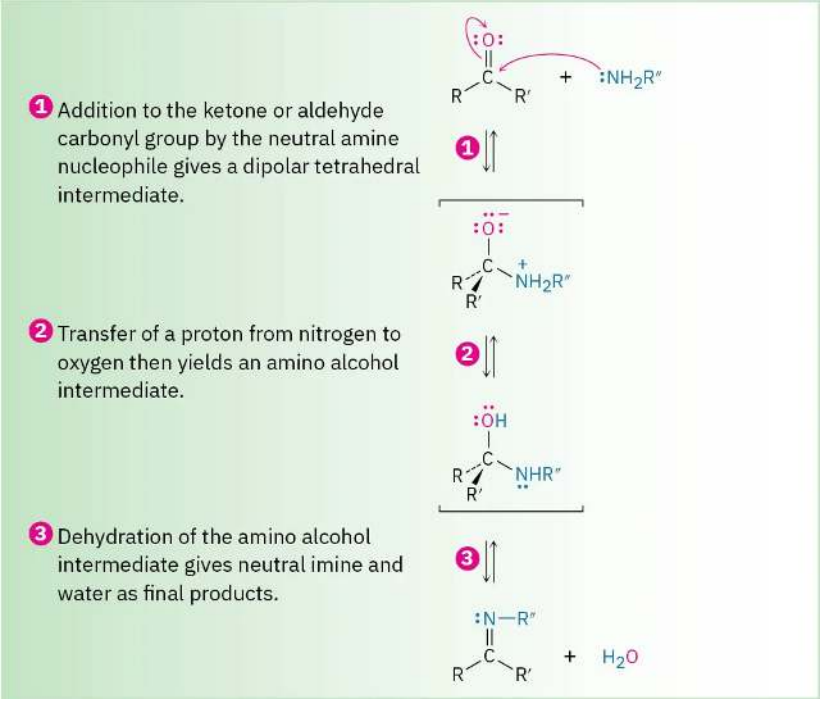
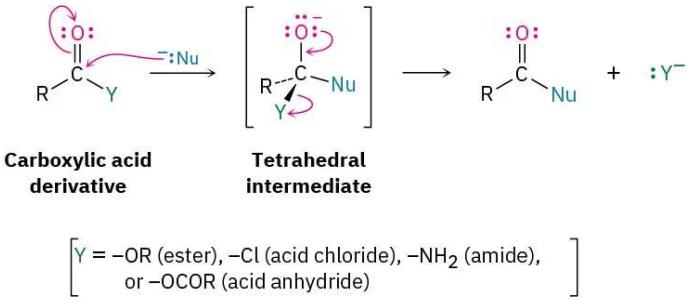


Figure 7.15.3: Formation of an imine, $R_2C{=}NR'$, by reaction of an amine with an aldehyde or a ketone.

Nucleophilic Acyl Substitution Reactions of Carboxylic Acid Derivatives (Chapter 21)

The second fundamental reaction of carbonyl compounds, **nucleophilic acyl substitution**, is related to the nucleophilic addition reaction just discussed but occurs only with carboxylic acid derivatives rather than with aldehydes and ketones. When the carbonyl group of a carboxylic acid derivative reacts with a nucleophile, addition occurs in the usual way, but the initially formed tetrahedral alkoxide intermediate is not isolated. Because carboxylic acid derivatives have a leaving group bonded to the carbonyl-group carbon, the tetrahedral intermediate can react further by expelling the leaving group and forming a new carbonyl compound:



The net effect of nucleophilic acyl substitution is the replacement of the leaving group by the entering nucleophile. We'll see in Chapter 21, for instance, that acid chlorides are rapidly converted into esters by treatment with alkoxide ions (Figure 7.15.4).

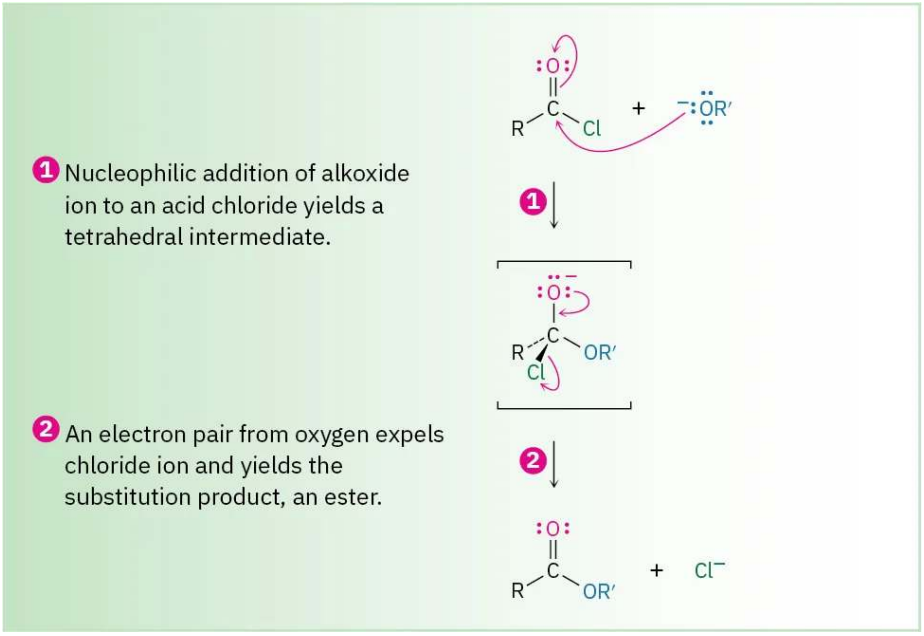
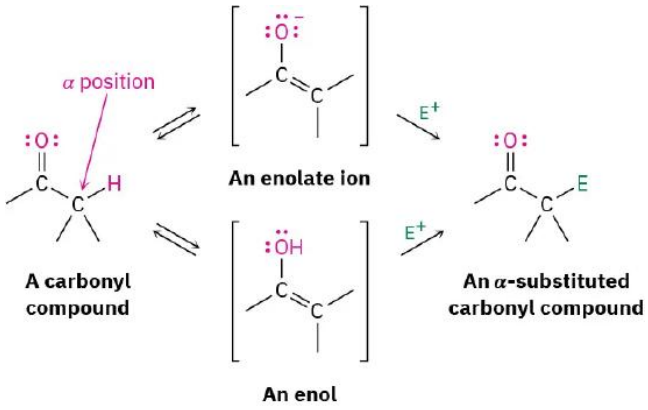


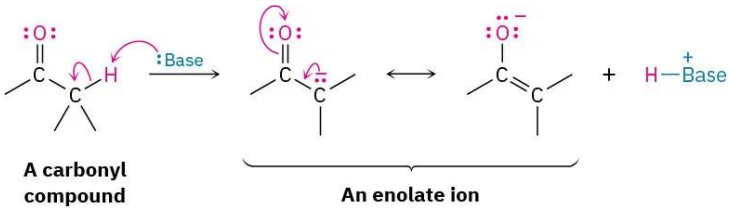
Figure 7.15.4: Nucleophilic acyl substitution of an acid chloride with an alkoxide ion yields an ester.

Alpha-Substitution Reactions (Chapter 22)

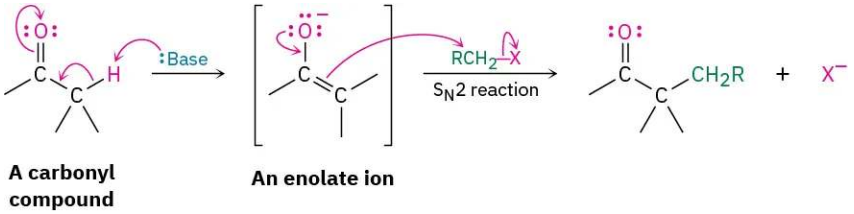
The third major reaction of carbonyl compounds, **alpha substitution**, occurs at the position next to the carbonyl group—the alpha (α) position. This reaction results in the substitution of an α hydrogen by an electrophile through the formation of an intermediate *enol* or *enolate ion:*



For reasons that we'll explore in Chapter 22, the presence of a carbonyl group renders the hydrogens on the α carbon acidic. Carbonyl compounds therefore react with strong base to yield enolate ions.



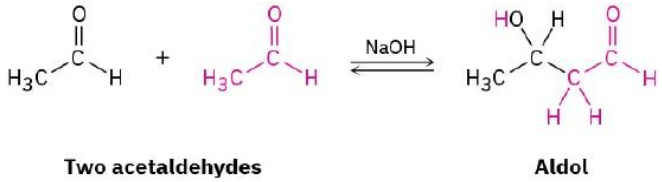
Because they're negatively charged, enolate ions act as nucleophiles and undergo many of the reactions we've already studied. For example, enolates react with primary alkyl halides in the S_N2 reaction. The nucleophilic enolate ion displaces halide ion, and a new C–C bond forms:



The S_N2 alkylation reaction between an enolate ion and an alkyl halide is a powerful method for making C–C bonds, thereby building up larger molecules from smaller precursors. We'll study the alkylation of many kinds of carbonyl compounds in Chapter 22.

Carbonyl Condensation Reactions (Chapter 23)

The fourth and last fundamental reaction of carbonyl groups, **carbonyl condensation**, takes place when two carbonyl compounds react with each other. When acetaldehyde is treated with base, for instance, two molecules combine to yield the hydroxy aldehyde product known as *aldol* (*ald*ehyde + alcoh*ol*):



Although carbonyl condensation appears to be different from the three processes already discussed, it's actually quite similar. A carbonyl condensation reaction is simply a combination of a nucleophilic addition step and an α-substitution step. The initially formed enolate ion of one acetaldehyde molecule acts as a nucleophile and adds to the carbonyl group of another acetaldehyde molecule, as shown in Figure 7.15.5.

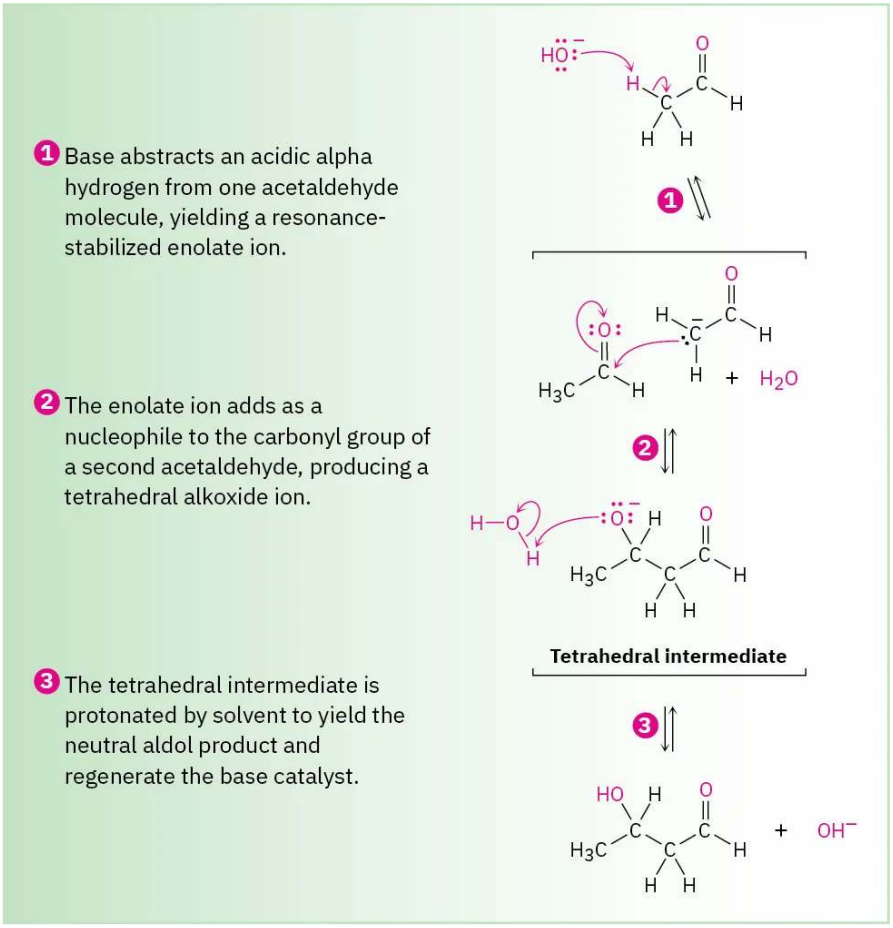


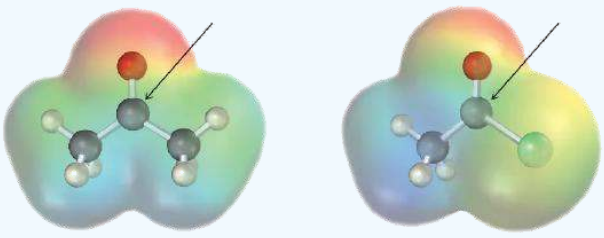
Figure 7.15.5: A carbonyl condensation reaction between two molecules of acetaldehyde yields a hydroxy aldehyde product.

IV Summary

To a great extent, the chemistry of living organisms is the chemistry of carbonyl compounds. We have not looked at the details of specific carbonyl reactions in this short preview but rather have laid the groundwork for the next five chapters. All the carbonyl-group reactions we'll be studying in Chapters 19 through 23 fall into one of the four fundamental categories discussed in this preview. Knowing where we'll be heading should help you keep matters straight in understanding this most important of all functional groups.

? Exercise 7.15.1

Judging from the following electrostatic potential maps, which kind of carbonyl compound has the more electrophilic carbonyl carbon atom, a ketone or an acid chloride? Which has the more nucleophilic carbonyl oxygen atom? Explain.



Acetone (ketone)

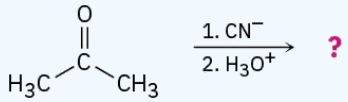
Acetyl chloride (acid chloride)

Answer

1,2-Epoxybutane

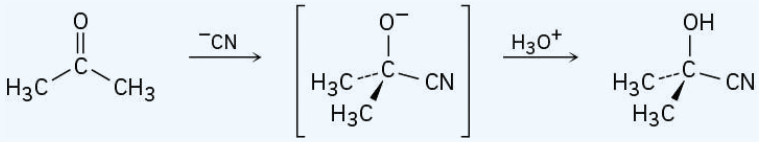
Exercise 7.15.2

Predict the product formed by nucleophilic addition of cyanide ion (CN^-) to the carbonyl group of acetone, followed by protonation to give an alcohol:



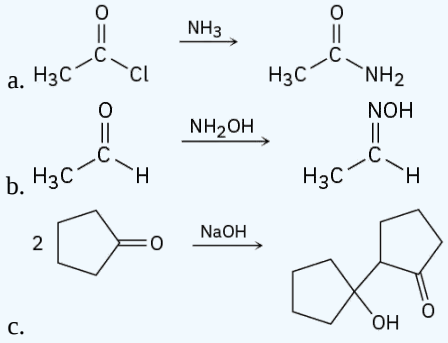
Acetone

Answer



Exercise 7.15.3

Identify each of the following reactions as a nucleophilic addition, nucleophilic acyl substitution, an α substitution, or a carbonyl condensation:



Answer

a. Nucleophilic acyl substitution
b. Nucleophilic addition
c. Carbonyl condensation

This page titled 7.15: Preview of Carbonyl Chemistry is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **18.14: Preview of Carbonyl Chemistry** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

CHAPTER OVERVIEW

8: Aldehydes and Ketones- Nucleophilic Addition Reactions

8.1: Why This Chapter?
8.2: Naming Aldehydes and Ketones
8.3: Preparing Aldehydes and Ketones
8.4: Oxidation of Aldehydes and Ketones
8.5: Nucleophilic Addition Reactions of Aldehydes and Ketones
8.6: Nucleophilic Addition of Water- Hydration
8.7: Nucleophilic Addition of HCN - Cyanohydrin Formation
8.8: Nucleophilic Addition of Hydride and Grignard Reagents- Alcohol Formation
8.9: Nucleophilic Addition of Amines- Imine and Enamine Formation
8.10: Nucleophilic Addition of Hydrazine - The Wolff-Kishner Reaction
8.11: Nucleophilic Addition of Alcohols - Acetal Formation
8.12: Nucleophilic Addition of Phosphorus Ylides- The Wittig Reaction
8.13: Biological Reductions
8.13.1: Amines and Heterocycles
8.13.1.1: Why This Chapter?
8.13.1.2: Naming Amines
8.13.1.3: Structure and Properties of Amines
8.13.1.4: Basicity of Amines
8.13.1.5: Basicity of Arylamines
8.13.1.6: Biological Amines and the Henderson-Hasselbalch Equation
8.13.1.7: Synthesis of Amines
8.13.1.8: Reactions of Amines
8.13.1.9: Reactions of Arylamines
8.13.1.10: Heterocyclic Amines
8.13.1.11: Spectroscopy of Amines
8.13.1.12: Chemistry Matters - Green Chemistry II- Ionic Liquids
8.13.1.13: Key Terms
8.13.1.14: Summary
8.13.1.15: Summary of Reactions
8.13.1.16: Additional Problems
8.14: Conjugate Nucleophilic Addition to α,β-Unsaturated Aldehydes and Ketones
8.15: Spectroscopy of Aldehydes and Ketones
8.16: Chemistry Matters—Enantioselective Synthesis
8.17: Key Terms
8.18: Summary
8.19: Summary of Reactions
8.20: Additional Problems
8.21: Carbonyl Condensation Reactions

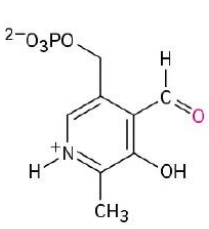
This page titled 8: Aldehydes and Ketones- Nucleophilic Addition Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

8.1: Why This Chapter?

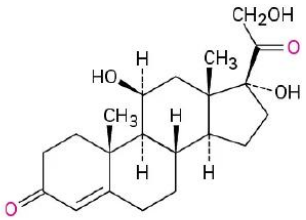
Much of organic chemistry is the chemistry of carbonyl compounds. Aldehydes and ketones, in particular, are intermediates in the synthesis of many pharmaceutical agents, in almost all biological pathways, and in numerous industrial processes, so an understanding of their properties and reactions is essential. In this chapter, we'll look at some of their most important reactions.

Figure 8.1.1: Few flowers are more beautiful or more fragrant than roses. Their perfumed odor is due to several simple organic compounds, including the ketone β-damascenone. (credit: "Rosa 'Precious Platinum'" by Bernard Spragg/Wikimedia Commons, CC BY 1.0)

Aldehydes (RCHO) and ketones (R_2CO) are among the most widely occurring of all compounds. In nature, many substances required by living organisms are aldehydes or ketones. The aldehyde pyridoxal phosphate, for instance, is a coenzyme involved in a large number of metabolic reactions; the ketone hydrocortisone is a steroid hormone secreted by the adrenal glands to regulate fat, protein, and carbohydrate metabolism.

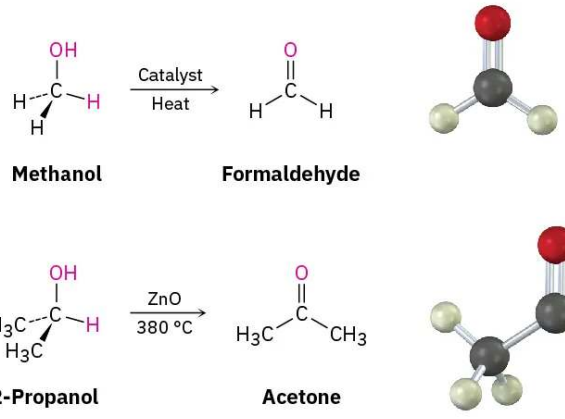


Pyridoxal phosphate (PLP)



Hydrocortisone

In the chemical industry, simple aldehydes and ketones are produced in large quantities for use as solvents and as starting materials to prepare a host of other compounds. For example, more than 50 million tons per year of formaldehyde, $H_2C{=}O$, is produced worldwide for use in building insulation materials and in the adhesive resins that bind particle board and plywood. Acetone, $(CH_3)_2C{=}O$, is widely used as an industrial solvent, with approximately 8 million tons per year produced worldwide. Formaldehyde is synthesized industrially by catalytic oxidation of methanol, and one method of acetone preparation involves oxidation of 2-propanol produced by hydration of propylene.

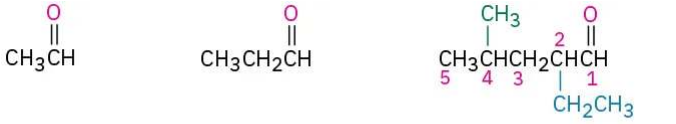


This page titled 8.1: Why This Chapter? is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **19.0: Why This Chapter?** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

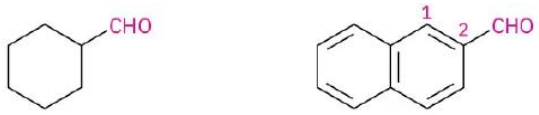
8.2: Naming Aldehydes and Ketones

Aldehydes are named by replacing the terminal *-e* of the corresponding alkane name with *-al*. The parent chain must contain the –CHO group, and the –CHO carbon is numbered as carbon 1. Note in the following examples that the longest chain in 2-ethyl-4-methylpentanal is actually a hexane, but this chain does not include the –CHO group and thus is not the parent.



Ethanal (acetaldehyde) **Propanal (propionaldehyde)** **2-Ethyl-4-methylpentanal**

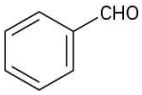
For cyclic aldehydes in which the –CHO group is directly attached to a ring, the ring name followed by *carbaldehyde* is used.



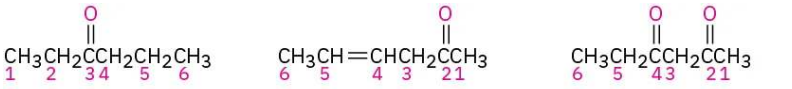
Cyclohexanecarbaldehyde **2-Naphthalenecarbaldehyde**

A few simple and well-known aldehydes have common names that are recognized by IUPAC. Several that you might encounter are listed in Table 8.2.1.

Table 8.2.1: Common Names of Some Simple Aldehydes

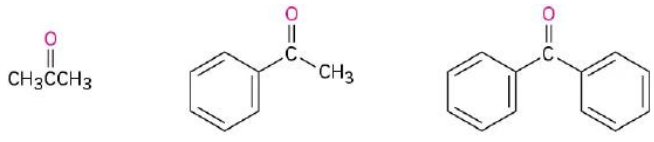
Formula	Common name	Systematic name
HCHO	Formaldehyde	Methanal
CH_3CHO	Acetaldehyde	Ethanal
$H_2C{=}CHCHO$	Acrolein	Propenal
$CH_3CH{=}CHCHO$	Crotonaldehyde	2-Butenal
	Benzaldehyde	Benzenecarbaldehyde

Ketones are named by replacing the terminal *-e* of the corresponding alkane name with *-one*. The parent chain is the longest one that includes the ketone group, and the numbering begins at the end nearer the carbonyl carbon. As with alkenes (Section 7.3) and alcohols (Section 17.1), the locant is placed before the parent name using older rules but before the suffix with the newer IUPAC guidelines. For example:



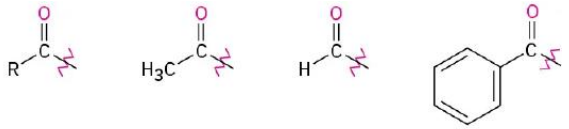
3-Hexanone (New: Hexan-3-one) **4-Hexen-2-one (New: Hex-4-en-2-one)** **2,4-Hexanedione (New: Hexane-2,4-dione)**

A few ketones are allowed by IUPAC to retain their common names.



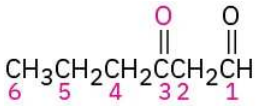
Acetone **Acetophenone** **Benzophenone**

When it's necessary to refer to the R–C═O group as a substituent, the name acyl (a-sil) group is used and the name ending *-yl* is attached. Thus, $–COCH_3$ is an *acetyl* group, –CHO is a *formyl* group, –COAr is an *aroyl* group, and $–COC_6H_5$ is a *benzoyl* group.



An acyl group Acetyl Formyl Benzoyl

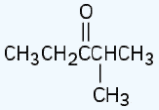
If other functional groups are present and the double-bonded oxygen is considered a substituent on a parent chain, the prefix *oxo-* is used. For example:

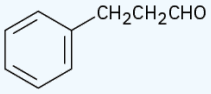


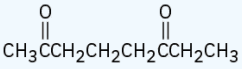
3-Oxohexanal

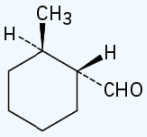
Exercise 8.2.1

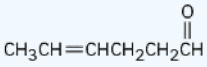
Name the following aldehydes and ketones:

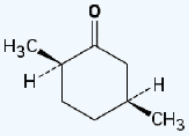
a. 

b. 

c. 

d. 

e. 

f. 

Answer

a. 2-Methyl-3-pentanone
b. 3-Phenylpropanal
c. 2,6-Octanedione
d. trans-2-Methylcyclohexanecarbaldehyde
e. 4-Hexenal
f. cis-2,5-Dimethylcyclohexanone

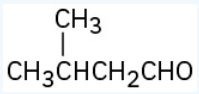
Exercise 8.2.2

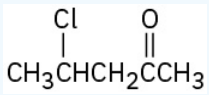
Draw structures corresponding to the following names:

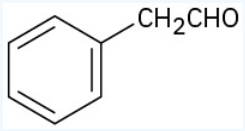
a. 3-Methylbutanal
b. 4-Chloro-2-pentanone
c. Phenylacetaldehyde
d. cis-3-tert-Butylcyclohexanecarbaldehyde
e. 3-Methyl-3-butenal

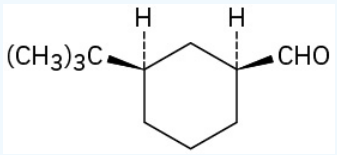
f. 2-(1-Chloroethyl)-5-methylheptanal

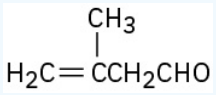
Answer

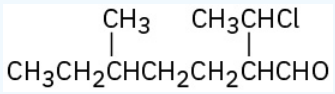
a. 

b. 

c. 

d. 

e. 

f. 

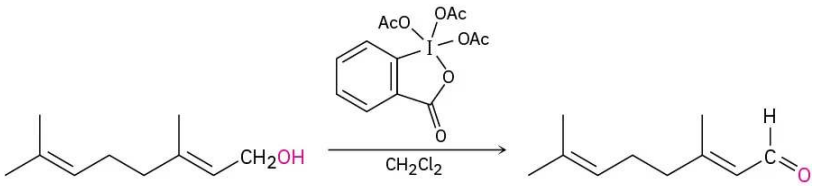
This page titled 8.2: Naming Aldehydes and Ketones is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **19.1: Naming Aldehydes and Ketones** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.3: Preparing Aldehydes and Ketones

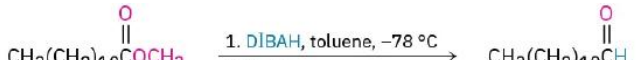
Preparing Aldehydes

Perhaps the best method of aldehyde synthesis is by oxidation of a primary alcohol, as we saw in Section 17.7. The reaction is usually carried out using the Dess–Martin periodinane reagent in dichloromethane solvent at room temperature:

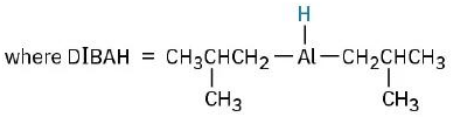


Geraniol **Geranial (84%)**

Another method of aldehyde synthesis is one that we'll mention here just briefly and then return to in **Section 21.7**. Certain carboxylic acid derivatives can be *partially* reduced to yield aldehydes. The partial reduction of an ester by diisobutylaluminum hydride (DIBAH, or DIBAL-H), for instance, is an important laboratory-scale method of aldehyde synthesis, and mechanistically related processes also occur in biological pathways. The reaction is normally carried out at –78 °C (dry-ice temperature) in toluene solution.



Methyl dodecanoate **Dodecanal (88%)**



? Exercise 8.3.1

How would you prepare pentanal from the following starting materials?

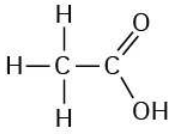
a. $CH_3CH_2CH_2CH_2CH_2OH$
b. $CH_3CH_2CH_2CH{=}CH_2$
c. $CH_3CH_2CH_2CH_2CO_2CH_3$
d. $CH_3CH_2CH_2CH{=}CH_2$

Answer

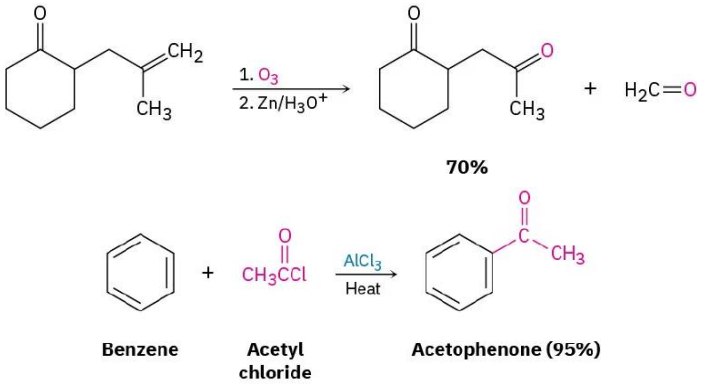
a. Dess–Martin periodinane
b. 1. O_3; 2. Zn
c. DIBAH
d. 1. BH_3, then H_2O_2, NaOH; 2. Dess–Martin periodinane

Preparing Ketones

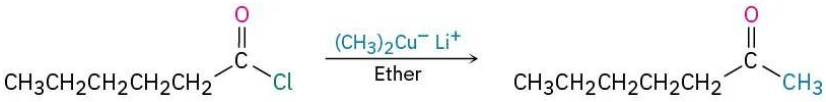
For the most part, methods of ketone synthesis are similar to those for aldehydes. Secondary alcohols are oxidized by a variety of reagents to give ketones (Section 17.7). The choice of oxidant depends on such factors as reaction scale, cost, and acid or base sensitivity of the alcohol. The Dess–Martin periodinane is a common choice although chromic acid (H_2CrO_4) was frequently used in older work.



Other methods include the ozonolysis of alkenes in which one of the unsaturated carbon atoms is disubstituted (Section 8.8) and Friedel–Crafts acylation of an aromatic ring with an acid chloride in the presence of $AlCl_3$ catalyst (Section 16.3).



In addition to those methods already discussed, ketones can also be prepared from certain carboxylic acid derivatives, just as aldehydes can. Among the most useful reactions of this sort is that between an acid chloride and a lithium diorganocopper reagent, as we saw in Section 10.7. We'll discuss this reaction in more detail in **Section 21.4**.



? Exercise 8.3.2

How would you carry out the following reactions? More than one step may be needed.

a. 3-Hexyne → 3-Hexanone
b. Benzene → m-Bromoacetophenone
c. Bromobenzene → Acetophenone
d. 1-Methylcyclohexene → 2-Methylcyclohexanone

Answer

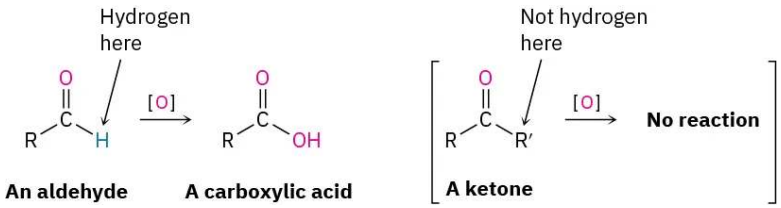
a. $HgSO_4$, H_3O^+
b. 1. CH_3COCl, $AlCl_3$; 2. Br_2, $FeBr_3$
c. 1. Mg; 2. CH_3CHO; 3. H_3O^+; 4. CrO_3
d. 1. BH_3; 2. H_2O_2, NaOH; 3. CrO_3

This page titled 8.3: Preparing Aldehydes and Ketones is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

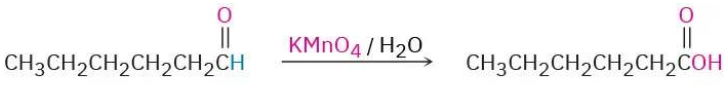
- **19.2: Preparing Aldehydes and Ketones** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.4: Oxidation of Aldehydes and Ketones

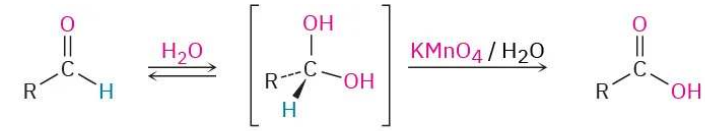
Aldehydes are easily oxidized to yield carboxylic acids, but ketones are generally inert toward oxidation. The difference is a consequence of structure: aldehydes have a –C**H**O proton that can be abstracted during oxidation, but ketones do not.



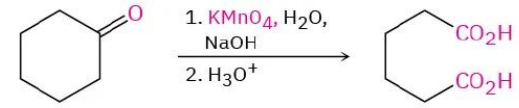
Many oxidizing agents, including alkaline $KMnO_4$ and hot HNO_3, convert aldehydes into carboxylic acids. The oxidation occurs rapidly at room temperature and generally works well.



Aldehyde oxidations occur through intermediate 1,1-diols, or *hydrates*, which are formed by a reversible nucleophilic addition of water to the carbonyl group. Even though it's formed to only a small extent at equilibrium, the hydrate reacts like any typical primary or secondary alcohol and is oxidized to a carbonyl compound (Section 17.7).



Ketones are inert to most oxidizing agents but undergo a slow cleavage reaction of the C–C bond next to the carbonyl group when treated with hot alkaline $KMnO_4$. The reaction is not often used, however, and is mentioned here only for completeness.



This page titled 8.4: Oxidation of Aldehydes and Ketones is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **19.3: Oxidation of Aldehydes and Ketones** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.5: Nucleophilic Addition Reactions of Aldehydes and Ketones

As we saw in the *Preview of Carbonyl Chemistry*, the most general reaction of aldehydes and ketones is the nucleophilic addition reaction. As shown in Figure 8.5.1, a nucleophile, :Nu⁻, approaches the carbonyl group from an angle of about 105° opposite the carbonyl oxygen and forms a bond to the electrophilic C–O carbon atom. At the same time, rehybridization of the carbonyl carbon from sp^2 to sp^3 occurs, an electron pair from the C=O bond moves toward the electronegative oxygen atom, and a tetrahedral alkoxide ion intermediate is produced. Protonation of the alkoxide by addition of acid then gives an alcohol.

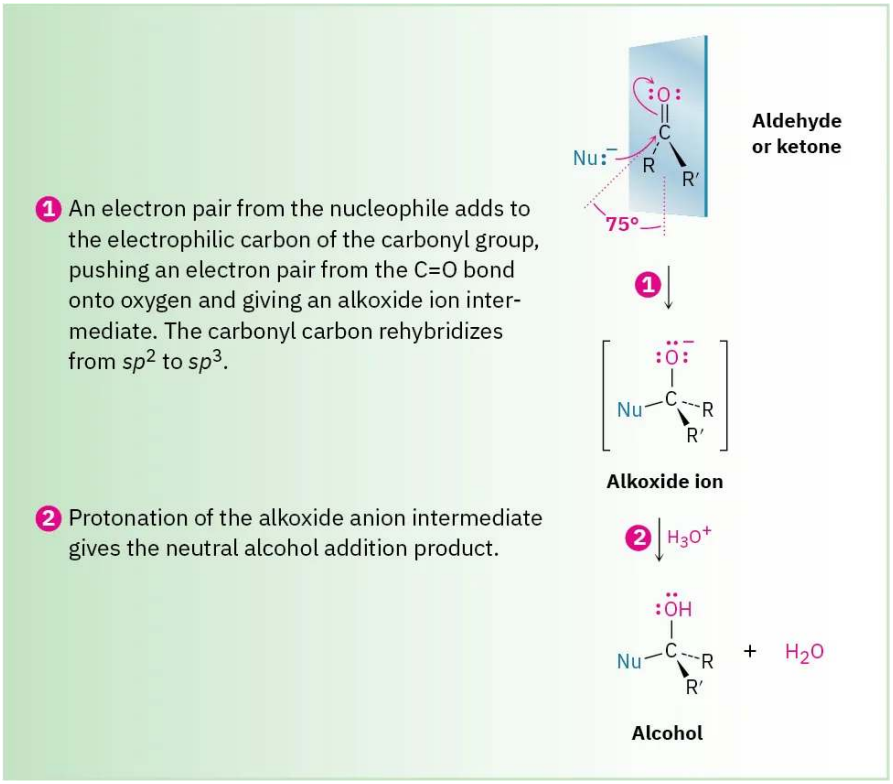


Figure 8.5.1: A nucleophilic addition reaction to an aldehyde or ketone. The nucleophile approaches the carbonyl group from an angle of approximately 75° to the plane of the sp^2 orbitals, the carbonyl carbon rehybridizes from sp^2 to sp^3, and an alkoxide ion is formed. Protonation by addition of acid then gives an alcohol./figcaption>

The nucleophile can be either negatively charged (:Nu⁻) or neutral (:Nu). If it's neutral, however, it usually carries a hydrogen atom that can subsequently be eliminated, :Nu–H. For example:

Some negatively charged nucleophiles

- $HO:^-$ (hydroxide ion)
- $H:^-$ (hydride ion)
- $R_3C:^-$ (a carbanion)
- $RO:^-$ (an alkoxide ion)
- $N\equiv C:^-$ (cyanide ion)

Some neutral nucleophiles

- HOH (water)
- ROH (an alcohol)
- H_3N: (ammonia)
- RNH_2 (an amine)

Nucleophilic additions to aldehydes and ketones have two general variations, as shown in Figure 8.5.2. In one variation, the tetrahedral intermediate is protonated by water or acid to give an alcohol as the final product. In the second variation, the carbonyl

oxygen atom is protonated and then eliminated as HO^- or H_2O to give a product with a C═ double bond.

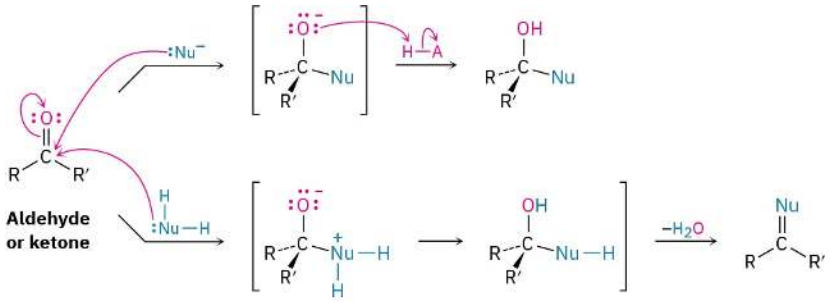


Figure 8.5.2: Two general reaction pathways following addition of a nucleophile to an aldehyde or ketone. The top pathway leads to an alcohol product; the bottom pathway leads to a product with a C═NuC═Nu double bond.

Aldehydes are generally more reactive than ketones in nucleophilic addition reactions for both steric and electronic reasons. Sterically, the presence of only one large substituent bonded to the C═OFigure 8.5.3).

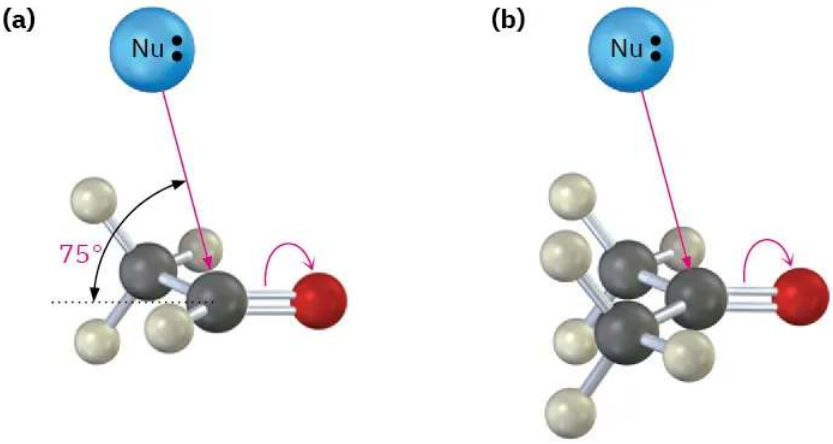
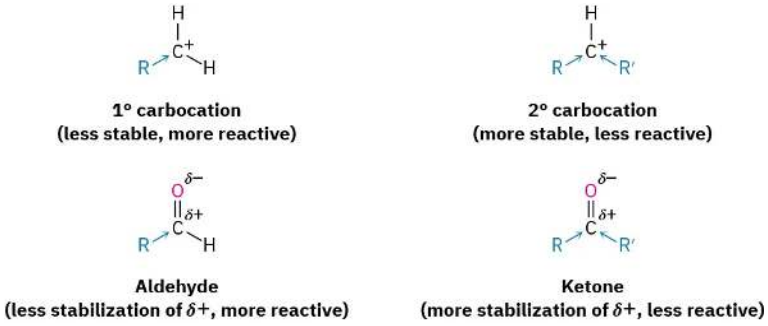
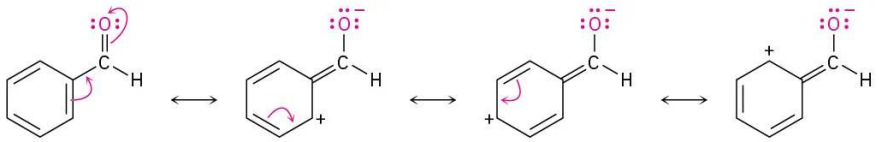


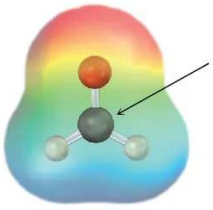
Figure 8.5.3: Steric hindrance in nucleophilic addition reactions. **(a)** Nucleophilic addition to an aldehyde is sterically less hindered because only one relatively large substituent is attached to the carbonyl-group carbon. **(b)** A ketone, however, has two large substituents and is more hindered. The approach of the nucleophile is along the C═O bond at an angle of about 75° to the plane of the carbon sp^2 orbitals.

Electronically, aldehydes are more reactive than ketones because of the greater polarization of aldehyde carbonyl groups. To see this polarity difference, recall the stability order of carbocations (Section 7.9). A primary carbocation is higher in energy and thus more reactive than a secondary carbocation since it has only one alkyl group inductively stabilizing the positive charge rather than two. In the same way, an aldehyde has only one alkyl group inductively stabilizing the partial positive charge on the carbonyl carbon rather than two, and is a bit more electrophilic, and, therefore, more reactive than a ketone.

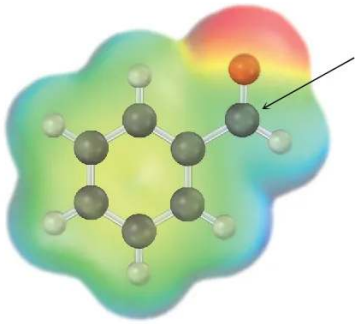


One further comparison: aromatic aldehydes, such as benzaldehyde, are less reactive in nucleophilic addition reactions than aliphatic aldehydes because the electron-donating resonance effect of the aromatic ring makes the carbonyl group less electrophilic. Comparing electrostatic potential maps of formaldehyde and benzaldehyde, for example, shows that the carbonyl carbon atom is less positive (less blue) in the aromatic aldehyde.





Formaldehyde

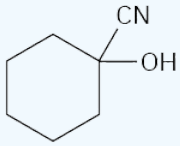


Benzaldehyde

? Exercise 8.5.1

Treatment of an aldehyde or ketone with cyanide ion ($^{-}:C\equiv N$), followed by protonation of the tetrahedral alkoxide ion intermediate, gives a cyanohydrin. Show the structure of the cyanohydrin obtained from cyclohexanone.

Answer



? Exercise 8.5.2

p-Nitrobenzaldehyde is more reactive toward nucleophilic additions than *p*-methoxybenzaldehyde. Explain.

Answer

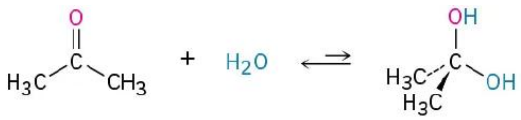
The electron-withdrawing nitro group in *p*-nitrobenzaldehyde polarizes the carbonyl group.

This page titled 8.5: Nucleophilic Addition Reactions of Aldehydes and Ketones is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **19.4: Nucleophilic Addition Reactions of Aldehydes and Ketones** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

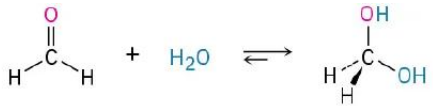
8.6: Nucleophilic Addition of Water- Hydration

Aldehydes and ketones react with water to yield 1,1-diols, or *geminal (gem)* diols. The hydration reaction is reversible, and a gem diol can eliminate water to regenerate an aldehyde or ketone.



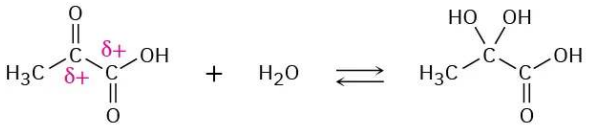
Acetone (99.9%) **Acetone hydrate (0.1%)**

The position of the equilibrium between a gem diol and an aldehyde or ketone depends on the structure of the carbonyl compound. Equilibrium generally favors the carbonyl compound for steric reasons, but the gem diol is favored for a few simple aldehydes. For example, an aqueous solution of formaldehyde consists of 99.9% gem diol and 0.1% aldehyde at equilibrium, whereas an aqueous solution of acetone consists of only about 0.1% gem diol and 99.9% ketone.

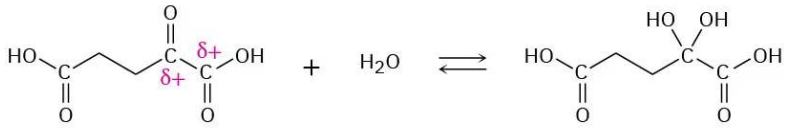


Formaldehyde (0.1%) **Formaldehyde hydrate (99.9%)**

The hydrate is also favored for α-keto carboxylic acids, which have adjacent positively charged carbons that destabilize the keto form and favor the hydrate. Such compounds occur commonly in many biological pathways. Pyruvic acid, which is 60% hydrate at equilibrium, and α-ketoglutaric acid, which is 50% hydrate, are examples.



Pyruvic acid (40%) **Pyruvic acid hydrate (60%)**



α-Ketoglutaric acid (50%) **α-Ketoglutaric acid hydrate (50%)**

The nucleophilic addition of water to an aldehyde or ketone is slow under neutral conditions but is catalyzed by both base and acid. Under basic conditions (Figure 8.6.1a), the nucleophile is negatively charged (OH^-) and uses a pair of its electrons to form a bond to the electrophilic carbon atom of the C═O group. At the same time, the C═O carbon atom rehybridizes from sp^2 to sp^3 and two electrons from the C═O π bond are pushed onto the oxygen atom, giving an alkoxide ion. Protonation of the alkoxide ion by water then yields a neutral addition product plus regenerated OH^-.

Under acidic conditions (Figure 8.6.1b), the carbonyl oxygen atom is first protonated by H_3O^+ to make the carbonyl group more strongly electrophilic. A neutral nucleophile, H_2O, then uses a pair of electrons to bond to the carbon atom of the C═O group, and two electrons from the C═O π bond move onto the oxygen atom. The positive charge on oxygen is thereby neutralized, while the nucleophile gains a positive charge. Finally, deprotonation by water gives the neutral addition product and regenerates the H_3O^+ catalyst.

Note the key difference between the base-catalyzed and acid-catalyzed reactions. The base-catalyzed reaction takes place rapidly because water is converted into hydroxide ion, a much better *nucleophile*. The acid-catalyzed reaction takes place rapidly because the carbonyl compound is converted by protonation into a much better *electrophile*.

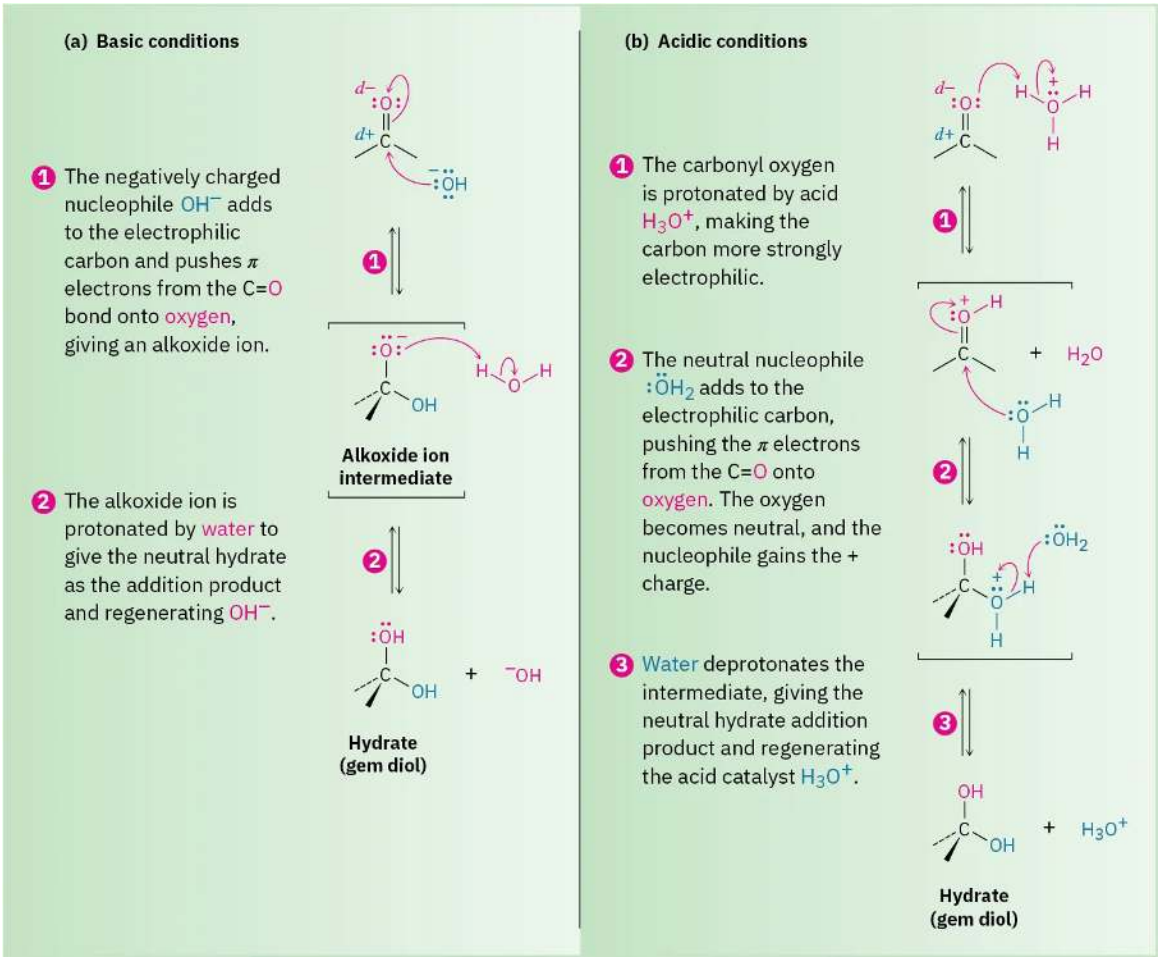
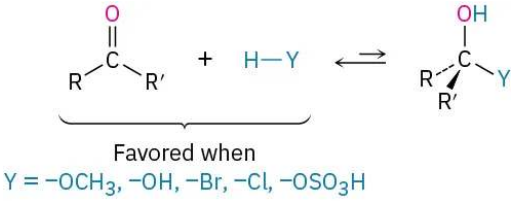


Figure 8.6.1: The mechanism for a nucleophilic addition reaction of aldehydes and ketones under both basic and acidic conditions. (a) Under basic conditions, a negatively charged nucleophile adds to the carbonyl group to give an alkoxide ion intermediate, which is subsequently protonated. (b) Under acidic conditions, protonation of the carbonyl group occurs first, followed by addition of a neutral nucleophile and subsequent deprotonation.

The hydration reaction just described is typical of what happens when an aldehyde or ketone is treated with a nucleophile of the type H–Y, where the Y atom is electronegative and can stabilize a negative charge (oxygen, halogen, or sulfur, for instance). In such reactions, the nucleophilic addition is reversible, with the equilibrium generally favoring the carbonyl reactant rather than the tetrahedral addition product. In other words, treatment of an aldehyde or ketone with CH_3OH, H_2O, HCl, HBr, or H_2SO_4 does not normally lead to a stable alcohol addition product.



? Exercise 8.6.1

When dissolved in water, trichloroacetaldehyde exists primarily as its hydrate, called chloral hydrate. Show the structure of chloral hydrate.

Answer

$CCl_3CH(OH)_2$

Exercise 8.6.2

The oxygen in water is primarily (99.8%) ^{16}O, but water enriched with the heavy isotope ^{18}O is also available. When an aldehyde or ketone is dissolved in ^{18}O-enriched water, the isotopic label becomes incorporated into the carbonyl group. Explain.

$$R_2C{=}O + H_2\mathrm{O} \rightleftharpoons R_2C{=}\mathrm{O} + H_2O$$

where O is short for ^{18}O.

Answer

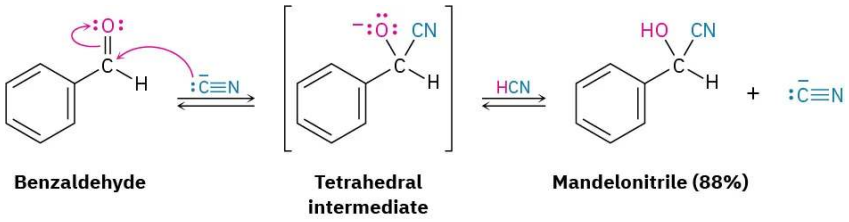
Labeled water adds reversibly to the carbonyl group.

This page titled 8.6: Nucleophilic Addition of Water- Hydration is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **19.5: Nucleophilic Addition of Water- Hydration** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

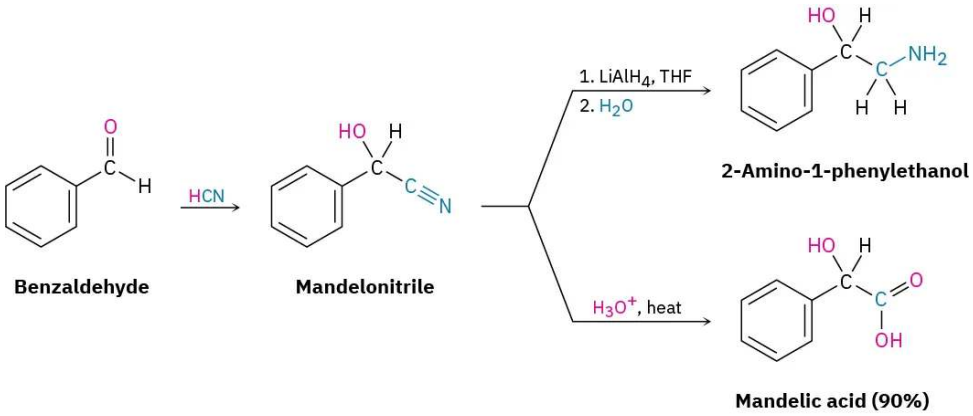
8.7: Nucleophilic Addition of HCN - Cyanohydrin Formation

Aldehydes and unhindered ketones undergo a nucleophilic addition reaction with HCN to yield cyanohydrins, $\mathrm{RCH(OH)C{\equiv}N}$. Studies carried out in the early 1900s by Arthur Lapworth showed that cyanohydrin formation is reversible and base-catalyzed. Reaction occurs slowly when pure HCN is used but rapidly when a small amount of base is added to generate the nucleophilic cyanide ion, CN^-. Addition of CN^- takes place by a typical nucleophilic addition pathway, yielding a tetrahedral intermediate that is protonated by HCN to give cyanohydrin product plus regenerated CN^-.



Cyanohydrin formation is somewhat unusual because it is one of the few examples of the addition of a protic acid (H–Y) to a carbonyl group. As noted in the previous section, protic acids such as H_2O, HBr, HCl, and H_2SO_4 don't normally yield carbonyl addition products because the equilibrium constants are unfavorable. With HCN, however, equilibrium favors the cyanohydrin adduct.

Cyanohydrin formation is useful because of the further chemistry that can be carried out on the product. For example, a nitrile (\ce{R–C≡N}\) can be reduced with $LiAlH_4$ to yield a primary amine (RCH_2NH_2) and can be hydrolyzed by hot aqueous acid to yield a carboxylic acid. Thus, cyanohydrin formation provides a method for transforming an aldehyde or ketone into a different functional group.



? Exercise 8.7.1

Cyclohexanone forms a cyanohydrin in good yield but 2,2,6-trimethylcyclohexanone does not. Explain.

Answer

The equilibrium is unfavorable for sterically hindered ketones.

This page titled 8.7: Nucleophilic Addition of HCN - Cyanohydrin Formation is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **19.6: Nucleophilic Addition of HCN - Cyanohydrin Formation** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

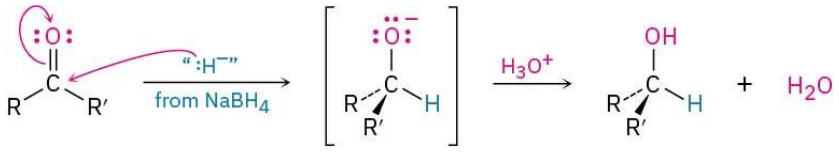
8.8: Nucleophilic Addition of Hydride and Grignard Reagents- Alcohol Formation

Addition of Hydride Reagents: Reduction

We saw in Section 17.4 that the most common method for preparing alcohols, both in the laboratory and in living organisms, is by the reduction of carbonyl compounds. Aldehydes are reduced with sodium borohydride ($NaBH_4$) to give primary alcohols, and ketones are reduced similarly to give secondary alcohols.

Aldehyde **1° Alcohol** **Ketone** **2° Alcohol**

Carbonyl reduction occurs by a typical nucleophilic addition mechanism under basic conditions, as shown earlier in Figure 19.5.1. Although the details of carbonyl-group reductions are complex, $LiAlH_4$ and $NaBH_4$ act as if they were donors of hydride ion nucleophile, $:H^-$, and the initially formed alkoxide ion intermediate is then protonated by addition of aqueous acid. The reaction is effectively irreversible because the reverse process would require expulsion of a very poor leaving group.



Addition of Grignard Reagents, RMgX

Just as aldehydes and ketones undergo nucleophilic addition with hydride ion to give alcohols, they undergo a similar addition with Grignard reagent nucleophiles, $R:^- {}^+MgX$. Aldehydes give secondary alcohols when reacting with Grignard reagents in an ether solution, and ketones give tertiary alcohols.

Aldehyde **2° Alcohol** **Ketone** **3° Alcohol**

As shown in Figure 8.8.1, a Grignard reaction begins with an acid–base complexation of Mg^{2+} to the carbonyl oxygen atom of the aldehyde or ketone, thereby making the carbonyl group a better electrophile. Nucleophilic addition of $R:^-$ then produces a tetrahedral magnesium alkoxide intermediate, and protonation by addition of water or dilute aqueous acid in a separate step yields the neutral alcohol. Like reduction, Grignard additions are effectively irreversible because a carbanion is too poor a leaving group to be expelled in a reversal step.

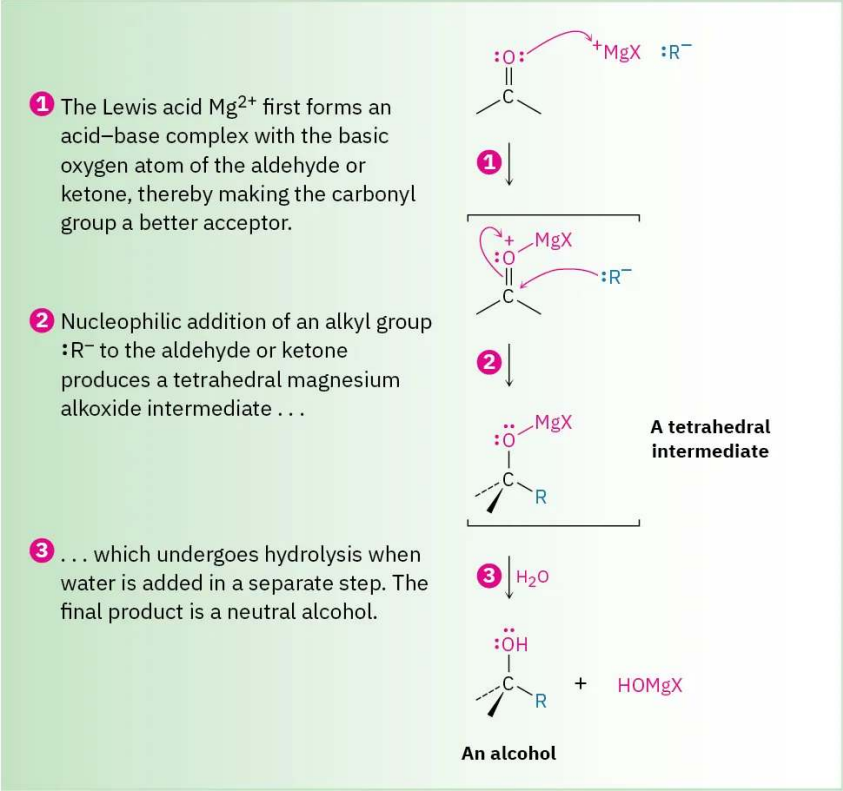


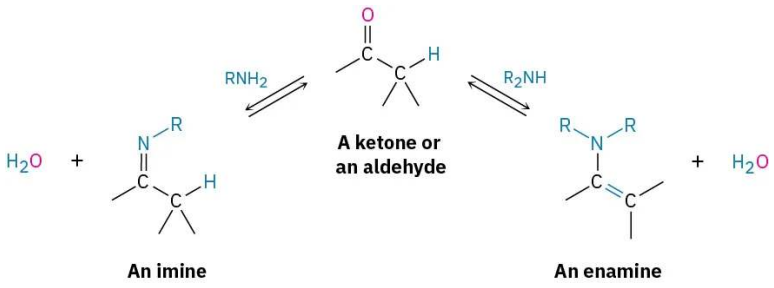
Figure 8.8.1: Mechanism of the Grignard reaction. Complexation of the carbonyl oxygen with the Lewis acid Mg^{2+} and subsequent nucleophilic addition of a carbanion to an aldehyde or ketone is followed by protonation of the alkoxide intermediate to yield an alcohol.

This page titled 8.8: Nucleophilic Addition of Hydride and Grignard Reagents- Alcohol Formation is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

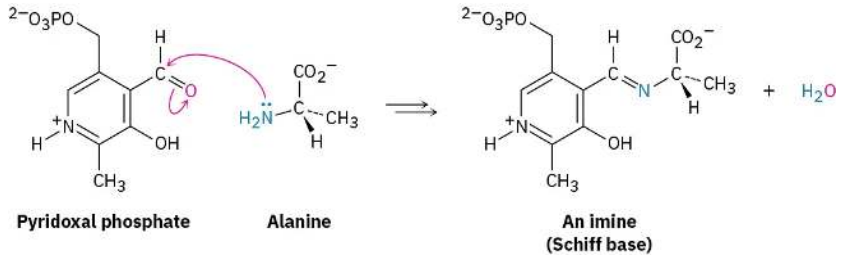
- **19.7: Nucleophilic Addition of Hydride and Grignard Reagents- Alcohol Formation** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.9: Nucleophilic Addition of Amines- Imine and Enamine Formation

Primary amines, RNH_2, add to aldehydes and ketones to yield **imines,** $R_2C{=}NR$. Secondary amines, R_2NH, add similarly to yield **enamines**, $R_2N{-}CR{=}CR_2$ (*ene* + *amine* = unsaturated amine).



Imines are particularly common as intermediates in biological pathways, where they are often called **Schiff bases**. The amino acid alanine, for instance, is metabolized in the body by reaction with the aldehyde pyridoxal phosphate (PLP), a derivative of vitamin B_6, to yield a Schiff base that is further degraded.



Imine formation and enamine formation seem different because one leads to a product with a $C{=}N$ bond and the other leads to a product with a $C{=}C$ bond. Actually, though, the reactions are quite similar. Both are typical examples of nucleophilic addition reactions in which water is eliminated from the initially formed tetrahedral intermediate and a new $C{=}NuC{=}Nu$ double bond is formed.

Imines are formed in a reversible, acid-catalyzed process (Figure 8.9.1) that begins with nucleophilic addition of the primary amine to the carbonyl group, followed by transfer of a proton from nitrogen to oxygen to yield a neutral amino alcohol, or carbinolamine. Protonation of the carbinolamine oxygen by an acid catalyst then converts the –OH into a better leaving group ($–OH_2^+$), and E1-like loss of water produces an iminium ion. Loss of a proton from nitrogen gives the final product and regenerates the acid catalyst.

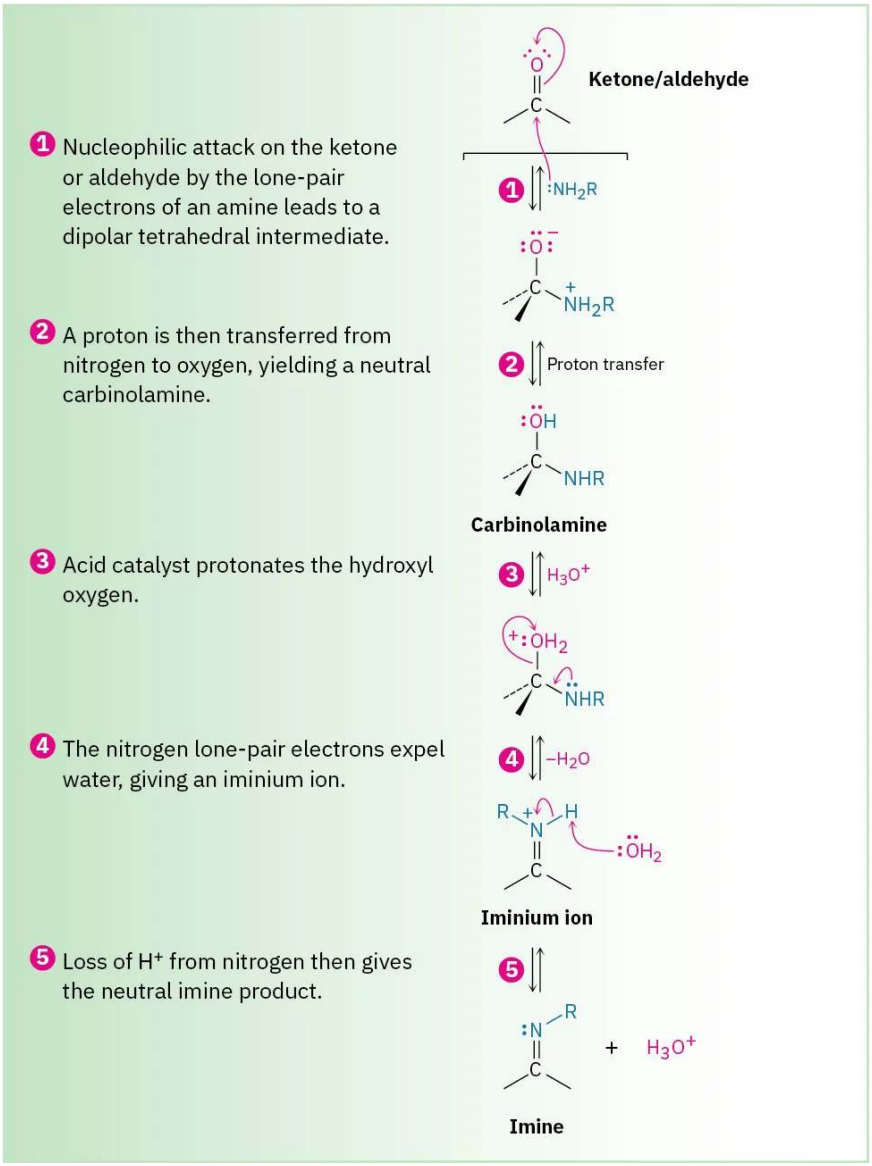
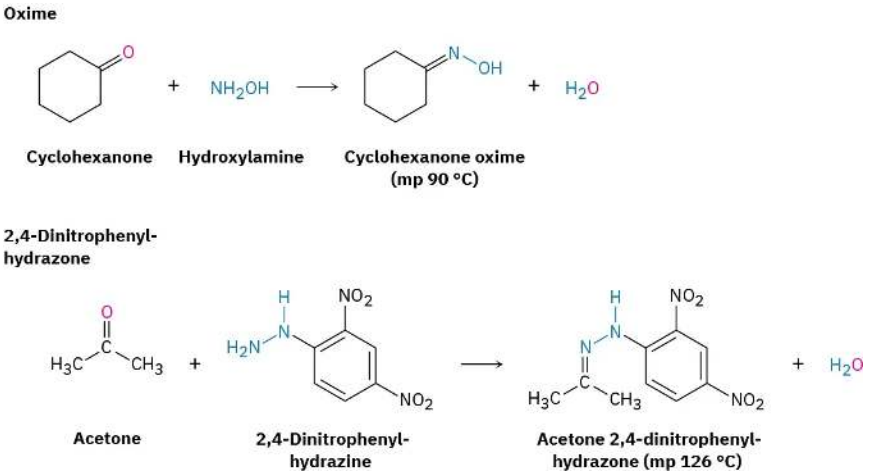


Figure 8.9.1: Mechanism of imine formation by reaction of an aldehyde or ketone with a primary amine. The key step is the initial nucleophilic addition to yield a carbinolamine intermediate, which then loses water to give the imine.

Imine formation with such reagents as hydroxylamine and 2,4-dinitrophenylhydrazine is sometimes useful because the products of these reactions—*oximes* and *2,4-dinitrophenylhydrazones (2,4-DNPs)*, respectively—are often crystalline and easy to handle. Such crystalline derivatives are occasionally prepared as a means of purifying and characterizing liquid ketones or aldehydes.



Reaction of an aldehyde or ketone with a secondary amine, R_2NH, rather than a primary amine yields an enamine. As shown in Figure 8.9.2, the process is identical to imine formation up to the iminium ion stage, but at this point there is no proton on nitrogen that can be lost to form a neutral imine product. Instead, a proton is lost from the *neighboring* carbon (the *α* carbon), yielding an enamine.

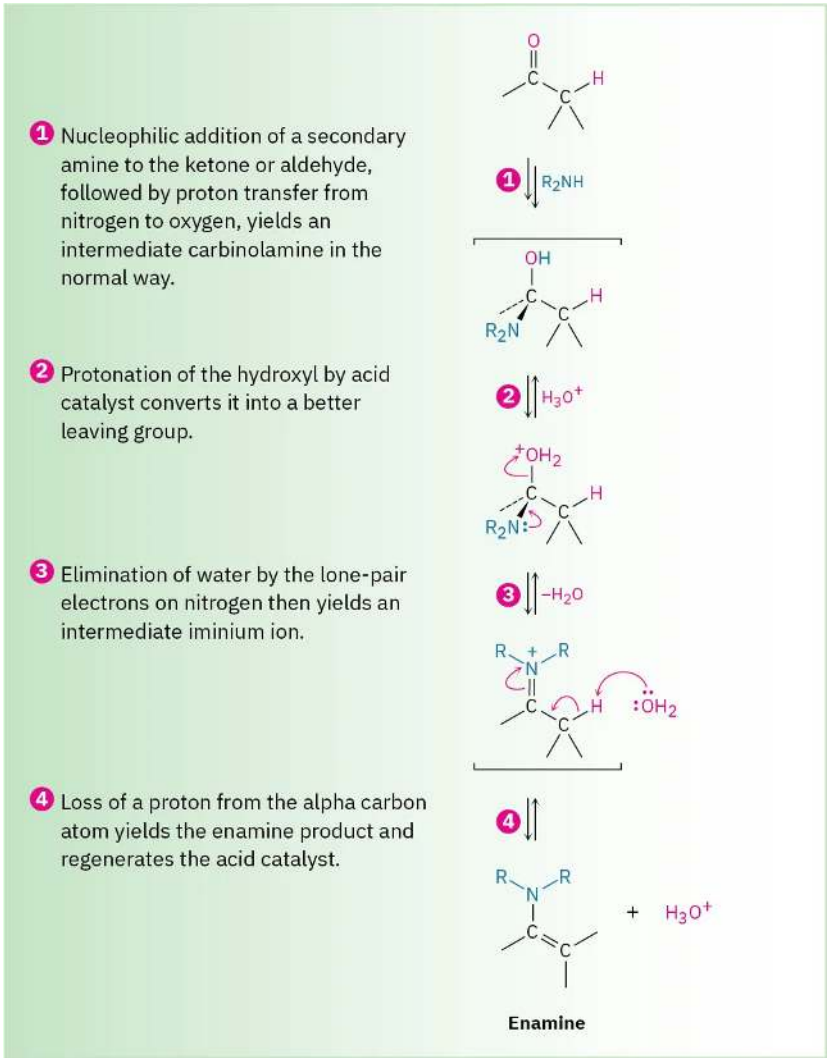


Figure 8.9.2: Mechanism for enamine formation by reaction of an aldehyde or ketone with a secondary amine, R_2NH. The iminium ion intermediate formed in step 3 has no hydrogen attached to N and so must lose H^+ from the carbon two atoms away.

Imine and enamine formation are slow at both high pH and low pH but reach a maximum rate at a weakly acidic pH around 4 to 5. For example, the profile of pH versus rate shown in Figure 8.9.3 for the reaction between acetone and hydroxylamine, NH_2OH, indicates that the maximum reaction rate occurs at pH 4.5.

We can explain the observed pH dependence of imine formation by looking at the individual steps in the mechanism. As indicated in Figure 8.9.2, an acid catalyst is required in step 3 to protonate the intermediate carbinolamine, thereby converting the –OH into a better leaving group. Thus, reaction will be slow if not enough acid is present (that is, at high pH). On the other hand, if too much acid is present (low pH), the basic amine nucleophile is completely protonated, so the initial nucleophilic addition step can't occur.

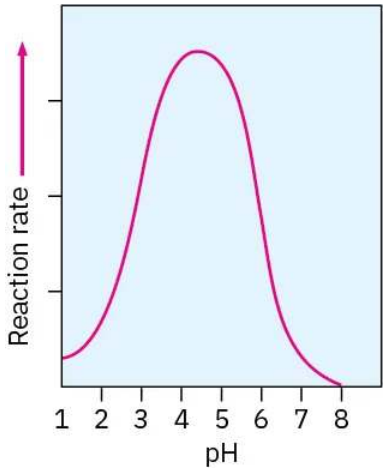


Figure 8.9.3: Dependence on pH of the rate of reaction between acetone and hydroxylamine: ($(CH_3)_2C{=}O^+NH_2OH \longrightarrow (CH_3)_2C{=}NOH^+H_2O$.

Evidently, a pH of 4.5 represents a compromise between the need for *some* acid to catalyze the rate-limiting dehydration step but *not too much* acid so as to avoid complete protonation of the amine. Each nucleophilic addition reaction has its own requirements, and conditions must be optimized to obtain maximum reaction rates.

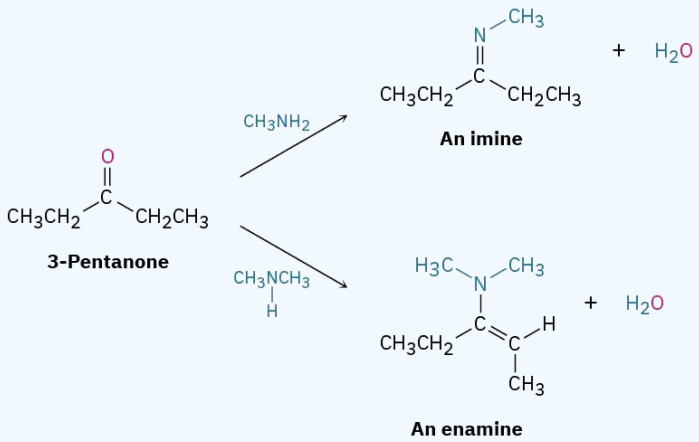
Worked Example 8.9.1: Predicting the Product of Reaction between a Ketone and an Amine

Show the products you would obtain by acid-catalyzed reaction of 3-pentanone with methylamine, CH_3NH_2, and with dimethylamine, $(CH_3)_2NH$.

Strategy

An aldehyde or ketone reacts with a primary amine, RNH_2, to yield an imine, in which the carbonyl oxygen atom has been replaced by the =N–R group of the amine. Reaction of the same aldehyde or ketone with a secondary amine, R_2NH, yields an enamine, in which the oxygen atom has been replaced by the $–NR_2$ group of the amine and the double bond has moved to a position between the former carbonyl carbon and the neighboring carbon.

Solution

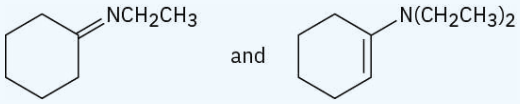


https://chem.libretexts.org/@go/page/564247

Exercise 8.9.1

Show the products you would obtain by acid-catalyzed reaction of cyclohexanone with ethylamine, $CH_3CH_2NH_2$, and with diethylamine, $(CH_3CH_2)_2NH$.

Answer



Exercise 8.9.2

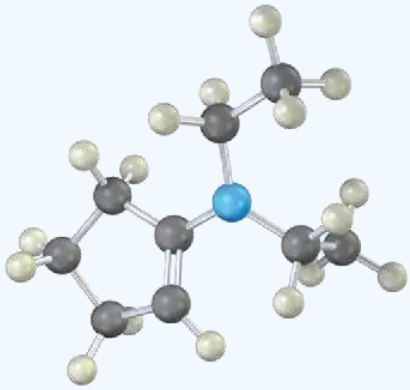
Imine formation is reversible. Show all the steps involved in the acid-catalyzed reaction of an imine with water (hydrolysis) to yield an aldehyde or ketone plus primary amine.

Answer

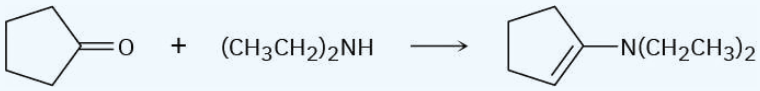
The steps are the exact reverse of the forward reaction shown in Figure 19.7.

Exercise 8.9.3

Draw the following molecule as a skeletal structure, and show how it can be prepared from a ketone and an amine.



Answer

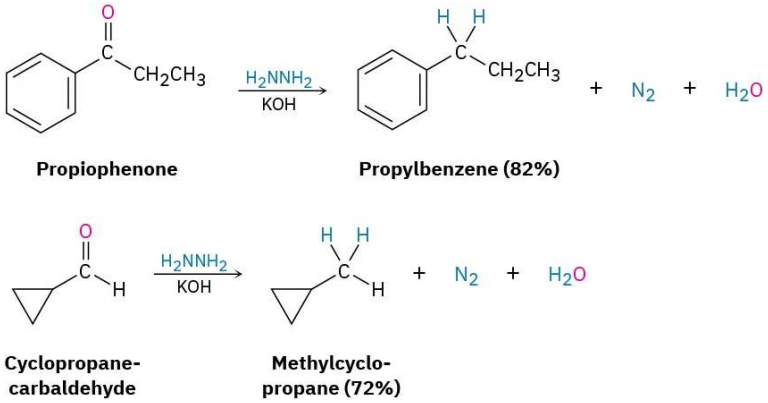


This page titled 8.9: Nucleophilic Addition of Amines- Imine and Enamine Formation is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **19.8: Nucleophilic Addition of Amines- Imine and Enamine Formation** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.10: Nucleophilic Addition of Hydrazine - The Wolff-Kishner Reaction

A useful variant of the imine-forming reaction just discussed involves the treatment of an aldehyde or ketone with hydrazine, $H_2N–NH_2$, in the presence of KOH. Called the **Wolff–Kishner reaction**, the process is a useful and general method for converting an aldehyde or ketone into an alkane, $R_2C{=}O \longrightarrow R_2CH_2$.



As shown in Figure 8.10.1, the Wolff–Kishner reaction involves formation of a *hydrazone* intermediate, \(\ce{R2C=N–NH2}\), followed by base-catalyzed double-bond migration, loss of N_2 gas to give a carbanion, and protonation to give the alkane product. The double-bond migration takes place when a base removes one of the weakly acidic NH protons in step 2 to generate a hydrazone anion, which has an allylic resonance structure that places the double bond between nitrogens and the negative charge on carbon. Reprotonation then occurs on carbon to generate the double-bond rearrangement product. The next step—loss of nitrogen and formation of an alkyl anion—is driven by the large thermodynamic stability of the N_2 molecule.

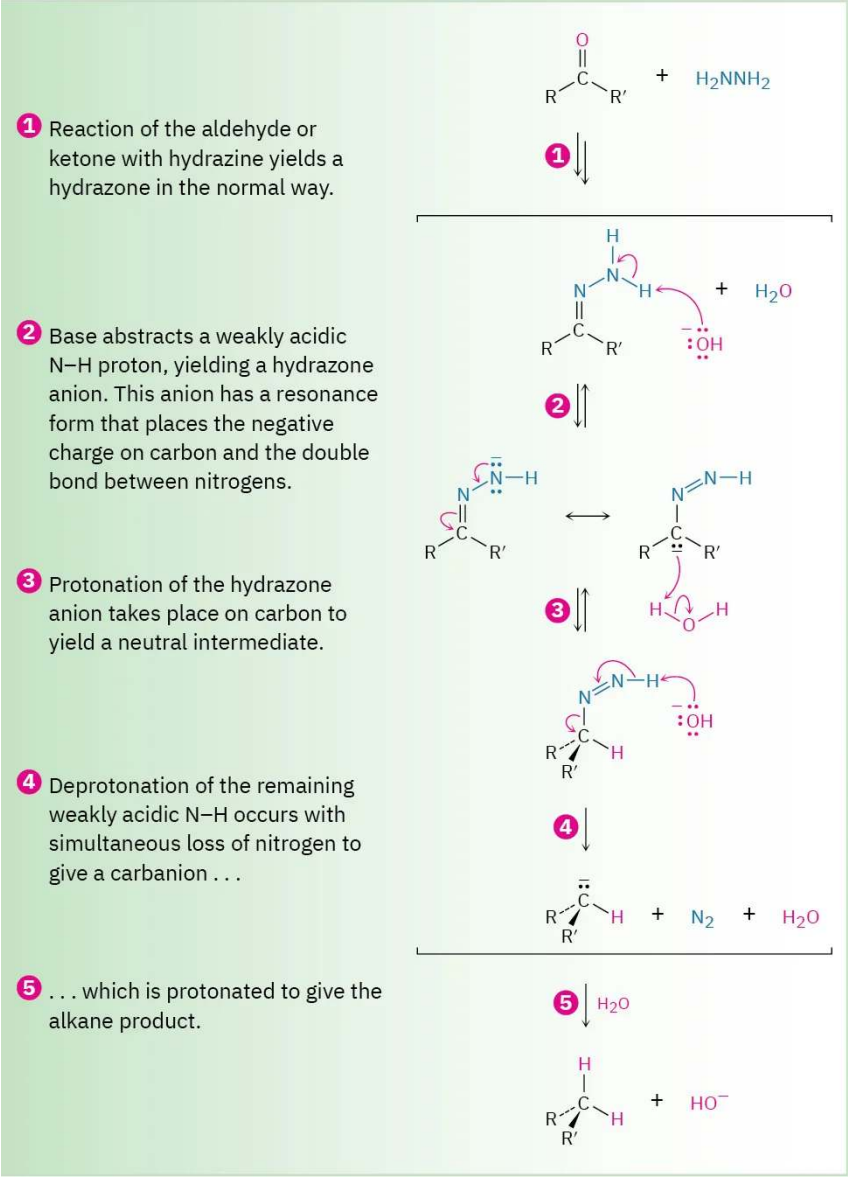


Figure 8.10.1: Mechanism for the Wolff–Kishner reduction of an aldehyde or ketone to yield an alkane.

Note that the Wolff–Kishner reduction accomplishes the same overall transformation as the catalytic hydrogenation of an acylbenzene to yield an alkylbenzene (Section 16.10). The Wolff–Kishner reduction is more general and more useful than catalytic hydrogenation, however, because it works well with both alkyl and aryl ketones.

? Exercise 8.10.1

Show how you could prepare the following compounds from 4-methyl-3-penten-2-one, $(CH_3)_2C{=}CHCOCH_3$.

a. $CH_3CHCH_2CCH_3$ (with CH_3 and O)

b. $CH_3C{=}CHCH_2CH_3$ (with CH_3)

c. $CH_3CHCH_2CH_2CH_3$ (with CH_3)

Answer

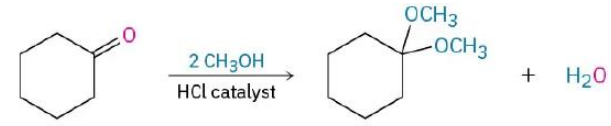
a. H_2/Pd
b. N_2H_4, KOH
c. 1. H_2/Pd; 2. N_2H_4, KOH

This page titled 8.10: Nucleophilic Addition of Hydrazine - The Wolff-Kishner Reaction is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **19.9: Nucleophilic Addition of Hydrazine - The Wolff-Kishner Reaction** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

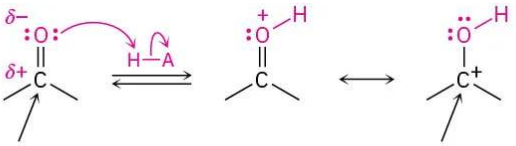
8.11: Nucleophilic Addition of Alcohols - Acetal Formation

Aldehydes and ketones react reversibly with 2 equivalents of an alcohol in the presence of an acid catalyst to yield **acetals**, $R_2C(OR')_2$, which are often called **ketals** if derived from a ketone. Cyclohexanone, for instance, reacts with methanol in the presence of HCl to give the corresponding dimethyl acetal.



Cyclohexanone **Cyclohexanone dimethyl acetal**

Acetal formation is similar to the hydration reaction discussed in Section 19.5. Like water, alcohols are weak nucleophiles that add to aldehydes and ketones slowly under neutral conditions. Under acidic conditions, however, the reactivity of the carbonyl group is increased by protonation, so addition of an alcohol occurs rapidly.



A neutral carbonyl group is moderately electrophilic because of the polarity of the C–O bond.

A protonated carbonyl group is strongly electrophilic because of the positive charge on carbon.

As shown in Figure 8.11.1, nucleophilic addition of an alcohol to the carbonyl group initially yields a hydroxy ether called a **hemiacetal**, analogous to the gem diol formed by addition of water. Hemiacetals are formed reversibly, with equilibrium normally favoring the carbonyl compound. In the presence of acid, however, a further reaction occurs. Protonation of the –OH group, followed by an E1-like loss of water, leads to an oxonium ion, R2C═O+RR2C═O+R, which undergoes a second nucleophilic addition of alcohol to yield the protonated acetal. Loss of a proton completes the reaction.

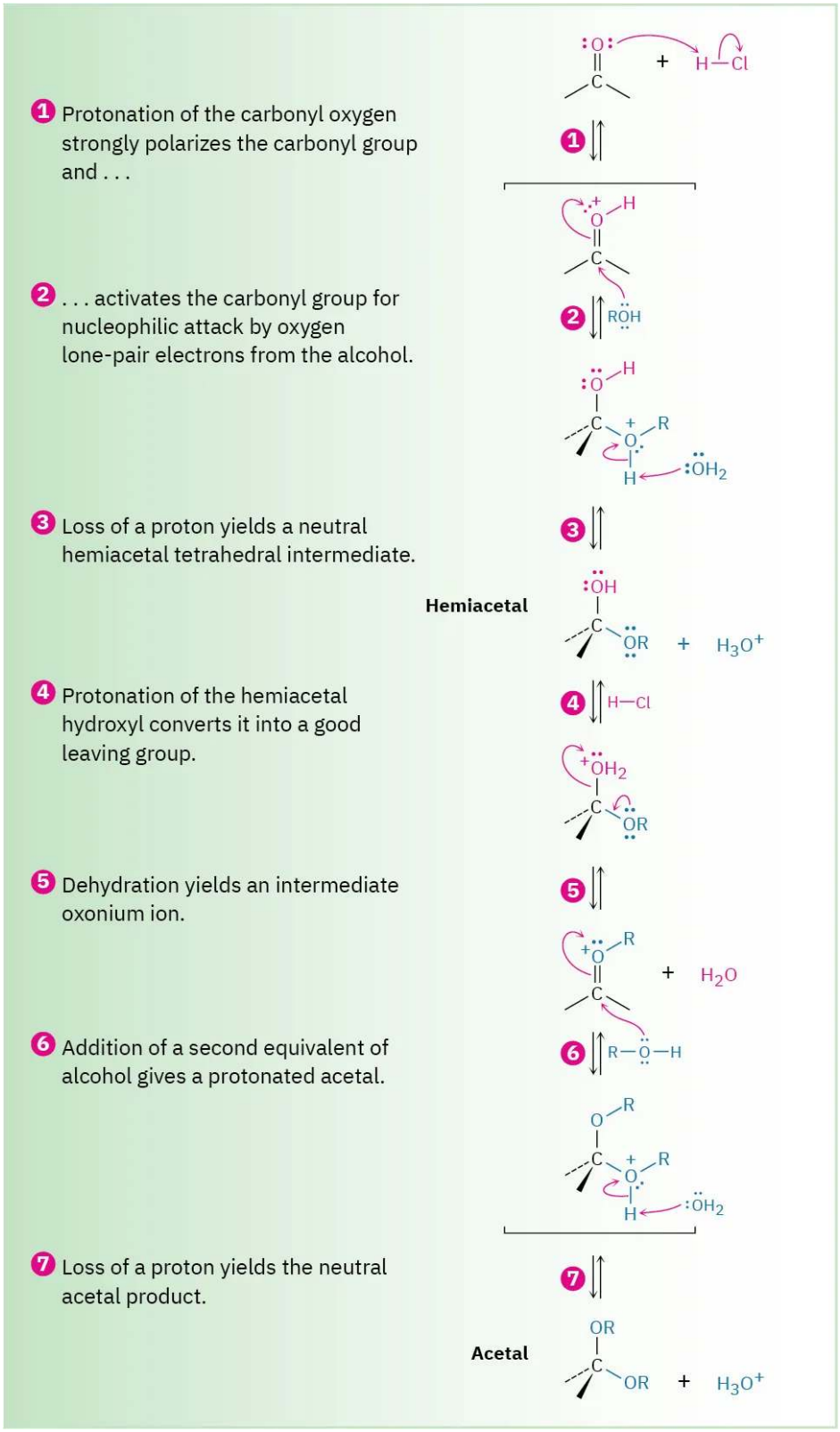


Figure 8.11.1: Mechanism of acid-catalyzed acetal formation by reaction of an aldehyde or ketone with an alcohol.

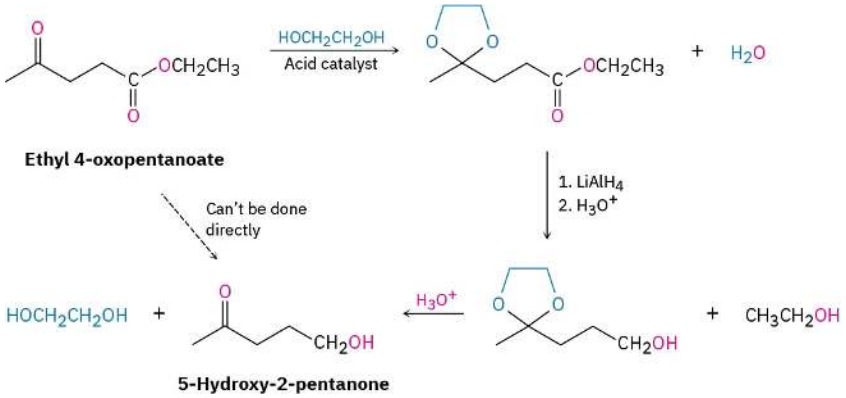
Because all the steps in acetal formation are reversible, the reaction can be driven either forward (from carbonyl compound to acetal) or backward (from acetal to carbonyl compound), depending on the conditions. The forward reaction is favored by conditions that remove water from the medium and thus drive the equilibrium to the right. In practice, this is often done by

distilling off water as it forms. The reverse reaction is favored by treating the acetal with a large excess of aqueous acid to drive the equilibrium to the left.

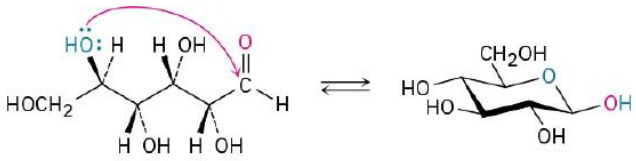
Acetals are useful because they can act as protecting groups for aldehydes and ketones in the same way that trimethylsilyl ethers act as protecting groups for alcohols (Section 17.8). As we saw previously, it sometimes happens that one functional group interferes with intended chemistry elsewhere in a complex molecule. For example, if we wanted to reduce only the ester group of ethyl 4-oxopentanoate, the ketone would interfere. Treatment of the starting keto ester with $LiAlH_4$ would reduce both the keto group and the ester group to give a diol product.

Ethyl 4-oxopentanoate **5-Hydroxy-2-pentanone**

By protecting the keto group as an acetal, however, the problem can be circumvented. Like other ethers, acetals are unreactive to bases, hydride reducing agents, Grignard reagents, and catalytic hydrogenation conditions, but they are cleaved by acid. Thus, we can accomplish the selective reduction of the ester group in ethyl 4-oxopentanoate by first converting the keto group to an acetal, then reducing the ester with $LiAlH_4$, and then removing the acetal by treatment with aqueous acid. (In practice, it's often convenient to use 1 equivalent of a diol such as ethylene glycol as the alcohol to form a *cyclic* acetal. The mechanism of cyclic acetal formation using 1 equivalent of ethylene glycol is exactly the same as that using 2 equivalents of methanol or other monoalcohols.)



Acetal and hemiacetal groups are particularly common in carbohydrate chemistry. Glucose, for instance, is a polyhydroxy aldehyde that undergoes an internal nucleophilic addition reaction and exists primarily as a cyclic hemiacetal.



Glucose—open chain **Glucose—cyclic hemiacetal**

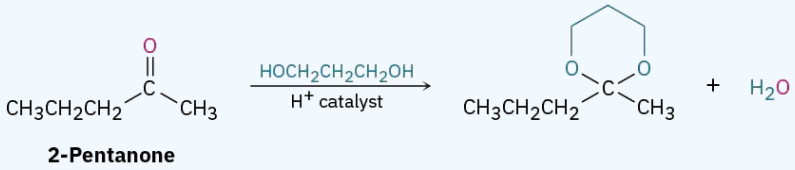
✔ Worked Example 8.11.1: Predicting the Product of Reaction between a Ketone and an Alcohol

Show the structure of the acetal you would obtain by acid-catalyzed reaction of 2-pentanone with 1,3-propanediol.

Strategy

Acid-catalyzed reaction of an aldehyde or ketone with 2 equivalents of a monoalcohol or 1 equivalent of a diol yields an acetal, in which the carbonyl oxygen atom is replaced by two –OR groups from the alcohol.

Solution



2-Pentanone

Exercise 8.11.1

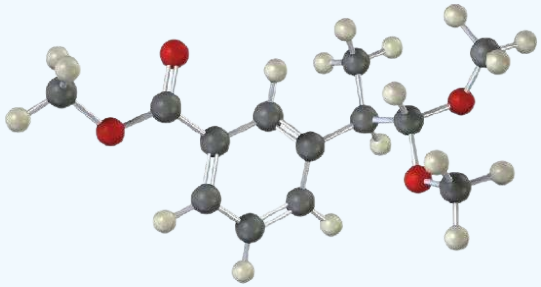
Show all the steps in the acid-catalyzed formation of a cyclic acetal from ethylene glycol and an aldehyde or ketone.

Answer

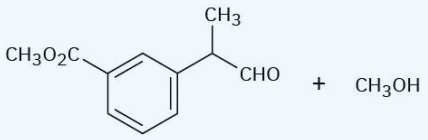
The mechanism is identical to that between a ketone and 2 equivalents of a monoalcohol, shown in Figure 8.11.1.

Exercise 8.11.2

Identify the carbonyl compound and the alcohol that were used to prepare the following acetal:



Answer



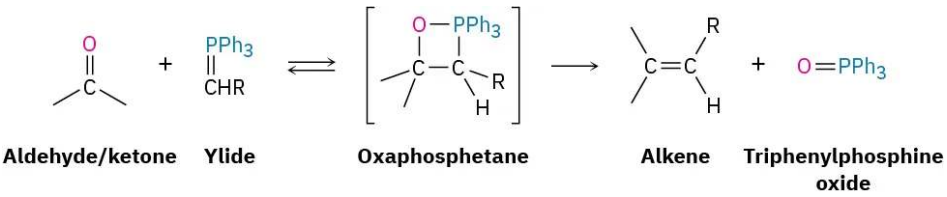
This page titled 8.11: Nucleophilic Addition of Alcohols - Acetal Formation is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **19.10: Nucleophilic Addition of Alcohols - Acetal Formation** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

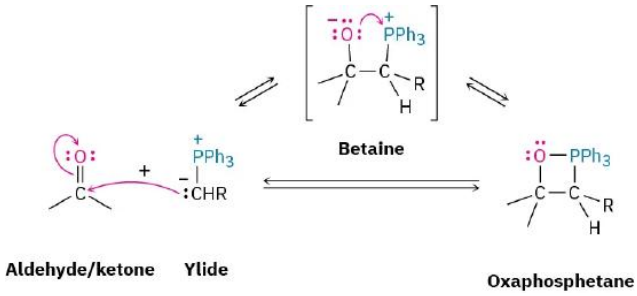
8.12: Nucleophilic Addition of Phosphorus Ylides- The Wittig Reaction

Aldehydes and ketones are converted into alkenes by means of a nucleophilic addition called the **Wittig reaction**, after the German chemist Georg Wittig who won the 1979 Nobel Prize in Chemistry. The reaction has no direct biological counterpart but is important both because of its wide use in drug manufacture and because of its mechanistic similarity to reactions of the coenzyme thiamin diphosphate, which we'll see in Section 29.6.

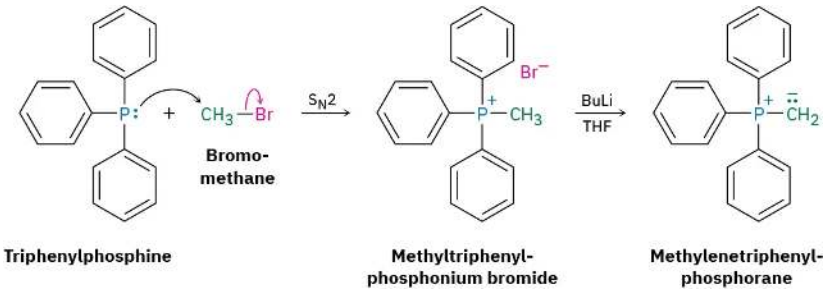
In the Wittig reaction, a triphenylphosphorus **ylide**, $R_2\overline{C} - \overset{+}{P}Ph_3$ also called a **phosphorane** and sometimes written in the resonance form \(\ce{R2C=P(Ph)}\), adds to an aldehyde or ketone to yield a four-membered cyclic intermediate called an *oxaphosphetane*. The oxaphosphetane is not isolated, but instead spontaneously decomposes to give an alkene plus triphenylphosphine oxide, $O{=}PPh_3$. In effect, the oxygen atom of the aldehyde or ketone and the \(\ce{R2C=}\) bonded to phosphorus exchange places. (An **ylide**—pronounced **ill**-id—is a neutral, dipolar compound with adjacent positive and negative charges.)



The initial addition takes place by different pathways depending on the structure of the reactants and the exact experimental conditions. One pathway involves a one-step cycloaddition process analogous to the Diels–Alder cycloaddition reaction (Section 14.4). The other pathway involves a nucleophilic addition reaction to give a dipolar intermediate called a *betaine* (**bay**-ta-een), which undergoes ring closure.

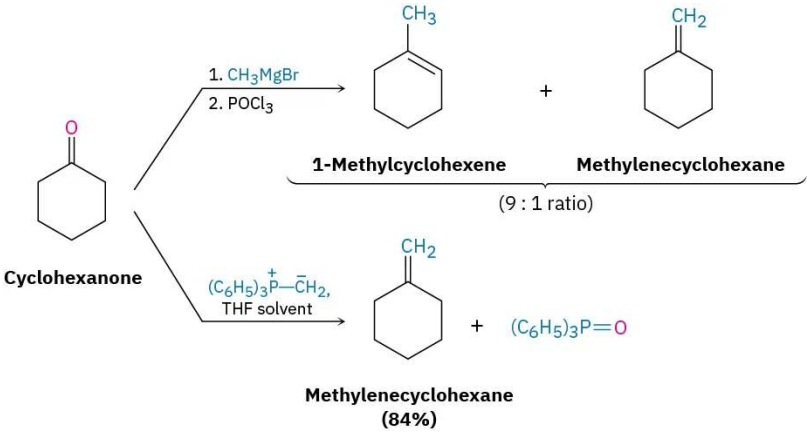


The phosphorus ylides necessary for Wittig reaction are easily prepared by S_N2 reaction of primary (and some secondary) alkyl halides with triphenylphosphine, $(Ph)_3P$, followed by treatment with base. Triphenylphosphine is a good nucleophile in S_N2 reactions, and yields of the resultant alkyltriphenylphosphonium salts are high. Because of the positive charge on phosphorus, the hydrogen on the neighboring carbon is weakly acidic and can be removed by a strong base such as butyllithium (BuLi) to generate the neutral ylide. For example:

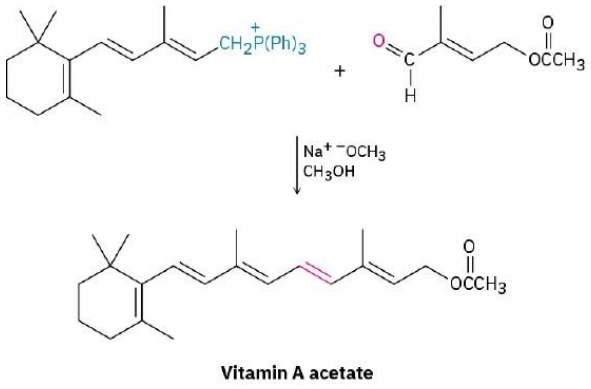


The Wittig reaction is extremely general, and a great many monosubstituted, disubstituted, and trisubstituted alkenes can be prepared from the appropriate combination of phosphorane and aldehyde or ketone. Tetrasubstituted alkenes, however, can't be prepared this way because of steric hindrance.

The real value of the Wittig reaction is that it yields a pure alkene of predictable structure. The C=C bond in the product is always exactly where the C=O group was in the reactant, and no alkene isomers (except *E*,*Z* isomers) are formed. For example, Wittig reaction of cyclohexanone with methylenetriphenylphosphorane yields only the single alkene product methylenecyclohexane. By contrast, addition of methylmagnesium bromide to cyclohexanone, followed by dehydration with $POCl_3$, yields a roughly 9 : 1 mixture of two alkenes.



Wittig reactions are used commercially in the synthesis of numerous pharmaceutical products. For example, the German chemical company BASF prepares vitamin A by using a Wittig reaction between a 15-carbon ylide and a 5-carbon aldehyde.



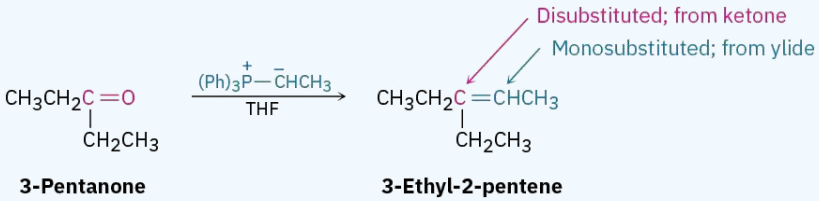
Worked Example 8.12.1: Synthesizing an Alkene Using a Wittig Reaction

What carbonyl compound and what phosphorus ylide might you use to prepare 3-ethyl-2-pentene?

Strategy

An aldehyde or ketone reacts with a phosphorus ylide to yield an alkene in which the oxygen atom of the carbonyl reactant is replaced by the $=CR_2$ of the ylide. Preparation of the phosphorus ylide itself usually involves S_N2 reaction of a primary alkyl halide with triphenylphosphine, so the ylide is typically primary, $RCH=P(Ph)_3$. This means that the disubstituted alkene carbon in the product comes from the carbonyl reactant, while the monosubstituted alkene carbon comes from the ylide.

Solution



https://chem.libretexts.org/@go/page/564250

Exercise 8.12.1

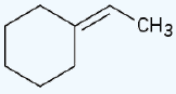
Add exercises text here.

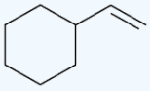
Answer

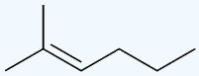
Add texts here. Do not delete this text first.

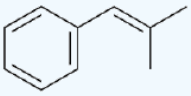
Exercise 8.12.2

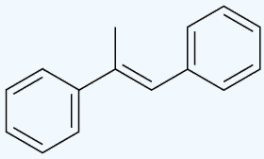
What carbonyl compound and what phosphorus ylide might you use to prepare each of the following compounds?

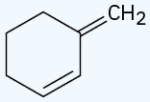
a. 

b. 

c. 

d. 

e. 

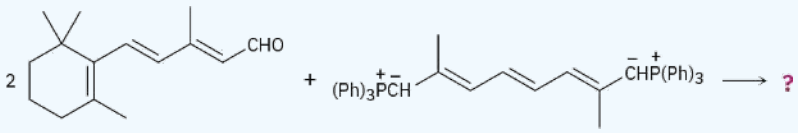
f. 

Answer

a. Cyclohexanone + (Ph)3P = CHCH3
b. Cyclohexanecarbaldehyde + (Ph)3P = CH2 (
c. Acetone + (Ph)3P = CHCH2CH2CH3
d. Acetone + (Ph)3P = CHPh
e. PhCOCH3 + (Ph)3P = CHPh
f. 2-Cyclohexenone + (Ph)3P = CH2

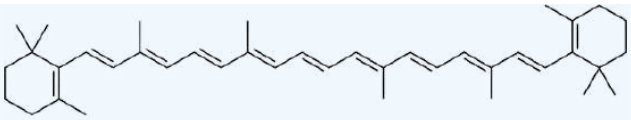
Exercise 8.12.2

β-Carotene, a yellow food-coloring agent and dietary source of vitamin A can be prepared by a *double* Wittig reaction between 2 equivalents of *β*-ionylideneacetaldehyde and a *diylide*. Show the structure of the *β*-carotene product.



β-Ionylideneacetaldehyde A diylide

Answer



***β*-Carotene**

This page titled 8.12: Nucleophilic Addition of Phosphorus Ylides- The Wittig Reaction is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **19.11: Nucleophilic Addition of Phosphorus Ylides- The Wittig Reaction** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.13: Biological Reductions

As a general rule, nucleophilic addition reactions are characteristic only of aldehydes and ketones, not of carboxylic acid derivatives. The reason for the difference is structural. As discussed previously and shown in Figure 8.13.1, the tetrahedral intermediate produced by addition of a nucleophile to a carboxylic acid derivative can eliminate a leaving group, leading to a net nucleophilic acyl substitution reaction. The tetrahedral intermediate produced by addition of a nucleophile to an aldehyde or ketone, however, has only alkyl or hydrogen substituents and thus can't usually expel a leaving group. One exception to this rule is the **Cannizzaro reaction**, discovered in 1853.

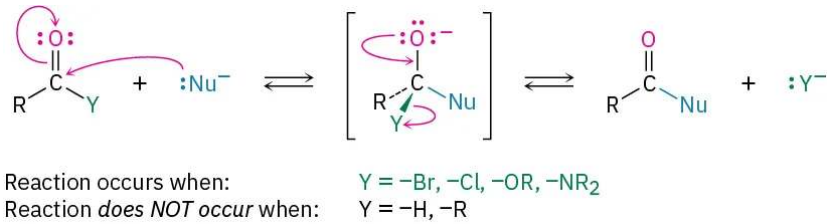


Figure 8.13.1: Carboxylic acid derivatives have an electronegative substituent Y = –Br, –Cl, –OR, –NR_2 that can be expelled as a leaving group from the tetrahedral intermediate formed by nucleophilic addition. Aldehydes and ketones have no such leaving group and thus do not usually undergo this reaction.

The Cannizzaro reaction takes place by nucleophilic addition of OH^- to an aldehyde to give a tetrahedral intermediate, which expels hydride ion as a leaving group and is thereby oxidized. A second aldehyde molecule accepts the hydride ion in another nucleophilic addition step and is thereby reduced. Benzaldehyde, for instance, yields benzyl alcohol plus benzoic acid when heated with aqueous NaOH.

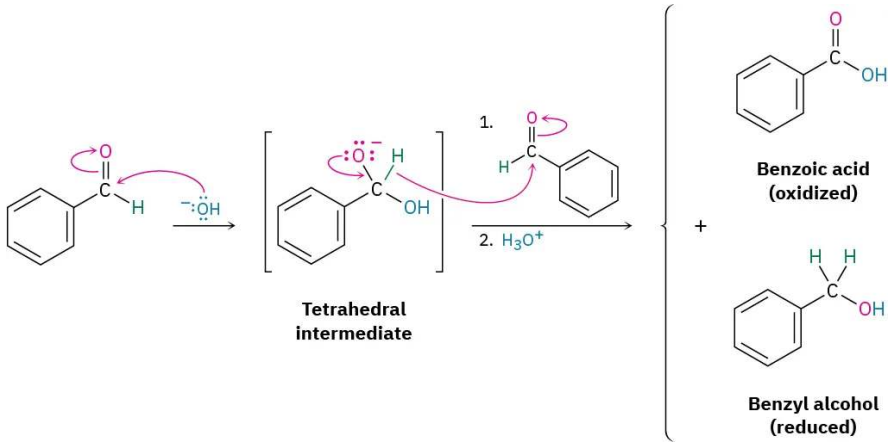
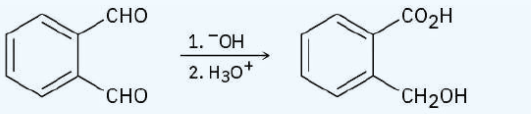


Figure 8.13.2: Mechanism of biological aldehyde and ketone reductions by the coenzyme NADH. The key step is an expulsion of hydride ion from NADH and donation to the carbonyl group.

? Exercise 8.13.1

When *o*-phthalaldehyde is treated with base, *o*-(hydroxymethyl)benzoic acid is formed. Show the mechanism of this reaction.



***o*-Phthalaldehyde** ***o*-(Hydroxymethyl)benzoic acid**

Answer

Intramolecular Cannizzaro reaction

Exercise 8.13.2

What is the stereochemistry of the pyruvate reduction shown in Figure 8.13.2? Does NADH lose its pro-*R* or pro-*S* hydrogen? Does addition occur to the Si face or Re face of pyruvate? (Review Section 5.11.)

Answer

Addition of the pro-R hydrogen of NADH takes place on the Re face of pyruvate.

This page titled 8.13: Biological Reductions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **19.12: Biological Reductions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

SECTION OVERVIEW

8.13.1: Amines and Heterocycles

Learning Objectives

When you have completed Chapter 24, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design a multi-step synthesis that involves the use of any of the reactions described in this unit, and any of the reactions described in any previous unit.
3. solve road-map problems that require a knowledge of amine chemistry in addition to any of the chemistry discussed in previous units.
4. define, and use in context, the key terms introduced.

Amines are the first nitrogen-containing compounds that we study in detail in this course. We begin the chapter with an explanation of the differences in structure among primary, secondary and tertiary amines. We explain the nomenclature of aliphatic and arylamines, and examine the structure and bonding of these compounds, relating these features to their physical properties and basicity. We describe the use of amines to resolve racemic mixtures of chiral carboxylic acids.

Amines may be prepared by a number of different synthetic methods. We describe each of these methods and assess the relative merits of each. After a description of the reactions of aliphatic amines, we devote sections to a discussion of the use of tetraalkylammonium salts as phase-transfer agents. The chapter concludes with a summary of the spectroscopic properties of amines.

8.13.1.1: Why This Chapter?

8.13.1.2: Naming Amines

8.13.1.3: Structure and Properties of Amines

8.13.1.4: Basicity of Amines

8.13.1.5: Basicity of Arylamines

8.13.1.6: Biological Amines and the Henderson-Hasselbalch Equation

8.13.1.7: Synthesis of Amines

8.13.1.8: Reactions of Amines

8.13.1.9: Reactions of Arylamines

8.13.1.10: Heterocyclic Amines

8.13.1.11: Spectroscopy of Amines

8.13.1.12: Chemistry Matters - Green Chemistry II- Ionic Liquids

8.13.1.13: Key Terms

8.13.1.14: Summary

8.13.1.15: Summary of Reactions

8.13.1.16: Additional Problems

This page titled 8.13.1: Amines and Heterocycles is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

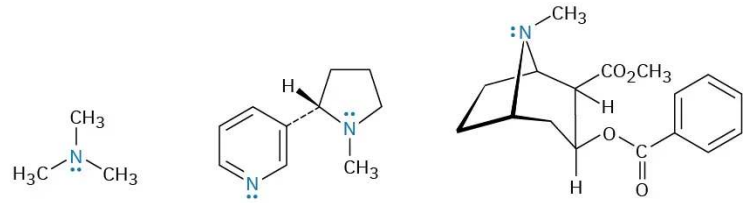
8.13.1.1: Why This Chapter?

By the end of this chapter, we will have seen all the common functional groups. Of those groups, carbonyl compounds and amines are the most abundant and have the richest chemistry. In addition to proteins and nucleic acids, the majority of pharmaceutical agents contain amine functional groups, and many of the common coenzymes necessary for biological catalysis are amines.

Figure 8.13.1.1.1: The characteristic and unmistakable odor of fish is due to a mixture of simple alkylamines. (credit: modification of work “Pike Place” by Sharat Ganapati/Flickr, CC BY 2.0)

Amines are organic derivatives of ammonia in the same way that alcohols and ethers are organic derivatives of water. Like ammonia, amines contain a nitrogen atom with a lone pair of electrons, making amines both basic and nucleophilic. We’ll soon see, in fact, that most of the chemistry of amines depends on the presence of this lone pair of electrons.

Amines occur widely in all living organisms. Trimethylamine, for instance, occurs in animal tissues and is partially responsible for the distinctive odor of fish; nicotine is found in tobacco; and cocaine is a stimulant found in the leaves of the South American coca bush. In addition, amino acids are the building blocks from which all proteins are made, and cyclic amine bases are constituents of nucleic acids.



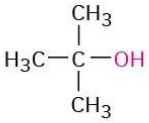
Trimethylamine **Nicotine** **Cocaine**

This page titled 8.13.1.1: Why This Chapter? is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

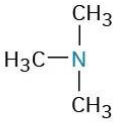
- **24.0: Why This Chapter?** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.13.1.2: Naming Amines

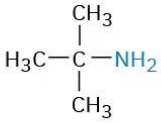
Amines can be either alkyl-substituted (alkylamines) or aryl-substituted (arylamines). Although much of the chemistry of the two classes is similar, there are also substantial differences. Amines are classified as primary (RNH_2), secondary (R_2NH), or tertiary (R_3N), depending on the number of organic substituents attached to nitrogen. Thus, methylamine (CH_3NH_2) is a primary amine, dimethylamine [$(CH_3)_2NH$] is a secondary amine, and trimethylamine [$(CH_3)_3N$] is a tertiary amine. Note that this usage of the terms *primary*, *secondary*, and *tertiary* differs from our previous usage. When we speak of a tertiary alcohol or alkyl halide, we refer to the degree of substitution at the alkyl carbon atom, but when we speak of a tertiary amine, we refer to the degree of substitution at the nitrogen atom.



***tert*-Butyl alcohol**
(a tertiary alcohol)

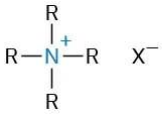


Trimethylamine
(a tertiary amine)



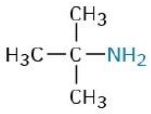
***tert*-Butylamine**
(a primary amine)

Compounds containing a nitrogen atom with four attached groups also exist, but the nitrogen atom must carry a formal positive charge. Such compounds are called quaternary ammonium salts.

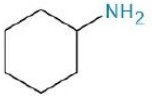


A quaternary ammonium salt

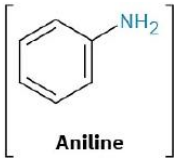
Primary amines are named in the IUPAC system in several ways. For simple amines, the suffix *-amine* is added to the name of the alkyl substituent. You might also recall from the chapter on Benzene and Aromaticity that the aromatic phenylamine, $H_2N–C_6H_5$, has the common name *aniline*.



***tert*-Butylamine**

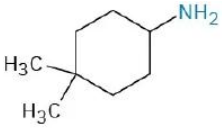


Cyclohexylamine

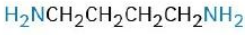


Aniline

Alternatively, the suffix *-amine* can be used in place of the final *-e* in the name of the parent compound.

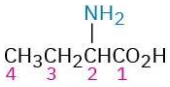


4,4-Dimethylcyclohexanamine

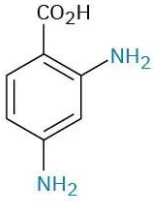


1,4-Butanediamine

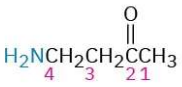
Amines with more than one functional group are named by considering the $-NH_2$ as an *amino* substituent on the parent molecule.



2-Aminobutanoic acid

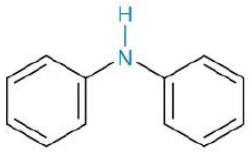


2,4-Diaminobenzoic acid

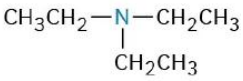


4-Amino-2-butanone

Symmetrical secondary and tertiary amines are named by adding the prefix *di-* or *tri-* to the alkyl group.

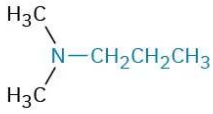


Diphenylamine

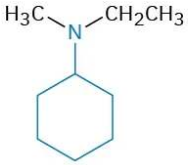


Triethylamine

Unsymmetrically substituted secondary and tertiary amines are referred to as *N*-substituted primary amines. The largest alkyl group takes the parent name, and the other alkyl groups are considered *N*-substituents on the parent (*N* because they're attached to nitrogen).



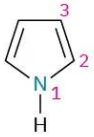
***N,N*-Dimethylpropylamine**



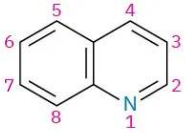
***N*-Ethyl-*N*-methylcyclohexylamine**

Heterocyclic amines—compounds in which the nitrogen atom occurs as part of a ring—are also common, and each different heterocyclic ring system has its own parent name. The heterocyclic nitrogen atom is always numbered as position 1.

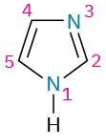
Pyridine



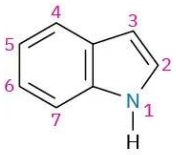
Pyrrole



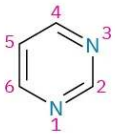
Quinoline



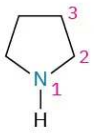
Imidazole



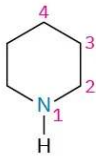
Indole



Pyrimidine



Pyrrolidine

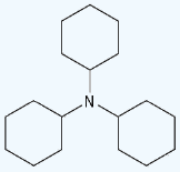


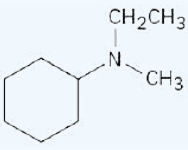
Piperidine

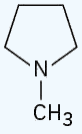
? Exercise 8.13.1.2.1

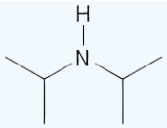
Name the following compounds:

a. $CH_3NHCH_2CH_3$

b. 

c. 

d. 

e. 

f. $H_2NCH_2CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HNH_2$

Answer

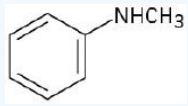
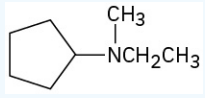
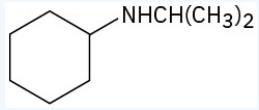
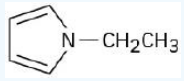
a. N-Methylethylamine
b. Tricyclohexylamine
c. N-Ethyl-N-methylcyclohexylamine
d. N-Methylpyrrolidine
e. Diisopropylamine
f. 1,3-Butanediamine

Exercise 8.13.1.2.2

Draw structures corresponding to the following IUPAC names:

a. Triisopropylamine
b. Triallylamine
c. N-Methylaniline
d. N-Ethyl-N-methylcyclopentylamine
e. N-Isopropylcyclohexylamine
f. N-Ethylpyrrole

Answer

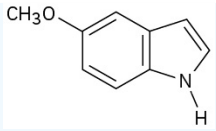
a. $[(CH_3)_2CH]_3N$
b. $(H_2C{=}CHCH_2)_3N$
c. 
d. 
e. 
f. 

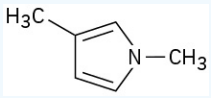
Exercise 8.13.1.2.3

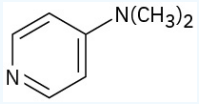
Draw structures for the following heterocyclic amines:

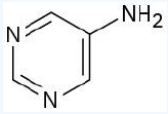
a. 5-Methoxyindole
b. 1,3-Dimethylpyrrole
c. 4-(N,N-Dimethylamino)pyridine
d. 5-aminopyrimidine

Answer

a. 

b. 

c. 

d. 

This page titled 8.13.1.2: Naming Amines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

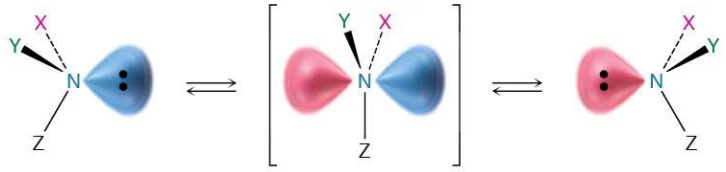
- **24.1: Naming Amines** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.13.1.3: Structure and Properties of Amines

The bonding in alkylamines is similar to the bonding in ammonia. The nitrogen atom is sp^3-hybridized, with its three substituents occupying three corners of a regular tetrahedron and the lone pair of electrons occupying the fourth corner. As you might expect, the C–N–C bond angles are close to the 109° tetrahedral value. For trimethylamine, the C–N–C bond angle is 108° and the C–N bond length is 147 pm.

Trimethylamine

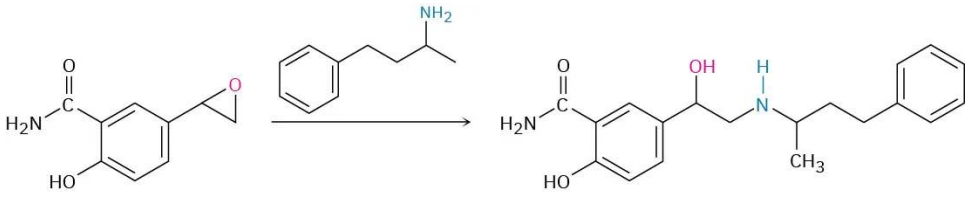
One consequence of tetrahedral geometry is that an amine with three different substituents on nitrogen is chiral, as we saw in Section 5.10. Unlike chiral carbon compounds, however, chiral amines can't usually be resolved because the two enantiomeric forms rapidly interconvert by a *pyramidal inversion*, much as an alkyl halide inverts in an S_N2 reaction. Pyramidal inversion occurs by a momentary rehybridization of the nitrogen atom to planar, sp^2 geometry, followed by rehybridization of the planar intermediate to tetrahedral, sp^3 geometry (Figure 24.2). The barrier to inversion is about 25 kJ/mol (6 kcal/mol), an amount only twice as large as the barrier to rotation about a C–C single bond.



sp^3-hybridized (tetrahedral) **sp^2-hybridized (planar)** **sp^3-hybridized (tetrahedral)**

Figure 24.2: Pyramidal inversion rapidly interconverts the two mirror-image (enantiomeric) forms of an amine.

Alkylamines have a variety of applications in the chemical industry as starting materials for the preparation of insecticides and pharmaceuticals. Labetalol, for instance, a so-called β-blocker used for the treatment of high blood pressure, is prepared by S_N2 reaction of an epoxide with a primary amine. The substance marketed for drug use is a mixture of all four possible stereoisomers, but the biological activity results primarily from the (*R*,*R*) isomer.



Labetalol

Like alcohols, amines with fewer than five carbon atoms are generally water-soluble. Also like alcohols, primary and secondary amines form hydrogen bonds and are highly associated. As a result, amines have higher boiling points than alkanes of similar molecular weight. Diethylamine (MW = 73 amu) boils at 56.3 °C, for instance, while pentane (MW = 72 amu) boils at 36.1 °C.

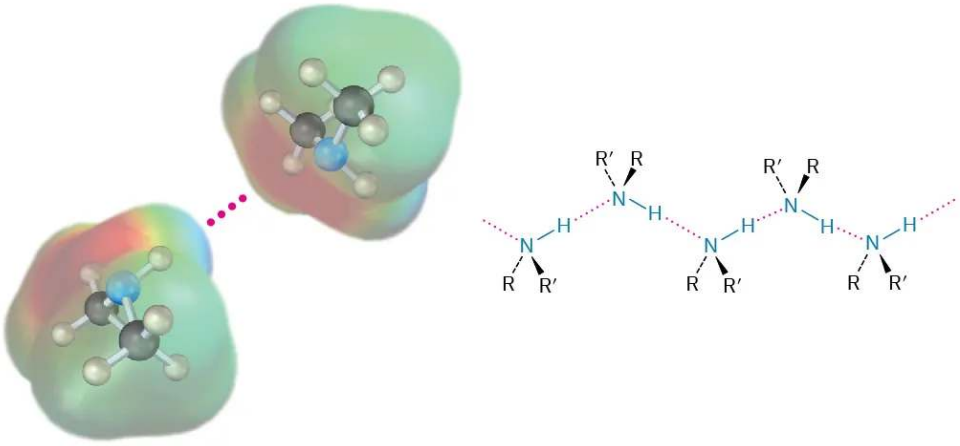


Figure 8.13.1.3.1: Hydrogen bonding in amines.

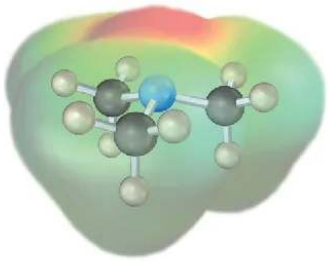
One other characteristic of amines is their odor. Low-molecular-weight amines such as trimethylamine have a distinctive fishlike aroma, while diamines such as cadaverine (1,5-pentanediamine) and putrescine (1,4-butanediamine) have the appalling odors you might expect from their common names. Both of these diamines arise from the decomposition of decaying tissue.

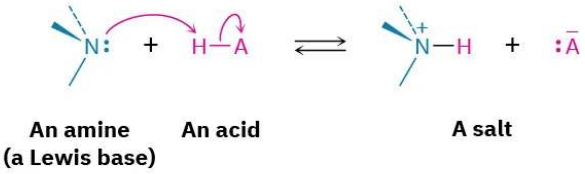
This page titled 8.13.1.3: Structure and Properties of Amines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.2: Structure and Properties of Amines** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.13.1.4: Basicity of Amines

The chemistry of amines is dominated by the lone pair of electrons on nitrogen, which makes amines both basic and nucleophilic. They react with acids to form acid–base salts, and they react with electrophiles in many of the polar reactions seen in past chapters. Note in the following electrostatic potential map of trimethylamine how the negative (red) region corresponds to the lone pair of electrons on nitrogen.





Amines are much stronger bases than alcohols and ethers, their oxygen-containing analogs. When an amine is dissolved in water, an equilibrium is established in which water acts as an acid and transfers a proton to the amine. Just as the acid strength of a carboxylic acid can be measured by defining an acidity constant K_a (Section 2.8), the base strength of an amine can be measured by defining an analogous *basicity constant* K_b. The larger the value of K_b and the smaller the value of pK_b, the more favorable the proton-transfer equilibrium and the stronger the base.

For the reaction

msub

RNH2 + H2O ⇄ RNH3+ + OH–Kb = [RNH3+] [OH–][RNH2]pKb = –log KbRNH2 + H2O ⇄ RNH3+ + OH–Kb = [RNH3+] [OH–][RNH2]pKb = –log Kb

In practice, K_b values are not often used. Instead, the most convenient way to measure the *basicity* of an amine (RNH_2) is to look at the *acidity* of the corresponding ammonium ion (RNH_3^+).

For the reaction

msub

RNH3+ + H2O ⇄ RNH2 + H3O+Ka = [RNH2] [H3O+][RNH3+]RNH3+ + H2O ⇄ RNH2 + H3O+Ka = [RNH2] [H3O+] [RNH3+]

so

$$K_a \cdot K_b = [\text{mfrac}]$$

RNH2] [H3O+][RNH3+][RNH3+] [OH–][RNH2]= [H3O+] [OH–] = Kw = 1.00 × 10–14Ka · Kb = [RNH2] [H3O+][RNH3+] [RNH3+] [OH–][RNH2]= [H3O+] [OH–] = Kw = 1.00 × 10–14

Thus

$$K_a = \text{mfrac}$$

KwKb and Kb = KwKaKa = KwKb and Kb = KwKa

and

pKa+ pKb = 14pKa+ pKb = 14

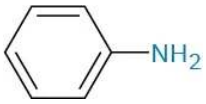
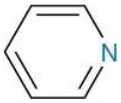
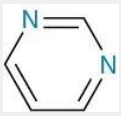
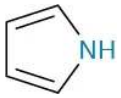
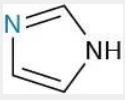
These equations say that the K_b of an amine multiplied by the K_a of the corresponding ammonium ion is equal to K_w, the ion-product constant for water (1.00×10^{-14}). Thus, if we know K_a for an ammonium ion, we also know K_b for the corresponding

amine base because $K_b = K_w/K_a$. The more acidic the ammonium ion, the less tightly the proton is held and the weaker the corresponding base. That is, a weaker base has an ammonium ion with a smaller pK_a and a stronger base has an ammonium ion with a larger pK_a.

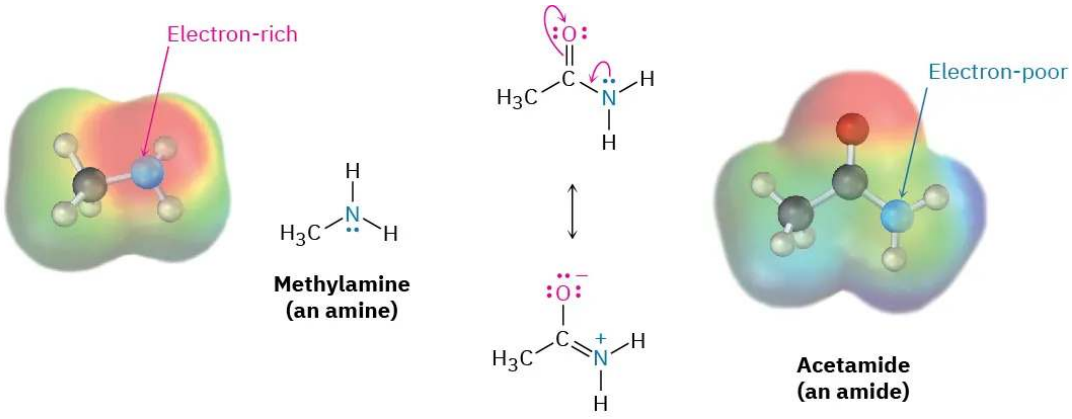
Weaker base	Smaller pK_a for ammonium ion
Stronger base	Larger pK_a for ammonium ion

Table 8.13.1.4.1 lists pK_a values of the ammonium ions from a variety of amines and indicates that there is a substantial range of amine basicities. Most simple alkylamines are similar in their base strength, with pK_a's for their ammonium ions in the narrow range 10 to 11. Arylamines, however, are considerably less basic than alkylamines, as are the heterocyclic amines pyridine and pyrrole.

Table 8.13.1.4.1 Basicity of Some Common Amines

Name	Structure	pK_a of ammonium ion
Ammonia	NH_3	9.26
Primary alkylamine		
Methylamine	CH_3NH_2	10.64
Ethylamine	$CH_3CH_2NH_2$	10.75
Secondary alkylamine		
Diethylamine	$(CH_3CH_2)_2NH$	10.98
Pyrrolidine		11.27
Tertiary alkylamine		
Triethylamine	$(CH_3CH_2)_3N$	10.76
Arylamine		
Aniline		4.63
Heterocyclic amine		
Pyridine		5.25
Pyrimidine		1.3
Pyrrole		0.4
Imidazole		6.95

In contrast with amines, amides ($RCONH_2$) are nonbasic. Amides aren't protonated by aqueous acids, and they are poor nucleophiles. The main reason for this difference in basicity between amines and amides is that an amide is stabilized by delocalization of the nitrogen lone-pair electrons through orbital overlap with the carbonyl group. In resonance terms, amides are more stable and less reactive than amines because they are hybrids of two resonance forms. This amide resonance stabilization is lost when the nitrogen atom is protonated, so protonation is disfavored. The following electrostatic potential maps clearly show a reduced electron density on the amide nitrogen.



To purify amines, it's often possible to take advantage of their basicity. For example, if a mixture of a basic amine and a neutral compound such as a ketone or alcohol is dissolved in an organic solvent and aqueous acid is added, the basic amine dissolves in the water layer as its protonated salt, while the neutral compound remains in the organic solvent layer. Separation of the water layer and neutralization of the ammonium ion by addition of NaOH then provides the pure amine (Figure 8.13.1.4.1).

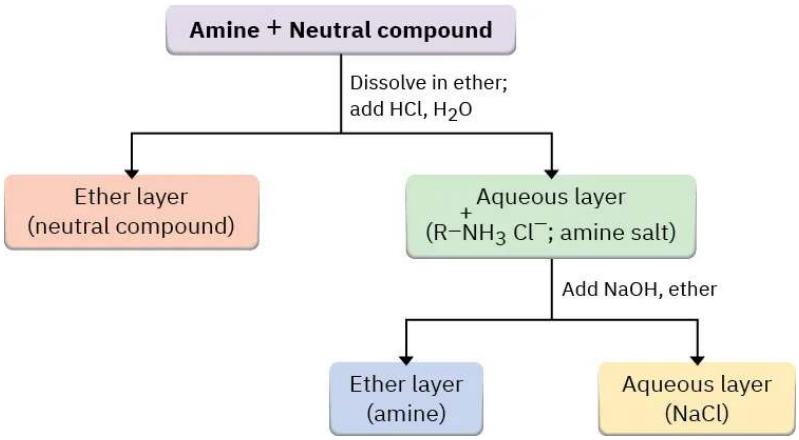
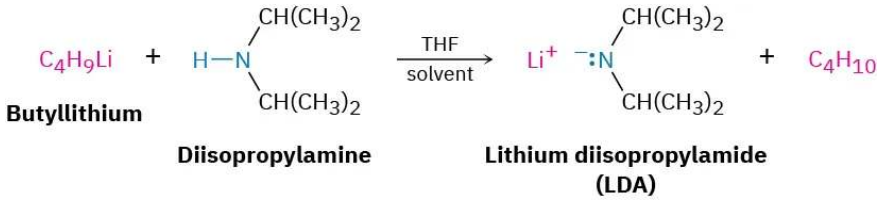


Figure 8.13.1.4.1: Separation and purification of an amine component from a mixture by extraction of its ammonium salt into water.

In addition to their behavior as bases, primary and secondary amines can also act as very weak acids because an N–H proton can be removed by a sufficiently strong base. We've seen, for example, how diisopropylamine ($pK_a \approx 36$) reacts with butyllithium to yield lithium diisopropylamide (LDA; Section 22.5). Dialkylamine anions like LDA are very strong bases that are often used in laboratory organic chemistry for the generation of enolate ions from carbonyl compounds (Section 22.7). They are not, however, encountered in biological chemistry.



Exercise 8.13.1.4.1

Select the more basic amine from each of the following pairs of compounds.

a. CH3CH2NH2 or CH3CH2CONH2
b. NaOH or CH3NH2
c. CH3NHCH3 or pyridine

Answer

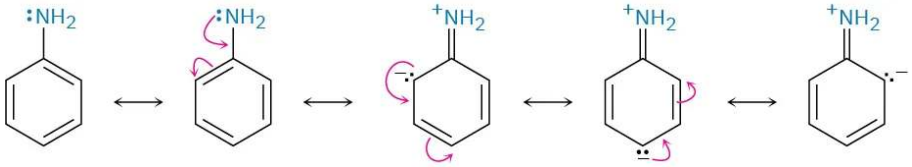
(a) $CH_3CH_2NH_2$
(b) NaOH
(c) CH_3NHCH_3

This page titled 8.13.1.4: Basicity of Amines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.3: Basicity of Amines** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.
- **24.3: Basicity of Amines** by Dietmar Kennepohl, Layne Morsch, Steven Farmer, Tim Soderberg, William Reusch is licensed CC BY-SA 4.0.

8.13.1.5: Basicity of Arylamines

As noted previously, arylamines are generally less basic than alkylamines. Anilinium ion has pK_a = 4.63, for instance, whereas methylammonium ion has pK_a = 10.64. Arylamines are less basic than alkylamines because the nitrogen lone-pair electrons are delocalized by interaction with the aromatic ring's π electron system and are less available for bonding to H^+. In resonance terms, arylamines are stabilized relative to alkylamines because of their five resonance forms.



Much of the resonance stabilization is lost on protonation, however, so the energy difference between protonated and nonprotonated forms is higher for arylamines than it is for alkylamines. As a result, arylamines are less basic. Figure 8.13.1.5.1 illustrates this difference.

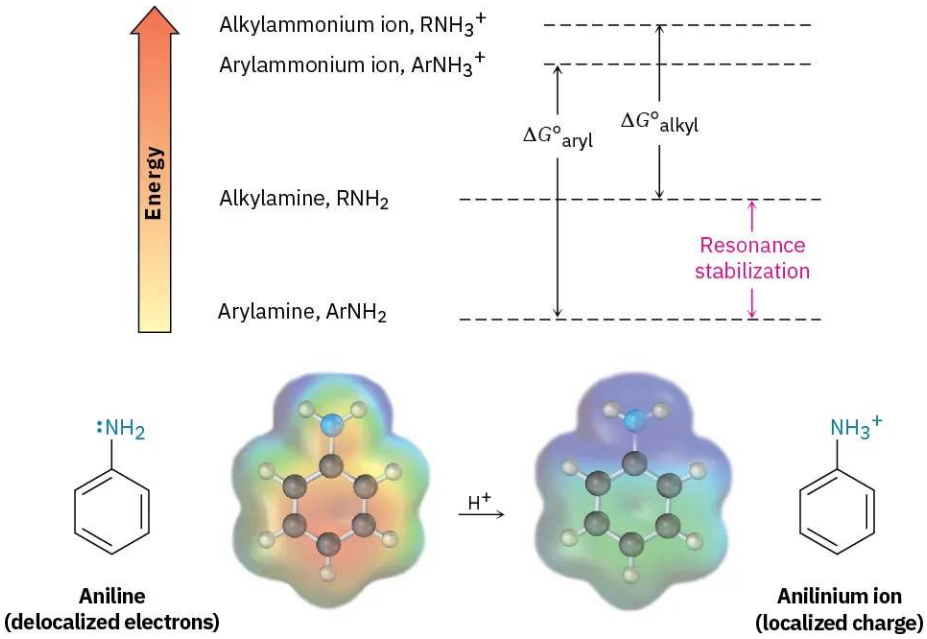


Figure 8.13.1.5.1: Arylamines have a larger positive $\Delta G°$ for protonation and are therefore less basic than alkylamines, primarily because of resonance stabilization of the ground state. Electrostatic potential maps show that lone-pair electron density is delocalized in the amine but the charge is localized in the corresponding ammonium ion.

Substituted arylamines can be either more basic or less basic than aniline, depending on the substituent. Electron-donating substituents, such as $–CH_3$, $–NH_2$, and $–OCH_3$, which increase the reactivity of an aromatic ring toward electrophilic substitution (Section 16.4), also increase the basicity of the corresponding arylamine. Electron-withdrawing substituents, such as –Cl, $–NO_2$, and –CN, which decrease ring reactivity toward electrophilic substitution, also decrease arylamine basicity. Table 8.13.1.5.2 considers only *p*-substituted anilines, but similar trends are observed for ortho and meta derivatives.

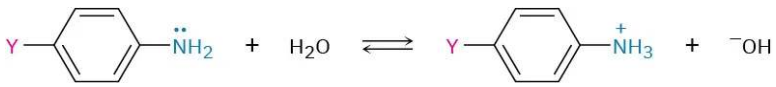
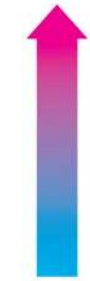


Table 8.13.1.5.2 Base Strength of Some *p*-Substituted Anilines

	Substituent, Y	pK_a	
Stronger base  Weaker base	$-NH_2$	6.15	Activating groups
	$-OCH_3$	5.34	
	$-CH_3$	5.08	
	–H	4.63	
	–Cl	3.98	Deactivating groups
	–Br	3.86	
	–CN	1.74	
	$-NO_2$	1.00	

? Exercise 8.13.1.5.1

Add exercises text here.

Answer

Add texts here. Do not delete this text first.

This page titled 8.13.1.5: Basicity of Arylamines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.4: Basicity of Arylamines** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.13.1.6: Biological Amines and the Henderson-Hasselbalch Equation

We saw in Section 20.3 that the extent of dissociation of a carboxylic acid HA in an aqueous solution buffered to a given pH can be calculated with the Henderson–Hasselbalch equation. Furthermore, we concluded that at the physiological pH of 7.3 inside living cells, carboxylic acids are almost entirely dissociated into their carboxylate anions, RCO_2^-.

Henderson–Hasselbalch equation:

$$\text{pH} = \text{p}K\text{a} + \log\frac{[\text{A}^-]}{[\text{HA}]} \quad \text{so} \quad \log\frac{[\text{A}^-]}{[\text{HA}]} = \text{pH} -$$

What about amine bases? In what form do they exist at physiological pH? As the amine (A^- = RNH_2), or as the ammonium ion (HA = RNH_3^+)? Let's take a 0.0010 M solution of methylamine at pH = 7.3, for example. According to Table 24.1, the pK_a of methylammonium ion is 10.64, so from the Henderson–Hasselbalch equation, we have

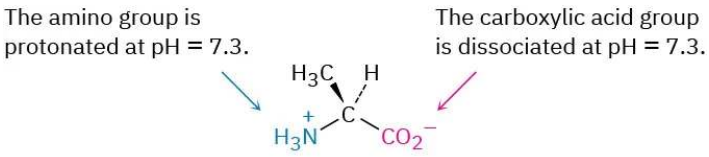
$$\log\frac{\text{msub}]}{\text{msub}^+]} = \text{pH} - \text{p}K_\text{a} = 7.3 - 10.64 = -3.34$$

$$\frac{\text{msub}]}{\text{msub}^+]} = \text{antilog}(-3.34) = 4.6 \times 10^{-4} \quad \text{so} \quad \text{msub}] = (4.6 \times 10^{-4}\text{msub}^+]$$

In addition, we know that

$$\text{msubmsub}^+] = 0.0010 \text{ M}$$

Solving the two simultaneous equations gives [RNH_3^+] = 0.0010 M and [RNH_2] = 5×10^{-7} M. In other words, at a physiological pH of 7.3, essentially 100% of the methylamine in a 0.0010 M solution exists in its protonated form as methylammonium ion. The same is true of other amine bases, so we always write cellular amines in their protonated form and amino acids in their ammonium carboxylate form to reflect their structures at physiological pH.



Alanine
(an amino acid)

Exercise 8.13.1.6.1

Add exercises text here.

Answer

Add texts here. Do not delete this text first.

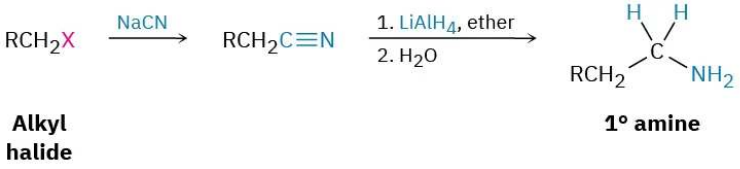
This page titled 8.13.1.6: Biological Amines and the Henderson-Hasselbalch Equation is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.5: Biological Amines and the Henderson-Hasselbalch Equation** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

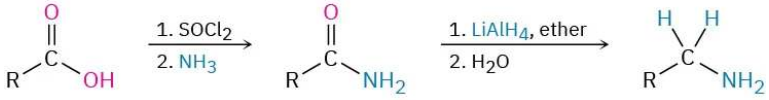
8.13.1.7: Synthesis of Amines

Reduction of Nitriles, Amides, and Nitro Compounds

We've already seen in Section 20.7 and Section 21.7 how amines can be prepared by reduction of nitriles and amides with $LiAlH_4$. The two-step sequence of S_N2 displacement with CN^- followed by reduction thus converts an alkyl halide into a primary alkylamine having an additional carbon atom. Amide reduction converts carboxylic acids and their derivatives into amines with the same number of carbon atoms.

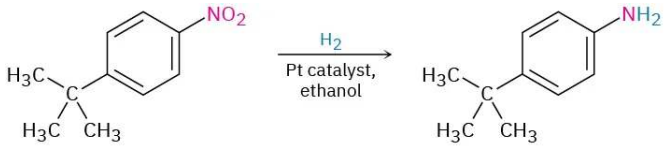


Alkyl halide **1° amine**

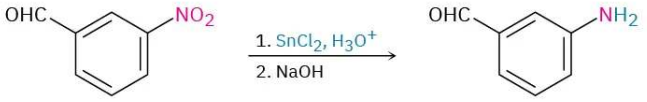


Carboxylic acid **1° amine**

Arylamines are usually prepared by nitration of an aromatic starting material, followed by reduction of the nitro group (Section 16.2). The reduction step can be carried out in many different ways, depending on the circumstances. Catalytic hydrogenation over platinum works well but is often incompatible with the presence elsewhere in the molecule of other reducible groups, such as C=C bonds or carbonyl groups. Iron, zinc, tin, and tin(II) chloride ($SnCl_2$) are also effective when used in acidic aqueous solution. Tin(II) chloride is particularly mild and is often used when other reducible functional groups are present.



***p*-*tert*-Butylnitrobenzene** ***p*-*tert*-Butylaniline (100%)**



***m*-Nitrobenzaldehyde** ***m*-Aminobenzaldehyde (90%)**

? Exercise 8.13.1.7.1

Propose structures for either a nitrile or an amide that might be a precursor of each of the following amines:

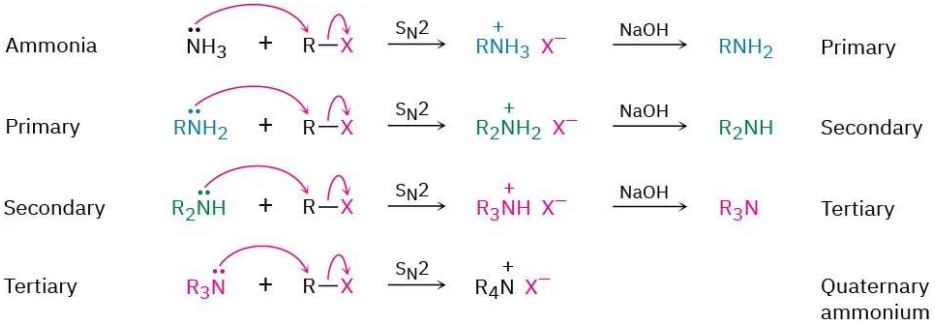
a. $CH_3CH_2CH_2NH_2$
b. $(CH_3CH_2CH_2)_2NH$
c. Benzylamine, $C_6H_5CH_2NH_2$
d. *N*-Ethylaniline

Answer

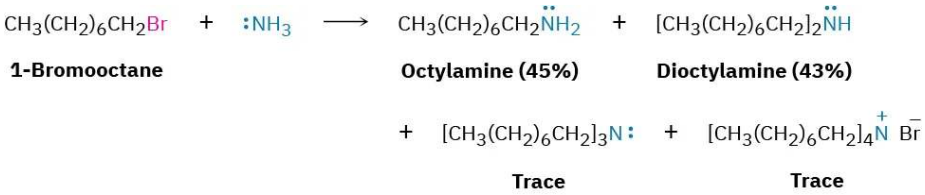
a. Propanenitrile or propanamide
b. *N*-Propylpropanamide
c. Benzonitrile or benzamide
d. *N*-Phenylacetamide

S_N2 Reactions of Alkyl Halides

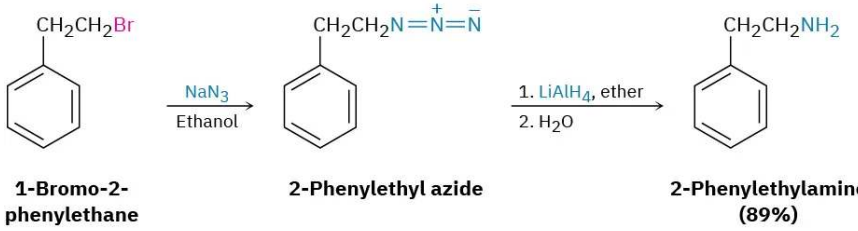
Ammonia and other amines are good nucleophiles in S_N2 reactions. As a result, the simplest method of alkylamine synthesis is by S_N2 alkylation of ammonia or an alkylamine with an alkyl halide. If ammonia is used, a primary amine results; if a primary amine is used, a secondary amine results; and so on. Even tertiary amines react rapidly with alkyl halides to yield quaternary ammonium salts, $R_4N^+ X^-$.



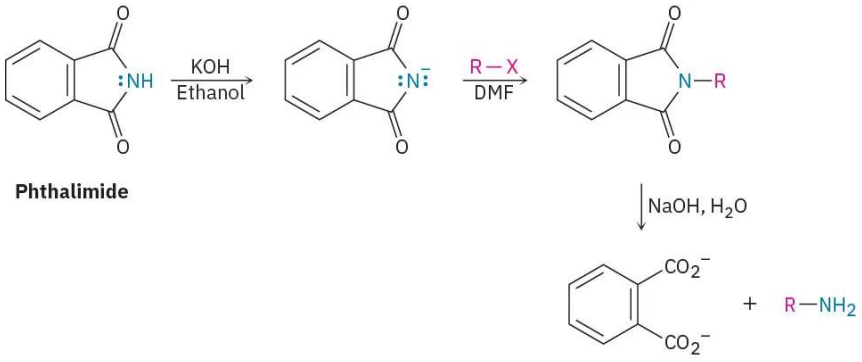
Unfortunately, these reactions don't stop cleanly after a single alkylation has occurred. Because ammonia and primary amines have similar reactivity, the initially formed monoalkylated substance often undergoes further reaction to yield a mixture of products. Even secondary and tertiary amines undergo further alkylation, although to a lesser extent. For example, treatment of 1-bromooctane with a twofold excess of ammonia leads to a mixture containing only 45% octylamine. A nearly equal amount of dioctylamine is produced by double alkylation, along with smaller amounts of trioctylamine and tetraoctylammonium bromide.



A better method for preparing primary amines is to use azide ion, N_3^-, rather than ammonia, as the nucleophile for S_N2 reaction with a primary or secondary alkyl halide. The product is an alkyl azide, which is not nucleophilic, so overalkylation can't occur. Subsequent reduction of the alkyl azide with $LiAlH_4$ then leads to the desired primary amine. Although this method works well, low-molecular-weight alkyl azides are explosive and must be handled carefully.



Another alternative for preparing a primary amine from an alkyl halide is the Gabriel amine synthesis, which uses a *phthalimide* alkylation. An imide (O=C–N–C=OSection 22.7). Basic hydrolysis of the *N*-alkylated imide then yields a primary amine product. The imide hydrolysis step is analogous to the hydrolysis of an amide (Section 21.7).



Phthalimide

? Exercise 8.13.1.7.2

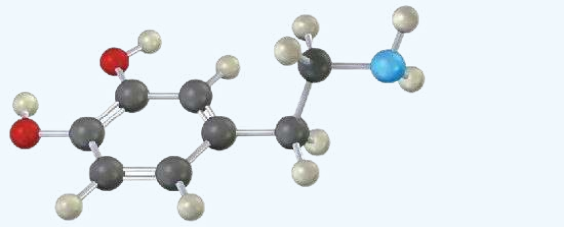
Write the mechanism of the last step in Gabriel amine synthesis, the base-promoted hydrolysis of a phthalimide to yield an amine plus phthalate ion.

Answer

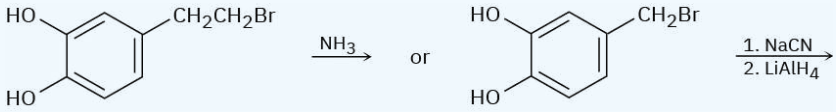
The reaction takes place by two nucleophilic acyl substitution reactions.

? Exercise 8.13.1.7.3

Show two methods for the synthesis of dopamine, a neurotransmitter involved in regulation of the central nervous system. Use any alkyl halide needed.

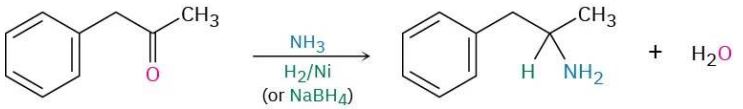


Answer



Reductive Amination of Aldehydes and Ketones

Amines can be synthesized in a single step by treatment of an aldehyde or ketone with ammonia or an amine in the presence of a reducing agent, a process called reductive amination. For example, amphetamine, a central nervous system stimulant, is prepared commercially by reductive amination of phenyl-2-propanone with ammonia using hydrogen gas over a nickel catalyst as the reducing agent. In the laboratory, either $NaBH_4$ or the related $NaBH(OAc)_3$ is commonly used (OAc = acetate).



Phenyl-2-propanone **Amphetamine**

Reductive amination takes place by the pathway shown in Figure 8.13.1.7.1. An imine intermediate is first formed by a nucleophilic addition reaction (Section 19.8), and the C═N bond of the imine is then reduced to the amine, much as the C═O bond of a ketone can be reduced to an alcohol.

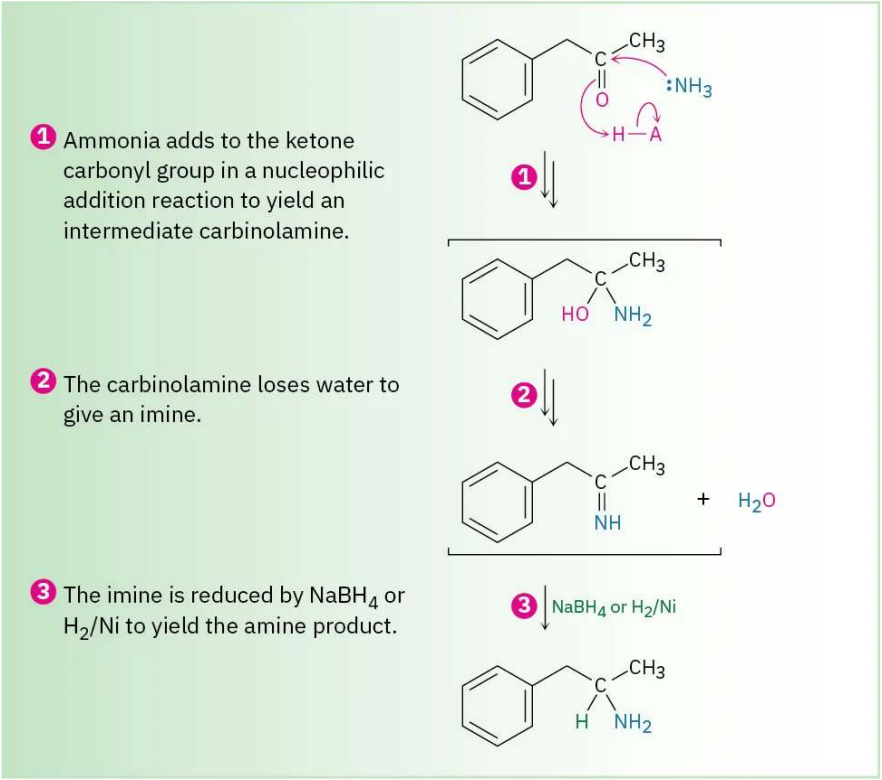
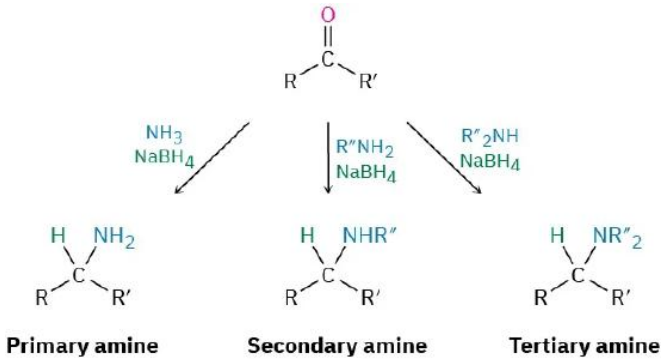
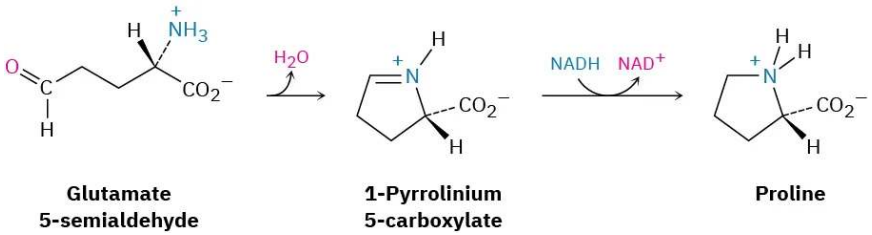


Figure 8.13.1.7.1: Mechanism for reductive amination of a ketone to yield an amine.

Ammonia, primary amines, and secondary amines can all be used in the reductive amination reaction, yielding primary, secondary, and tertiary amines, respectively.

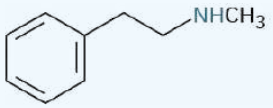


Reductive aminations also occur in various biological pathways. In the biosynthesis of the amino acid proline, for instance, glutamate 5-semialdehyde undergoes internal imine formation to give 1-pyrrolinium 5-carboxylate, which is then reduced by nucleophilic addition of hydride ion to the C=N bond. Reduced nicotinamide adenine dinucleotide, NADH, acts as the biological reducing agent.



Worked Example 8.13.1.7.1: Using a Reductive Amination Reaction

How might you prepare *N*-methyl-2-phenylethylamine using a reductive amination reaction?

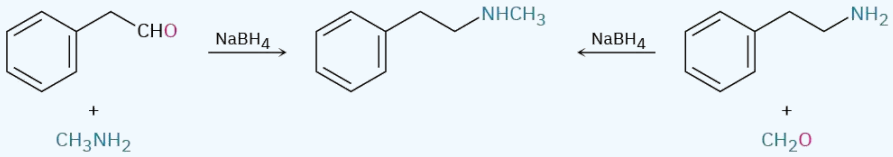


***N*-Methyl-2-phenylethylamine**

Strategy

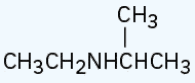
Look at the target molecule, and identify the groups attached to nitrogen. One of the groups must be derived from the aldehyde or ketone component, and the other must be derived from the amine component. In the case of *N*-methyl-2-phenylethylamine, two combinations can lead to the product: phenylacetaldehyde plus methylamine or formaldehyde plus 2-phenylethylamine. It's usually better to choose the combination with the simpler amine component—methylamine in this case—and to use an excess of that amine as reactant.

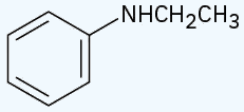
Solution

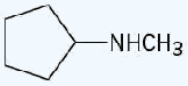


Exercise 8.13.1.7.4

How might the following amines be prepared using reductive amination reactions? Show all precursors if more than one is possible.

a. 

b. 

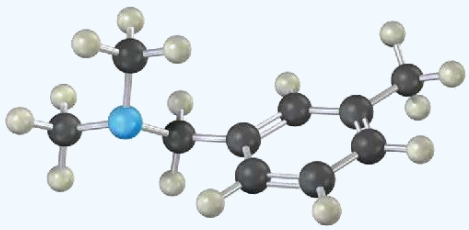
c. 

Answer

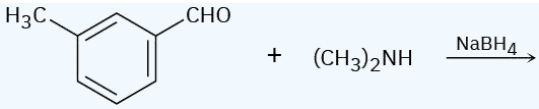
a. Ethylamine + acetone, or isopropylamine + acetaldehyde
b. Aniline + acetaldehyde
c. Cyclopentylamine + formaldehyde, or methylamine + cyclopentanone

Exercise 8.13.1.7.5

How could you prepare the following amine using a reductive amination reaction?



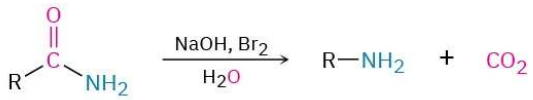
Answer



Hofmann and Curtius Rearrangements

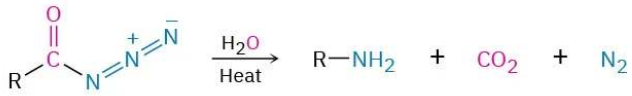
Carboxylic acid derivatives can be converted into primary amines with loss of one carbon atom by both the Hofmann rearrangement and the Curtius rearrangement. Although the Hofmann rearrangement involves a primary amide and the Curtius rearrangement involves an acyl azide, both proceed through similar mechanisms.

Hofmann rearrangement



An amide

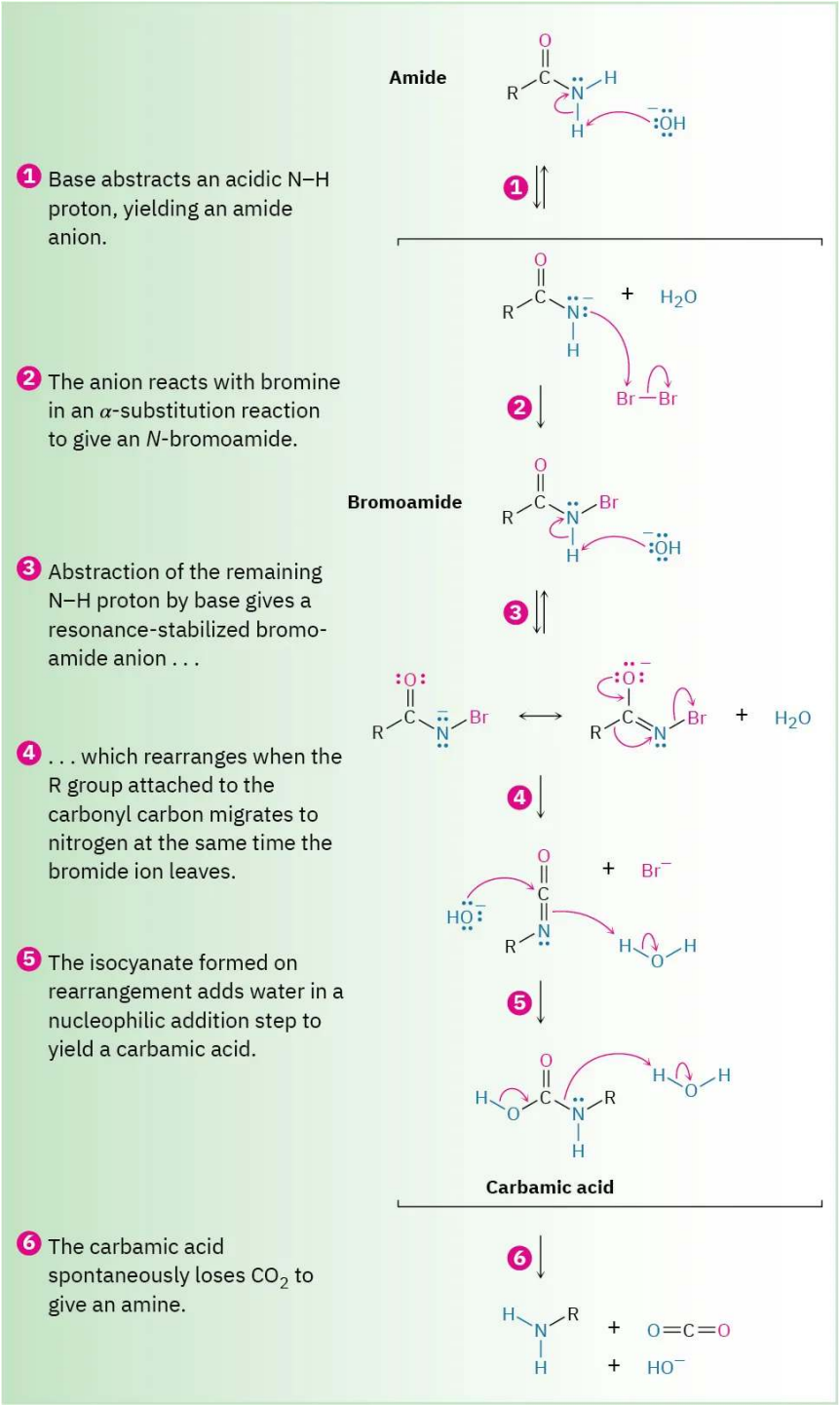
Curtius rearrangement



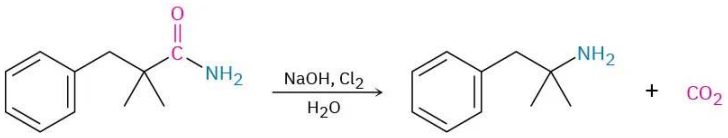
An acyl azide

Hofmann rearrangement occurs when a primary amide, $RCONH_2$, is treated with Br_2 and base (Figure 24.7). The overall mechanism is lengthy, but most of the individual steps have been encountered before. Thus, the bromination of an amide in steps **1** and **2** is analogous to the base-promoted bromination of a ketone enolate ion (Section 22.6), and the rearrangement of the bromoamide anion in step **4** is analogous to a carbocation rearrangement (Section 7.11). Nucleophilic addition of water to the isocyanate carbonyl group in step **5** is a typical carbonyl-group process (Section 19.4), as is the final decarboxylation step **6** (Section 22.7).

Figure 8.13.1.7.2: Mechanism of the Hofmann rearrangement of an amide to an amine. Each step is analogous to a reaction studied previously.

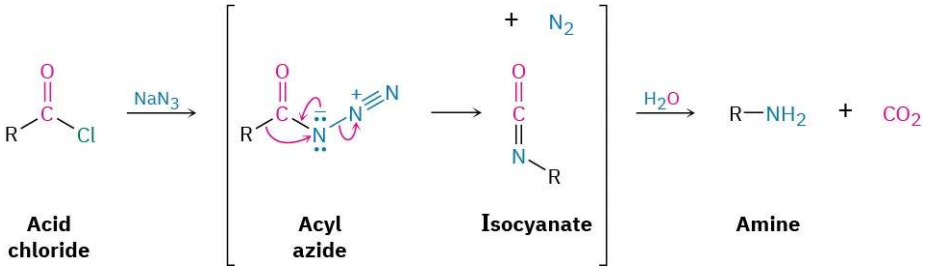


Despite its mechanistic complexity, the Hofmann rearrangement often gives high yields of both arylamines and alkylamines. For example, the appetite-suppressant drug phentermine is prepared commercially by Hofmann rearrangement of a primary amide. Commonly known by the name Fen-Phen, the combination of phentermine with another appetite-suppressant, fenfluramine, is suspected of causing heart damage.



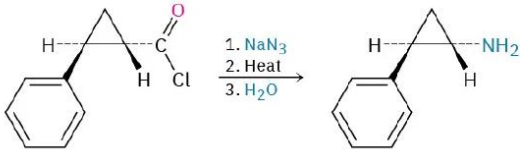
2,2-Dimethyl-3-phenyl-propanamide **Phentermine**

The **Curtius rearrangement**, like the Hofmann rearrangement, involves migration of an –R group from the C═O carbon atom to the neighboring nitrogen with simultaneous loss of a leaving group. The reaction takes place on heating an acyl azide that is itself prepared by nucleophilic acyl substitution of an acid chloride.



Acid chloride **Acyl azide** **Isocyanate** **Amine**

Also like the Hofmann rearrangement, the Curtius rearrangement is often used commercially. The antidepressant drug tranylcypromine, for instance, is made by Curtius rearrangement of 2-phenylcyclopropanecarbonyl chloride.



***trans*-2-Phenylcyclo-propanecarbonyl chloride** **Tranylcypromine**

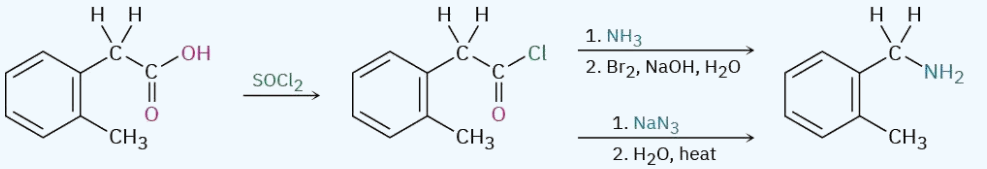
Worked Example 8.13.1.7.2: Using the Hofmann and Curtius Rearrangements

How would you prepare *o*-methylbenzylamine from a carboxylic acid, using both Hofmann and Curtius rearrangements?

Strategy

Both Hofmann and Curtius rearrangements convert a carboxylic acid derivative—either an amide (Hofmann) or an acid chloride (Curtius)—into a primary amine with loss of one carbon, RCOY → RNH_2. Both reactions begin with the same carboxylic acid, which can be identified by replacing the $–NH_2$ group of the amine product by a $–CO_2H$ group. In the present instance, *o*-methylphenylacetic acid is needed.

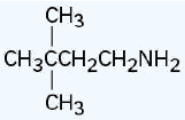
Solution

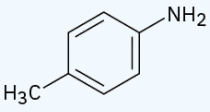


***o*-Methylphenyl-acetic acid** ***o*-Methylbenzylamine**

Exercise 8.13.1.7.6

How would you prepare the following amines, using both Hofmann and Curtius rearrangements on a carboxylic acid derivative?

a. 

b. 

Answer

a. 4,4-Dimethylpentanamide or 4,4-dimethylpentanoyl azide

b. *p*-Methylbenzamide or *p*-methylbenzoyl azide

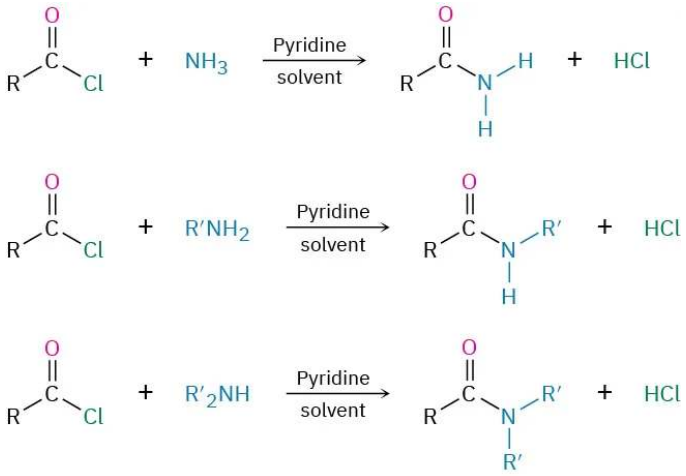
This page titled 8.13.1.7: Synthesis of Amines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.6: Synthesis of Amines** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.13.1.8: Reactions of Amines

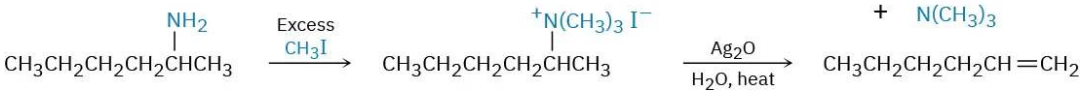
Alkylation and Acylation

We've already studied the two most general reactions of amines—alkylation and acylation. As we saw earlier in this chapter, primary, secondary, and tertiary amines can be alkylated by reaction with a primary alkyl halide. Alkylations of primary and secondary amines are difficult to control and often give mixtures of products, but tertiary amines are cleanly alkylated to give quaternary ammonium salts. Primary and secondary (but not tertiary) amines can also be acylated by nucleophilic acyl substitution reaction with an acid chloride or an acid anhydride to yield an amide (Section 21.4 and Section 21.5). Note that overacylation of the nitrogen does not occur because the amide product is much less nucleophilic and less reactive than the starting amine.



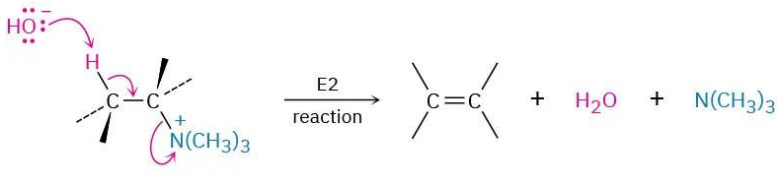
Hofmann Elimination Reaction

Like alcohols, amines can be converted into alkenes by an elimination reaction. But because an amide ion, NH_2^-, is such a poor leaving group, it must first be converted into a better leaving group. In the Hofmann elimination reaction, an amine is completely methylated by reaction with an excess amount of iodomethane to produce the corresponding quaternary ammonium salt. This salt then undergoes elimination to give an alkene on heating with a base, typically silver oxide, Ag_2O. For example, 1-methylpentylamine is converted into 1-hexene.



1-Methylpentylamine | **(1-Methylpentyl)trimethylammonium iodide** | **1-Hexene (60%)**

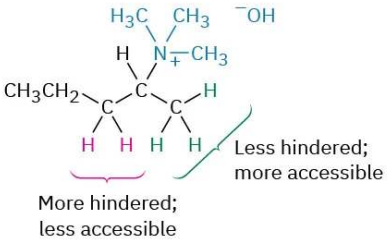
Silver oxide acts by exchanging iodide ion for hydroxide ion in the quaternary salt, thus providing the base necessary for elimination. The actual elimination step is an E2 reaction (Section 11.8) in which hydroxide ion removes a proton while the positively charged nitrogen atom leaves.



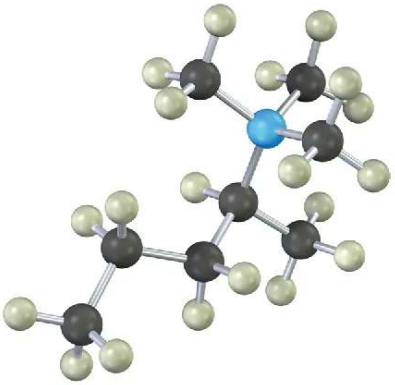
Quaternary ammonium salt | **Alkene**

Unlike what happens in other E2 reactions, the major product of Hofmann elimination is the less highly substituted alkene rather than the more highly substituted one, as shown by the reaction of (1-methylbutyl)trimethylammonium hydroxide to give 1-pentene

rather than the alternative 2-pentene. The reason for this non-Zaitsev result is probably steric. Because of the large size of the trialkylamine leaving group, the base must abstract a hydrogen from the more accessible, least hindered position.



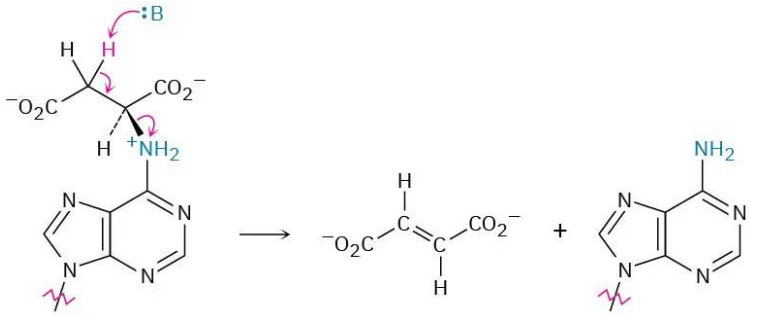
(1-Methylbutyl)trimethylammonium hydroxide



$CH_3CH_2CH_2CH{=}CH_2$ + $CH_3CH_2CH{=}CHCH_3$

1-Pentene (94%) **2-Pentene (6%)**

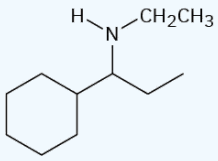
The Hofmann elimination reaction is not often currently used in the laboratory, but analogous biological eliminations occur frequently, although usually with protonated ammonium ions rather than quaternary ammonium salts. In the biosynthesis of nucleic acids, for instance, a substance called adenylosuccinate undergoes an elimination of a positively charged nitrogen to give fumarate plus adenosine monophosphate.



Adenylosuccinate **Fumarate** **Adenosine monophosphate**

✔ Worked Example 8.13.1.8.1: Predicting the Product of a Hofmann Elimination

What product would you expect from Hofmann elimination of the following amine?

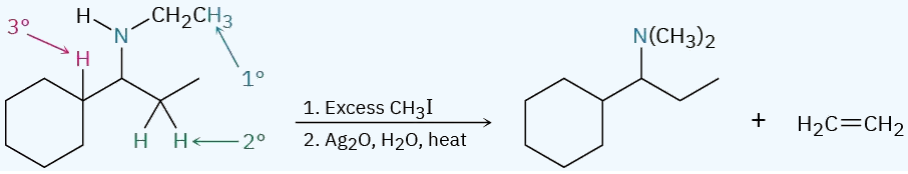


Strategy

The Hofmann elimination is an E2 reaction that converts an amine into an alkene and occurs with non-Zaitsev regiochemistry to form the less highly substituted double bond. To predict the product, look at the reactant and identify the positions from which elimination might occur (the positions two carbons away from nitrogen). Then, carry out an elimination using the most accessible hydrogen. In the present instance, there are three possible positions from which elimination might occur—one

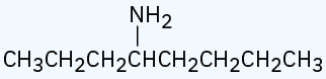
primary, one secondary, and one tertiary. The primary position is the most accessible and leads to the least highly substituted alkene, ethylene.

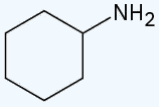
Solution

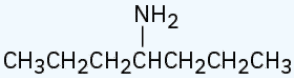


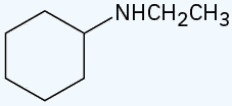
Exercise 8.13.1.8.1

What products would you expect from Hofmann elimination of the following amines? If more than one product is formed, indicate which is major.

a. 

b. 

c. 

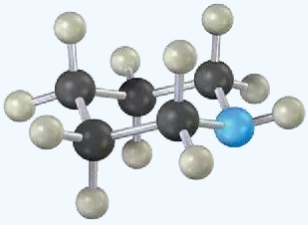
d. 

Answer

a. 3-Octene and 4-octene
b. Cyclohexene
c. 3-Heptene
d. Ethylene and cyclohexene

Exercise 8.13.1.8.2

What product would you expect from Hofmann elimination of a heterocyclic amine such as piperidine? Write all the steps.



Piperidine

Answer

$H_2C=CHCH_2CH_2CH_2N(CH_3)_2$

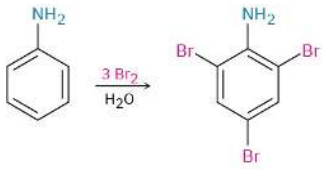
This page titled 8.13.1.8: Reactions of Amines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.7: Reactions of Amines** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.13.1.9: Reactions of Arylamines

Electrophilic Aromatic Substitutions

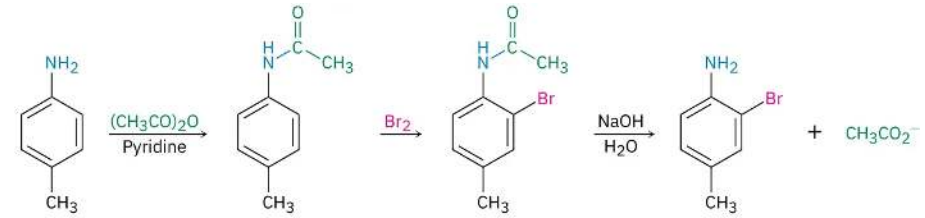
An amino group is strongly activating and ortho- and para-directing in electrophilic aromatic substitution reactions (Section 16.4). This high reactivity of amino-substituted benzenes can be a drawback at times because it's often difficult to prevent polysubstitution. Reaction of aniline with Br_2, for instance, takes place rapidly and yields the 2,4,6-tribrominated product. The amino group is so strongly activating that it's not possible to stop at the monobromo stage.



Aniline **2,4,6-Tribromoaniline (100%)**

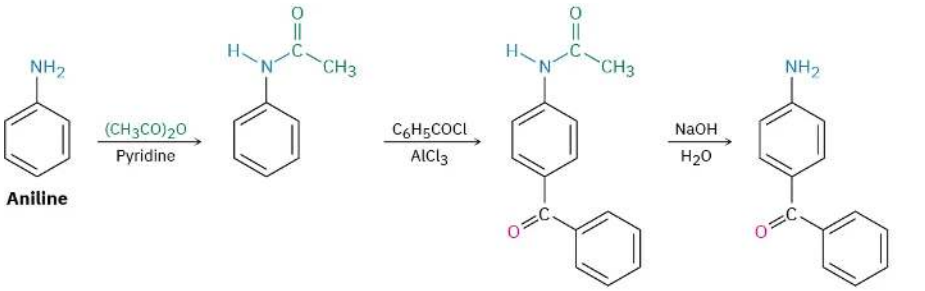
Another drawback to the use of amino-substituted benzenes in electrophilic aromatic substitution reactions is that Friedel–Crafts reactions are not successful (Section 16.3). The amino group forms an acid–base complex with the $AlCl_3$ catalyst, which prevents further reaction. Both drawbacks can be overcome, however, by carrying out electrophilic aromatic substitution reactions on the corresponding amide rather than on the free amine.

As we saw in Section 21.5, treatment of an amine with acetic anhydride yields the corresponding acetyl amide, or acetamide. Although still activating and ortho-, para-directing, amido substituents (R–N–C=O) are less strongly activating and less basic than amino groups because their nitrogen lone-pair electrons are delocalized by the neighboring carbonyl group. As a result, bromination of an *N*-arylamide occurs cleanly to give a monobromo product, and hydrolysis of the amide with aqueous base then gives the free amine. For example, *p*-toluidine (4-methylaniline) can be acetylated, brominated, and hydrolyzed to yield 2-bromo-4-methylaniline. None of the 2,6-dibrominated product is obtained.



***p*-Toluidine** **2-Bromo-4-methylaniline (79%)**

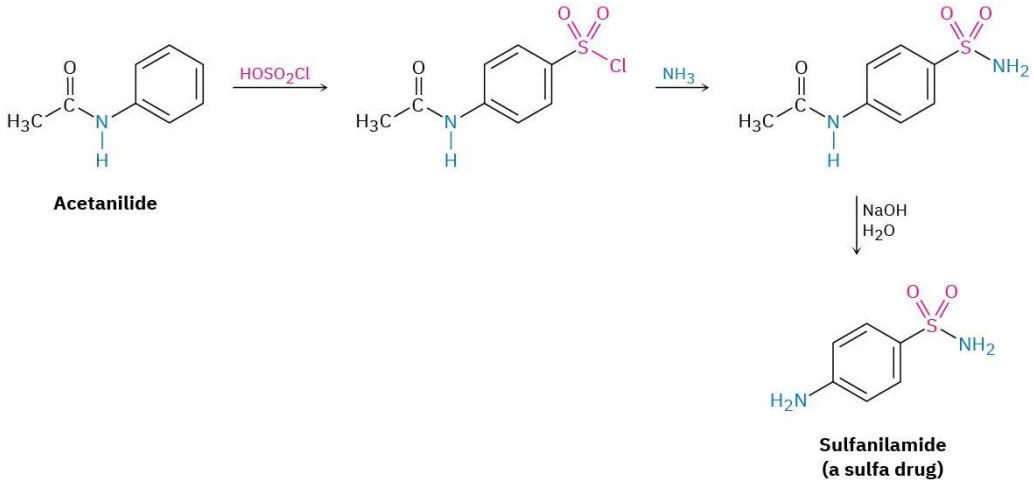
Friedel–Crafts alkylations and acylations of *N*-arylamides also proceed normally. For example, benzoylation of acetanilide (*N*-acetylaniline) under Friedel–Crafts conditions gives 4-aminobenzophenone in 80% yield after hydrolysis.



Aniline **4-Aminobenzophenone (80%)**

Moderating the reactivity of an amino-substituted benzene by forming an amide is a useful trick that allows many kinds of electrophilic aromatic substitutions to be carried out that would otherwise be impossible. One example is the preparation of the sulfa drugs, such as sulfanilamide.

Sulfa drugs were among the first pharmaceutical agents to be used clinically against bacterial infection. Although they have largely been replaced today by safer and more powerful antibiotics, sulfa drugs are credited with saving the lives of thousands of wounded during World War II and are still prescribed for urinary tract infections. They are prepared by chlorosulfonation of acetanilide, followed by reaction of *p*-(*N*-acetylamino)benzenesulfonyl chloride with ammonia or some other amine to give a sulfonamide. Hydrolysis of the amide then yields the sulfa drug. Note that hydrolysis of the amide can be carried out in the presence of the sulfonamide group because sulfonamides hydrolyze very slowly.

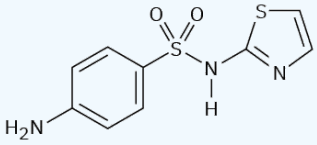


Acetanilide

Sulfanilamide (a sulfa drug)

Exercise 8.13.1.9.1

Propose a synthesis of the drug sulfathiazole from benzene and any necessary amine.



Sulfathiazole

Answer

1. HNO_3, H_2SO_4; 2. H_2/PtO_2; 3. $(CH_3CO)_2O$; 4. $HOSO_2Cl$; 5. aminothiazole; 6. H_2O, NaOH

Exercise 8.13.1.9.2

Propose syntheses of the following compounds from benzene:

a. *N*,*N*-Dimethylaniline
b. *p*-Chloroaniline
c. *m*-Chloroaniline
d. 2,4-Dimethylaniline

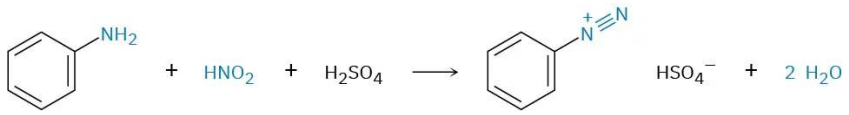
Answer

a. 1. HNO_3, H_2SO_4; 2. H_2/PtO_2; 3. 2 CH_3Br
b. 1. HNO_3, H_2SO_4; 2. H_2/PtO_2; 3. $(CH_3CO)_2O$; 4. Cl_2; 5. H_2O, NaOH
c. 1. HNO_3, H_2SO_4; 2. Cl_2, $FeCl_3$; 3. $SnCl_2$
d. 1. HNO_3, H_2SO_4; 2. H_2/PtO_2; 3. $(CH_3CO)_2O$; 4. 2 CH_3Cl, $AlCl_3$; 5. H_2O, NaOH

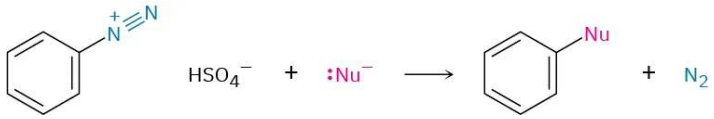
Diazonium Salts: The Sandmeyer Reaction

Primary arylamines react with nitrous acid, HNO_2, to yield stable arenediazonium salts, $Ar-\overset{+}{N}\equiv NX^-$ a process called a **diazotization reaction**. Alkylamines also react with nitrous acid, but the corresponding alkanediazonium products are so reactive

they can't be isolated. Instead, they lose nitrogen instantly to yield carbocations. The analogous loss of N_2 from an arenediazonium ion to yield an aryl cation is disfavored by the instability of the cation.

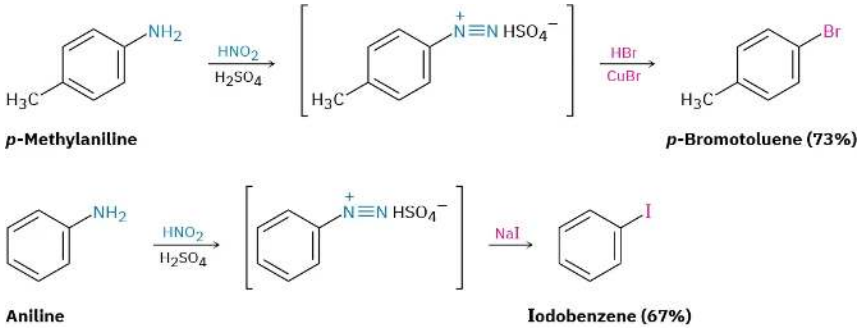


Arenediazonium salts are useful because the diazonio group (–N≡N) can be replaced by a nucleophile in a substitution reaction.

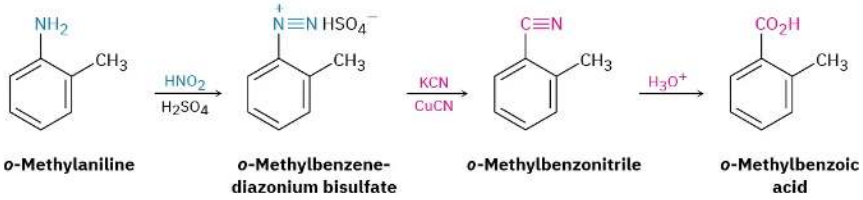


Many different nucleophiles—halide, hydride, cyanide, and hydroxide among others—react with arenediazonium salts, yielding many different kinds of substituted benzenes. The overall sequence of (**1**) nitration, (**2**) reduction, (**3**) diazotization, and (**4**) nucleophilic substitution is perhaps the single most versatile method of aromatic substitution.

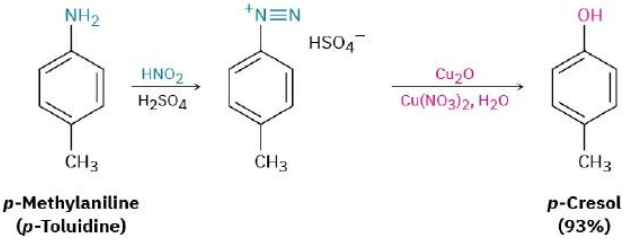
Aryl chlorides and bromides are prepared by reaction of an arenediazonium salt with the corresponding copper(I) halide, CuX, a process called the **Sandmeyer reaction**. Aryl iodides can be prepared by direct reaction with NaI without using a copper(I) salt. Yields generally fall between 60% and 80%.



Similar treatment of an arenediazonium salt with CuCN yields the nitrile ArCN, which can then be further converted into other functional groups such as carboxyl. For example, Sandmeyer reaction of o-methylbenzenediazonium bisulfate with CuCN yields o-methylbenzonitrile, which can be hydrolyzed to give o-methylbenzoic acid. This product can't be prepared from o-xylene by the usual side-chain oxidation route because both methyl groups would be oxidized.

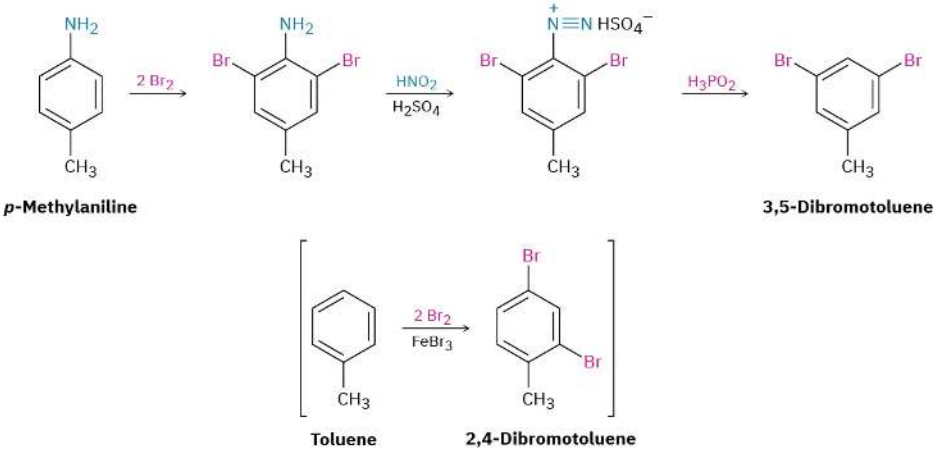


The diazonio group can also be replaced by –OH to yield a phenol and by –H to yield an arene. A phenol is prepared by reaction of the arenediazonium salt with copper(I) oxide in an aqueous solution of copper(II) nitrate, a reaction that is especially useful because few other general methods exist for introducing an –OH group onto an aromatic ring.

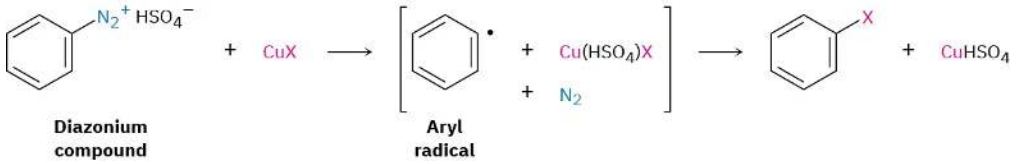


Reduction of a diazonium salt to give an arene occurs on treatment with hypophosphorous acid, H_3PO_2. This reaction is used primarily when there is a need for temporarily introducing an amino substituent onto a ring to take advantage of its directing effect.

Suppose, for instance, that you needed to make 3,5-dibromotoluene. This product can't be made by direct bromination of toluene because reaction would occur at positions 2 and 4. Starting with p-methylaniline (p-toluidine), however, dibromination occurs ortho to the strongly directing amino substituent, and diazotization followed by treatment with H_3PO_2 to remove the amino group yields the desired product.

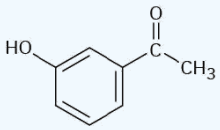


Mechanistically, these diazonio replacement reactions occur through radical rather than polar pathways. In the presence of a copper(I) compound, for instance, it's thought that the arenediazonium ion is first converted to an aryl radical plus copper(II), followed by subsequent reaction to give product plus regenerated copper(I) catalyst.



Worked Example 8.13.1.9.1: Using Diazonium Replacement Reactions

How would you prepare m-hydroxyacetophenone from benzene, using a diazonium replacement reaction in your scheme?



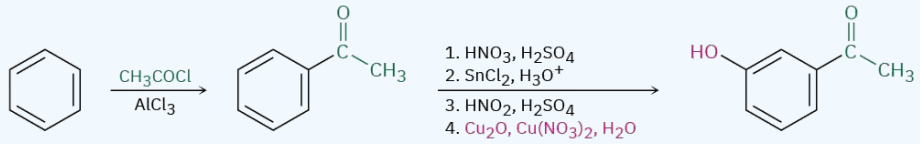
***m*-Hydroxyacetophenone**

Strategy

As always, organic syntheses are planned by working retrosynthetically from the final product, one step at a time. First, identify the functional groups in the product and recall how those groups can be synthesized. m-Hydroxyacetophenone has an –OH group and a $–COCH_3$ group in a meta relationship on a benzene ring. A hydroxyl group is generally introduced onto an aromatic ring by a four-step sequence of nitration, reduction, diazotization, and diazonio replacement. An acetyl group is introduced by a Friedel–Crafts acylation reaction.

Next, ask yourself what an immediate precursor of the target might be. Since an acetyl group is a meta director while a hydroxyl group is an ortho and para director, acetophenone might be a precursor of m-hydroxyacetophenone. Benzene, in turn, is a precursor of acetophenone.

Solution



https://chem.libretexts.org/@go/page/564261

? Exercise 8.13.1.9.3

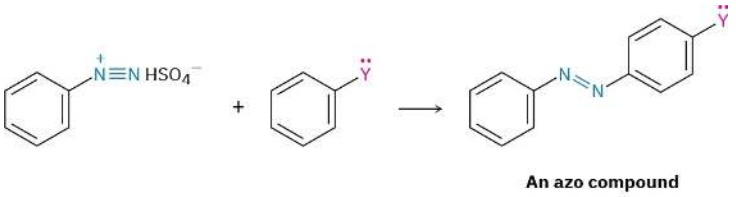
a. p-Bromobenzoic acid
b. m-Bromobenzoic acid
c. m-Bromochlorobenzene
d. p-Methylbenzoic acid
e. 1,2,4-Tribromobenzene

Answer

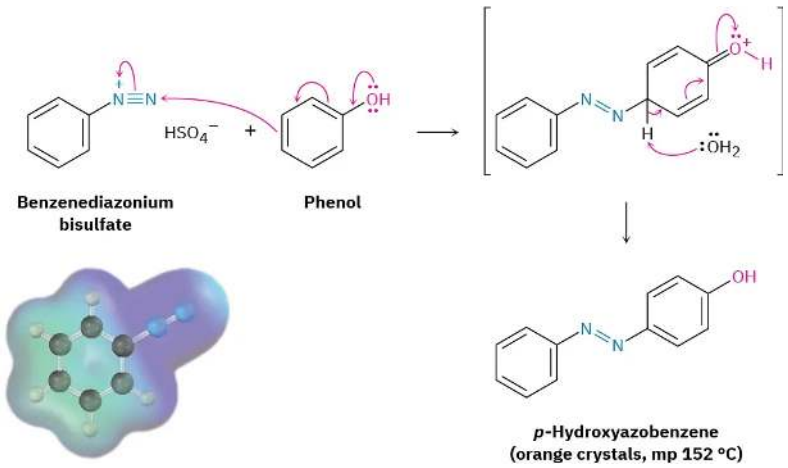
a. 1. CH_3Cl, $AlCl_3$; 2. HNO_3, H_2SO_4; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuBr; 6. $KMnO_4$, H_2O
b. 1. HNO_3, H_2SO_4; 2. Br_2, $FeBr_3$; 3. $SnCl_2$, H_3O^+; 4. $NaNO_2$, H_2SO_4; 5. CuCN; 6. H_3O^+
c. 1. HNO_3, H_2SO_4; 2. Cl_2, $FeCl_3$; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuBr
d. 1. CH_3Cl, $AlCl_3$; 2. HNO_3, H_2SO_4; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuCN; 6. H_3O^+
e. 1. HNO_3, H_2SO_4; 2. H_2/PtO_2; 3. $(CH_3CO)_2O$; 4. 2 Br_2; 5. H_2O, NaOH; 6. $NaNO_2$, H_2SO_4; 7. CuBr

Diazonium Coupling Reactions

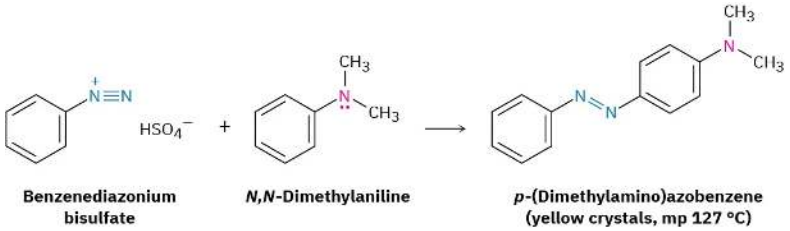
Arenediazonium salts undergo a coupling reaction with activated aromatic rings such as phenols and arylamines to yield brightly colored azo compounds, $\mathbf{Ar{-}N{=}N{-}Ar'}$.



Diazonium coupling reactions are typical electrophilic aromatic substitutions in which the positively charged diazonium ion is the electrophile that reacts with the electron-rich ring of a phenol or arylamine. Reaction usually occurs at the para position.



Azo-coupled products are widely used as dyes for textiles because their extended conjugated π electron system causes them to absorb in the visible region of the electromagnetic spectrum (Section 14.9). p-(Dimethylamino)-azobenzene, for instance, is a bright yellow compound that was at one time used as a coloring agent in margarine.



Exercise 8.13.1.9.4

Propose a synthesis of *p*-(dimethylamino)azobenzene with benzene as your only organic starting material.

Answer

1. HNO_3, H_2SO_4; 2. $SnCl_2$; 3a. 2 equiv. CH_3I; 3b. $NaNO_2$, H_2SO_4; 4. product of 3a + product of 3b

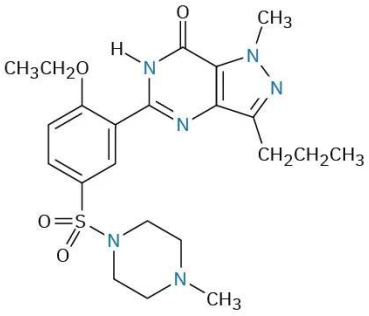
This page titled 8.13.1.9: Reactions of Arylamines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.8: Reactions of Arylamines** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

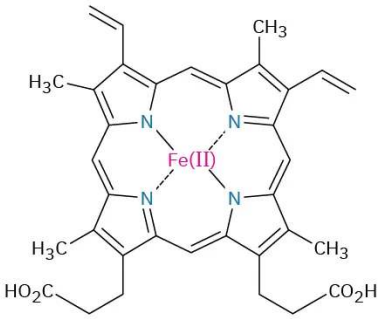
8.13.1.10: Heterocyclic Amines

As noted in Section 15.5 in connection with a discussion of aromaticity, a cyclic organic compound that contains atoms of two or more elements in its ring is a called a *heterocycle*. Heterocyclic amines are particularly common, and many have important biological properties. Pyridoxal phosphate, a coenzyme; sildenafil (Viagra), a well-known pharmaceutical; and heme, the oxygen carrier in blood, are a few examples.

Pyridoxal phosphate (a coenzyme)



Sildenafil (Viagra)

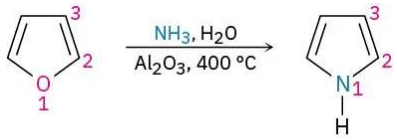


Heme

Most heterocycles have the same chemistry as their open-chain counterparts. Lactones and acyclic esters behave similarly, lactams and acyclic amides behave similarly, and cyclic and acyclic ethers behave similarly. In certain cases, however, particularly when the ring is unsaturated, heterocycles have unique and interesting properties.

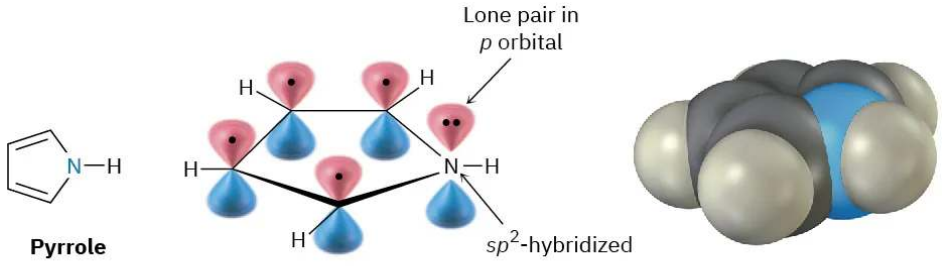
Pyrrole and Imidazole

Pyrrole, the simplest five-membered unsaturated heterocyclic amine, is obtained commercially by treatment of furan with ammonia over an alumina catalyst at 400 °C. Furan, the oxygen-containing analog of pyrrole, is obtained by acid-catalyzed dehydration of the five-carbon sugars found in oat hulls and corncobs.



Furan **Pyrrole**

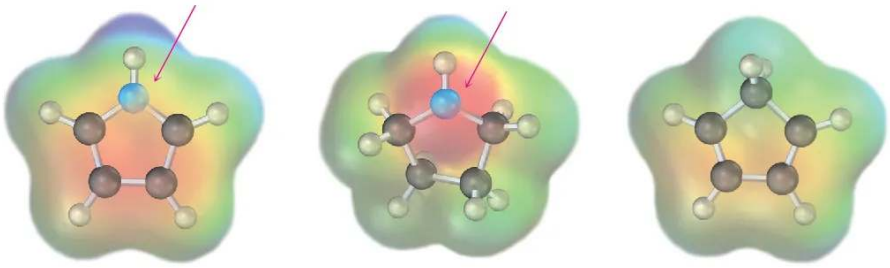
Although pyrrole appears to be both an amine and a conjugated diene, its chemical properties are not consistent with either of these structural features. Unlike most other amines, pyrrole is not basic—the pK_a of the pyrrolinium ion is 0.4; unlike most other conjugated dienes, pyrrole undergoes electrophilic substitution reactions rather than additions. The reason for both of these properties, as noted in Section 15.5, is that pyrrole has six π electrons and is aromatic. Each of the four carbons contributes one π electron, and the sp^2-hybridized nitrogen contributes two more from its lone pair.



Pyrrole **Six π electrons**

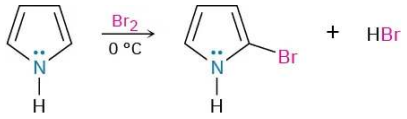
Because the nitrogen lone pair is a part of the aromatic sextet, protonation on nitrogen would destroy the aromaticity of the ring. The nitrogen atom in pyrrole is therefore less electron-rich, less basic, and less nucleophilic than the nitrogen in an aliphatic amine. By the same token, the carbon atoms of pyrrole are more electron-rich and more nucleophilic than typical double-bond carbons.

The pyrrole ring is therefore reactive toward electrophiles in the same way as enamines (Section 23.11). Electrostatic potential maps show how the pyrrole nitrogen is electron-poor (less red) compared with the nitrogen in its saturated counterpart pyrrolidine, while the pyrrole carbon atoms are electron-rich (more red) compared with the carbons in 1,3-cyclopentadiene.



Pyrrole **Pyrrolidine** **1,3-Cyclopentadiene**

The chemistry of pyrrole is similar to that of activated benzene rings. In general, however, the heterocycles are more reactive toward electrophiles than benzene rings, and low temperatures are often necessary to control the reactions. Halogenation, nitration, sulfonation, and Friedel–Crafts acylation can all be accomplished. For example:



Pyrrole **2-Bromopyrrole (92%)**

Electrophilic substitutions normally occur at C2, the position next to the nitrogen, because reaction at this position leads to a more stable intermediate cation having three resonance forms, whereas reaction at C3 gives a less stable cation with only two resonance forms (Figure 8.13.1.10.1).

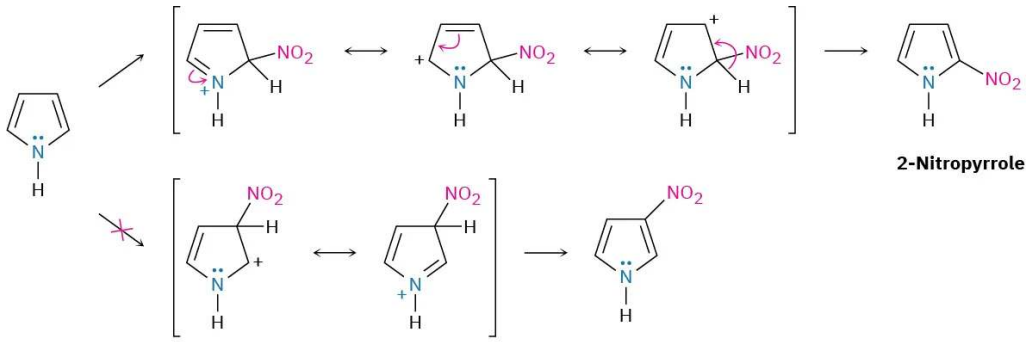
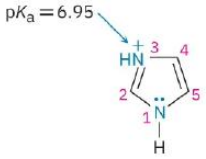
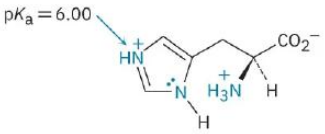


Figure 8.13.1.10.1: Electrophilic nitration of pyrrole. The intermediate produced by reaction at C2 is more stable than that produced by reaction at C3.

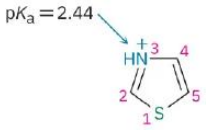
Other common five-membered heterocyclic amines include imidazole and thiazole. Imidazole, a constituent of the amino acid histidine, has two nitrogens, only one of which is basic. Thiazole, the five-membered ring system on which the structure of thiamin (vitamin B_1) is based, also contains a basic nitrogen that is alkylated in thiamin to form a quaternary ammonium ion.



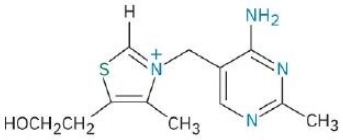
Imidazole



Histidine



Thiazole

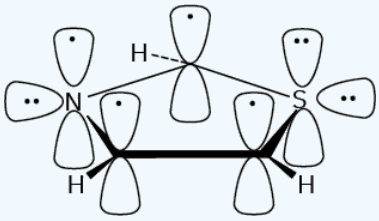


Thiamin (vitamin B_1)

? Exercise 8.13.1.10.1

Draw an orbital picture of thiazole. Assume that both the nitrogen and sulfur atoms are sp^2-hybridized, and show the orbitals that the lone pairs occupy.

Answer



? Exercise 8.13.1.10.2

What is the percent protonation of the imidazole nitrogen atom in histidine at a physiological pH of 7.3 **(Section 24.5)**?

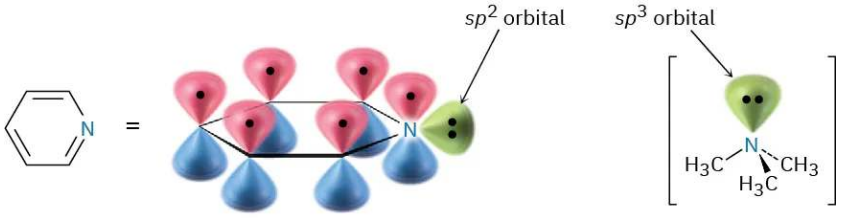
Answer

4.1% protonated

Pyridine and Pyrimidine

Pyridine is the nitrogen-containing heterocyclic analog of benzene. Like benzene, pyridine is a flat, aromatic molecule, with bond angles of 120° and C–C bond lengths of 139 pm, intermediate between typical single and double bonds. The five carbon atoms and the sp^2-hybridized nitrogen atom each contribute one π electron to the aromatic sextet, and the lone-pair electrons occupy an sp^2 orbital in the plane of the ring (Section 15.5).

As shown previously in Table 24.1, pyridine (pK_a = 5.25) is a stronger base than pyrrole but a weaker base than the alkylamines. The diminished basicity of pyridine compared with that of alkylamines is due to the fact that the lone-pair electrons on the pyridine nitrogen are in an sp^2 orbital, while those on an alkylamine nitrogen are in an sp^3 orbital. Because s orbitals have their maximum electron density at the nucleus but p orbitals have a node at the nucleus, electrons in an orbital with more s character are held more closely to the positively charged nucleus and are less available for bonding. As a result, the sp^2-hybridized nitrogen atom (33% s character) in pyridine is less basic than the sp^3-hybridized nitrogen in an alkylamine (25% s character).

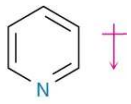


Pyridine

Unlike benzene, pyridine undergoes electrophilic aromatic substitution reactions with difficulty. Halogenation can be carried out under drastic conditions, but nitration occurs in very low yield, and Friedel–Crafts reactions are not successful. Reactions usually give the 3-substituted product.

Pyridine **3-Bromopyridine (30%)**

The low reactivity of pyridine toward electrophilic aromatic substitution is caused by a combination of factors. One is that acid–base complexation between the basic ring's nitrogen atom and the incoming electrophile places a positive charge on the ring, thereby deactivating it. Equally important is that the electron density of the ring is decreased by the electron-withdrawing inductive effect of the electronegative nitrogen atom. Thus, pyridine has a substantial dipole moment (μ = 2.26 D), with the ring carbons acting as the positive end of the dipole. Reaction of an electrophile with the positively polarized carbon atoms is therefore difficult.



μ = 2.26 D

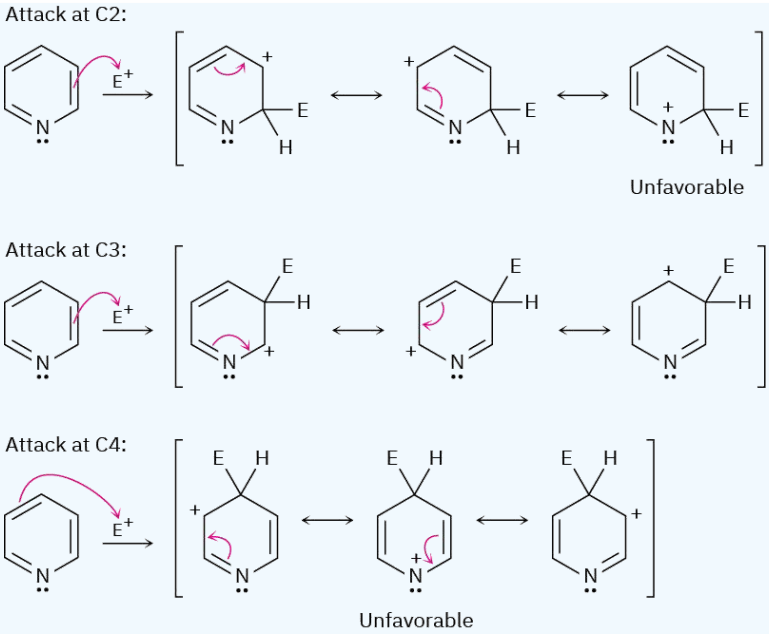
In addition to pyridine, the six-membered diamine pyrimidine is also found commonly in biological molecules, particularly as a constituent of nucleic acids. With a pK_a of 1.3, pyrimidine is substantially less basic than pyridine because of the inductive effect of the second nitrogen.

Pyrimidine
$pK_a = 1.3$

? Exercise 8.13.1.10.3

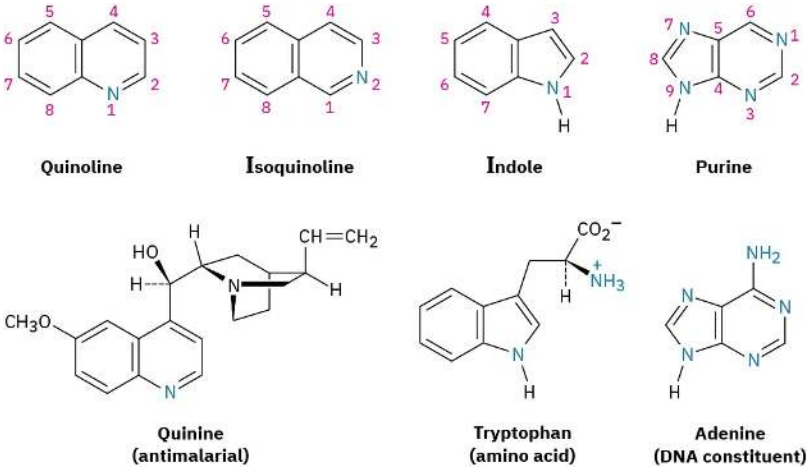
Electrophilic aromatic substitution reactions of pyridine normally occur at C3. Draw the carbocation intermediates resulting from reaction of an electrophile at C2, C3, and C4, and explain the observed result.

Answer

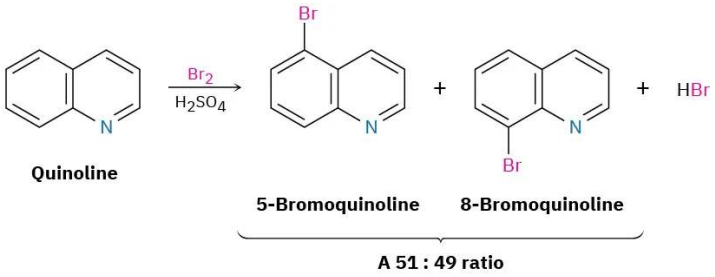


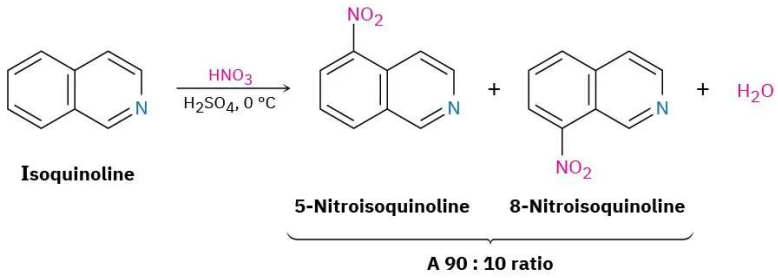
Polycyclic Heterocycles

As we saw in Section 15.6, quinoline, isoquinoline, indole, and purine are common polycyclic heterocycles. The first three contain both a benzene ring and a heterocyclic aromatic ring, while purine contains two heterocyclic rings joined together. All four ring systems occur commonly in nature, and many compounds with these rings have pronounced physiological activity. The quinoline alkaloid quinine, for instance, is widely used as an antimalarial drug; tryptophan is a common amino acid; and the purine adenine is a constituent of nucleic acids.



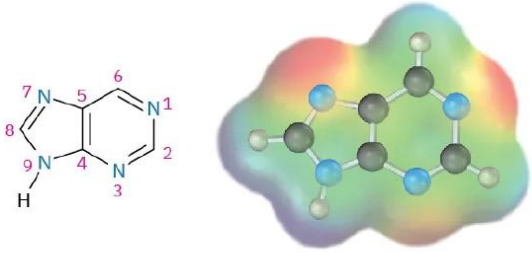
The chemistry of these polycyclic heterocycles is just what you might expect from a knowledge of the simpler heterocycles pyridine and pyrrole. Quinoline and isoquinoline both have basic, pyridine-like nitrogen atoms, and both undergo electrophilic substitutions. As with pyridine, both quinoline and isoquinoline are less reactive toward electrophilic substitution than benzene because of the electronegative nitrogen atom that withdraws electrons from the ring. Reaction occurs on the benzene ring rather than on the nitrogen-containing pyridine ring, and a mixture of substitution products is obtained.





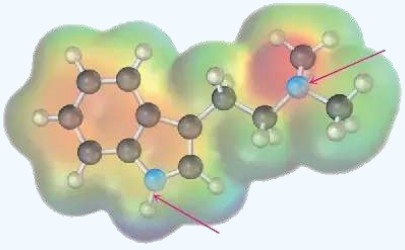
Indole has a nonbasic, pyrrole-like nitrogen and undergoes electrophilic substitution more easily than benzene. Substitution occurs at C3 of the electron-rich pyrrole ring rather than on the benzene ring.

Purine has three basic, pyridine-like nitrogens with lone-pair electrons in sp^2 orbitals in the plane of the ring. The remaining purine nitrogen is nonbasic and pyrrole-like, with its lone-pair electrons as part of the aromatic π electron system.



? Exercise 8.13.1.10.4

Which nitrogen atom in the hallucinogenic indole alkaloid N,N-dimethyltryptamine is more basic? Explain.



***N,N*-Dimethyltryptamine**

Answer

https://chem.libretexts.org/@go/page/564262

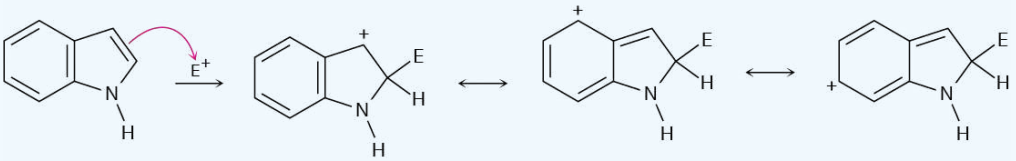
The side-chain nitrogen is more basic than the ring nitrogen.

Exercise 8.13.1.10.1

Indole reacts with electrophiles at C3 rather than at C2. Draw resonance forms of the intermediate cations resulting from reaction at C2 and C3, and explain the observed results.

Answer

Reaction at C2 is disfavored because the aromaticity of the benzene ring is lost.



This page titled 8.13.1.10: Heterocyclic Amines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.9: Heterocyclic Amines** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.13.1.11: Spectroscopy of Amines

Infrared Spectroscopy

Primary and secondary amines can be identified by a characteristic N–H stretching absorption in the 3300 to 3500 cm^{-1} range of the IR spectrum. Alcohols also absorb in this range (Section 17.11), but amine absorption bands are generally sharper and less intense than hydroxyl bands. Primary amines show a pair of bands at about 3350 and 3450 cm^{-1} from the symmetric and asymmetric stretching modes, and secondary amines show a single band at 3350 cm^{-1}. Tertiary amines have no absorption in this region because they have no N–H bonds. Figure 24.9 recalls the IR spectrum of cyclohexylamine from Section 12.8.

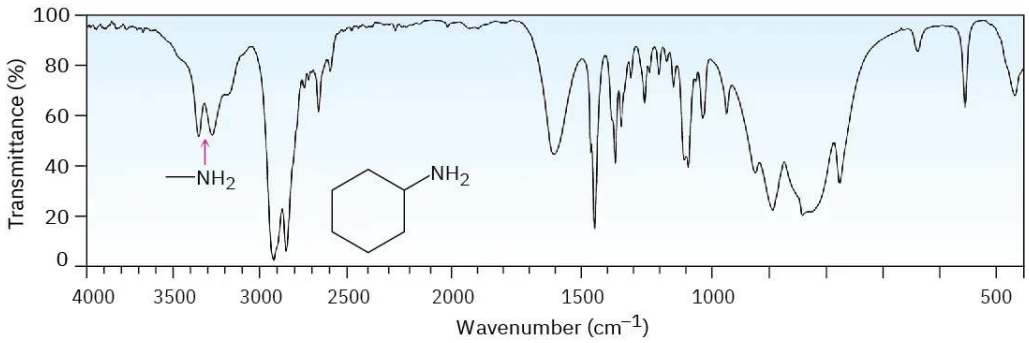
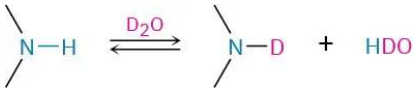


Figure 24.9: IR spectrum of cyclohexylamine.

Nuclear Magnetic Resonance Spectroscopy

Amines are difficult to identify solely by ^1H NMR spectroscopy because N–H hydrogens tend to appear as broad signals without clear-cut coupling to neighboring C–H hydrogens. As with O–H absorptions (Section 17.11), amine N–H absorptions can appear over a wide range and are best identified by adding a small amount of D_2O to the sample. Exchange of N–D for N–H occurs, and the N–H signal disappears from the NMR spectrum.



Hydrogens on the carbon next to nitrogen are deshielded because of the electron-withdrawing effect of the nitrogen, and they therefore absorb further downfield than alkane hydrogens. *N*-Methyl groups are particularly distinctive because they absorb as a sharp three-proton singlet at 2.2 to 2.6 δ. This *N*-methyl resonance at 2.42 δ is easily seen in the ^1H NMR spectrum of *N*-methylcyclohexylamine (Figure 8.13.1.11.1).

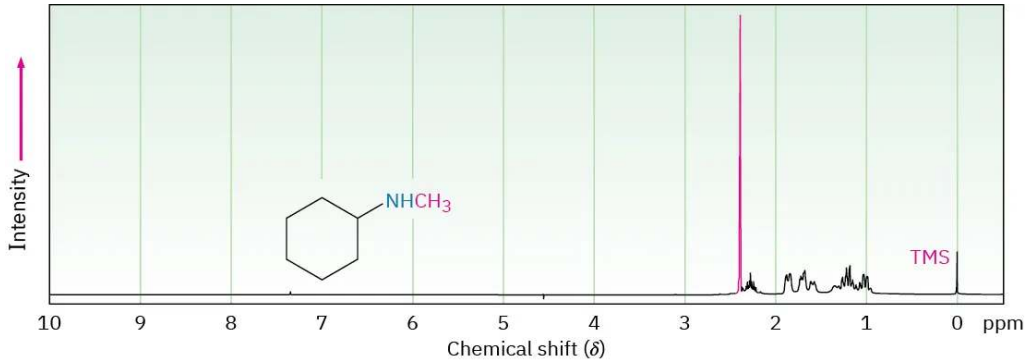
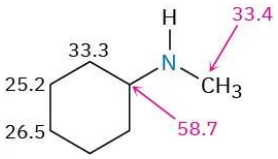


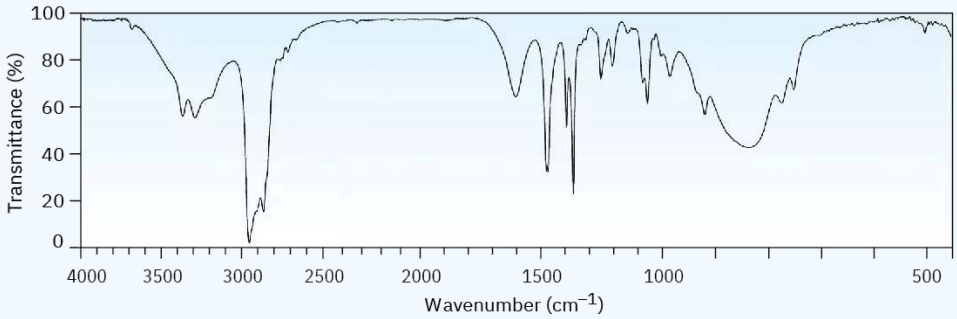
Figure 8.13.1.11.1: Proton NMR spectrum of *N*-methylcyclohexylamine.

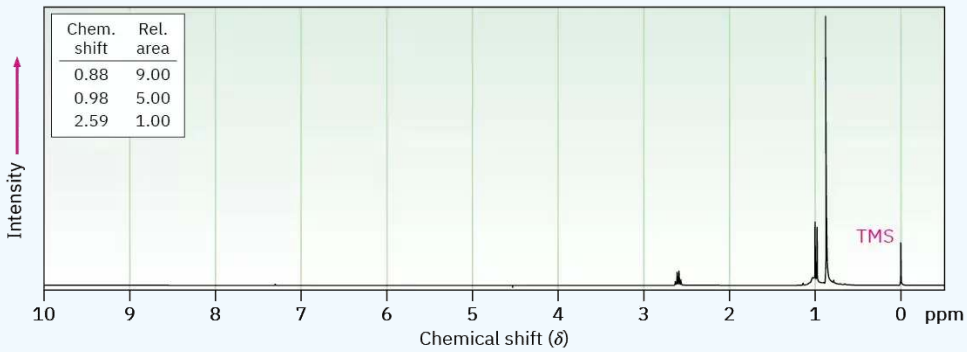
Carbons next to amine nitrogens are slightly deshielded in the ^{13}C NMR spectrum and absorb about 20 ppm downfield from where they would absorb in an alkane of similar structure. In *N*-methylcyclohexylamine, for example, the ring carbon to which nitrogen is attached absorbs at a position 24 ppm downfield from any other ring carbon.



? Exercise 8.13.1.11.1

Compound **A**, $C_6H_{12}O$, has an IR absorption at 1715 cm^{-1} and gives compound **B**, $C_6H_{15}N$, when treated with ammonia and $NaBH_4$. The IR and ^1H NMR spectra of **B** are shown. What are the structures of **A** and **B**?





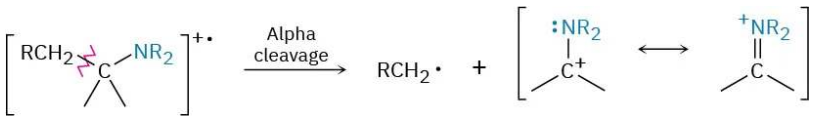
Answer

$(CH_3)_3CCOCH_3 \longrightarrow (CH_3)_3CCH(NH_2)CH_3$

Mass Spectrometry

The *nitrogen rule* of mass spectrometry says that a compound with an odd number of nitrogen atoms has an odd-numbered molecular weight. Thus, the presence of nitrogen in a molecule is detected simply by observing its mass spectrum. An odd-numbered molecular ion usually means that the unknown compound has one or three nitrogen atoms, and an even-numbered molecular ion usually means that a compound has either zero or two nitrogen atoms. The logic behind the rule derives from the fact that nitrogen is trivalent, thus requiring an odd number of hydrogen atoms. For example, morphine has the formula $C_{17}H_{19}NO_3$ and a molecular weight of 285 amu.

Alkylamines undergo a characteristic α cleavage in the mass spectrometer, similar to the cleavage observed for alcohols (Section 17.11). C–C bond nearest the nitrogen atom is broken, yielding an alkyl radical and a resonance-stabilized, nitrogen-containing cation.



As an example, the mass spectrum of *N*-ethylpropylamine shown in Figure 8.13.1.11.2 has peaks at m/z = 58 and m/z = 72, corresponding to the two possible modes of α cleavage.

https://chem.libretexts.org/@go/page/564263

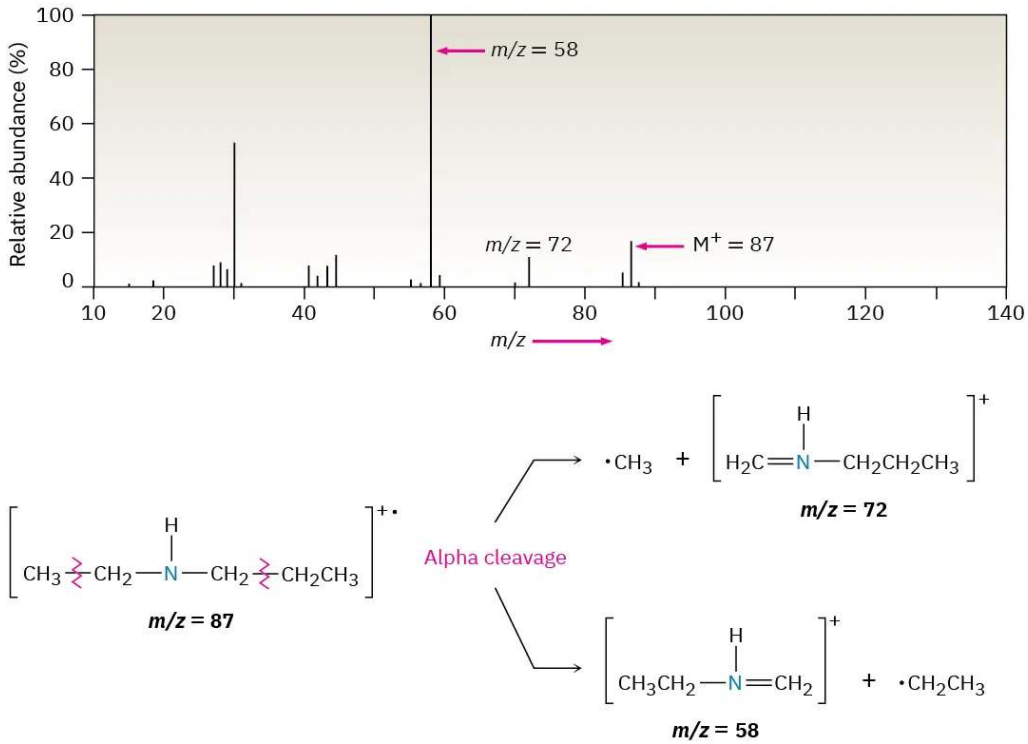


Figure 8.13.1.11.2: Mass spectrum of *N*-ethylpropylamine. The two possible modes of *α* cleavage lead to the observed fragment ions at *m*/*z* = 58 and *m*/*z* = 72.

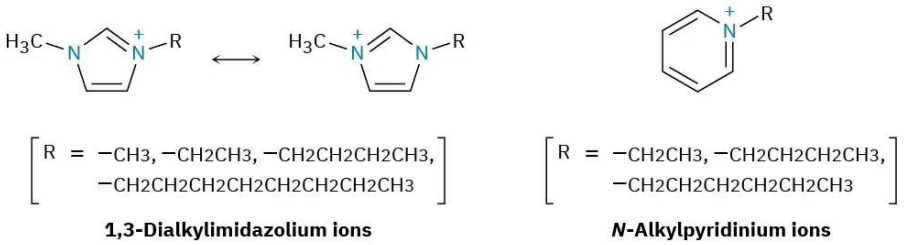
This page titled 8.13.1.11: Spectroscopy of Amines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.10: Spectroscopy of Amines** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.13.1.12: Chemistry Matters - Green Chemistry II- Ionic Liquids

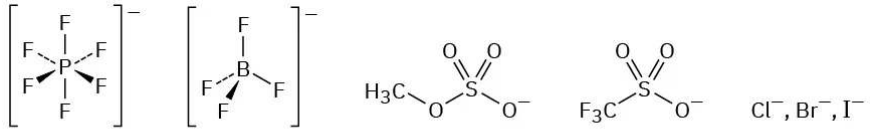
Liquids made of ions? Usually when we think of ionic compounds, we think of high-melting solids: sodium chloride, magnesium sulfate, lithium carbonate, and so forth. But yes, there are also ionic compounds that are liquid at room temperature, and they are gaining importance as reaction solvents, particularly for use in green chemistry processes (see the Chapter 11 *Chemistry Matters*). More than 1500 ionic liquids are known, and about 500 are available commercially.

Ionic liquids have been studied for nearly a century; the first to be discovered was ethylammonium nitrate, $CH_3CH_2NH_3^+\ NO_3^-$, with a melting point of 12 °C. More generally, however, the ionic liquids in use today are salts in which the cation is unsymmetrical and in which one or both of the ions are bulky so that the charges are dispersed over a large volume. Both factors minimize the crystal lattice energy and disfavor formation of the solid. Typical cations are quaternary ammonium ions from heterocyclic amines, either 1,3-dialkylimidazolium ions, *N*-alkylpyridinium ions, or ring-substituted *N*-alkylpyridinium ions.



1,3-Dialkylimidazolium ions **N-Alkylpyridinium ions**

Anions are just as varied as the cations. Hexafluorophosphate, tetrafluoroborate, alkyl sulfates, trifluoromethanesulfonates (triflates), and halides are some anion possibilities.

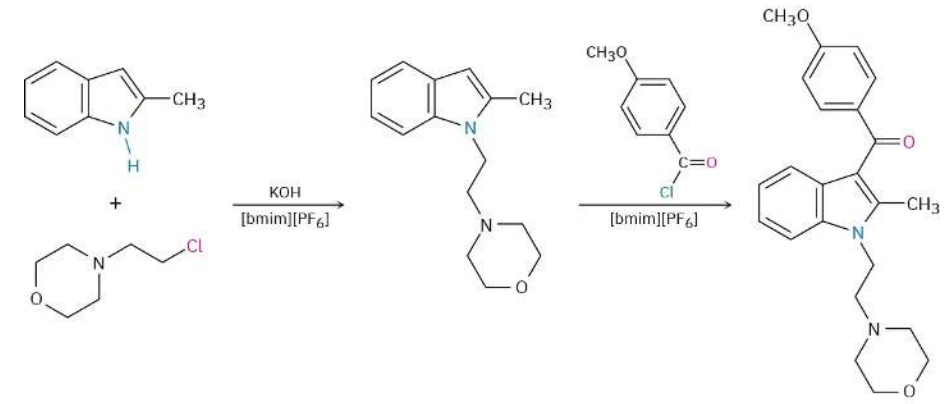


Hexafluoro-phosphate **Tetrafluoro-borate** **Methyl sulfate** **Trifluoromethane-sulfonate** **Halide**

Ionic liquids have several important features that make them attractive for use, both as solvents in green chemistry and as specialty chemicals in such applications as paint additives and refrigerants:

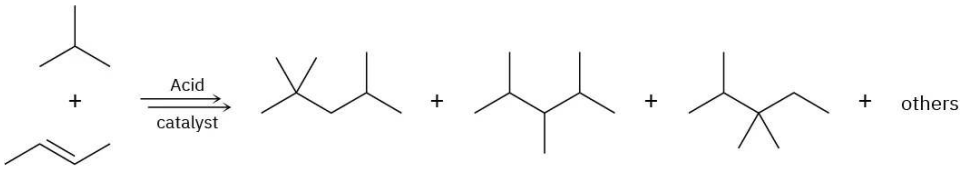
- They dissolve both polar and nonpolar organic compounds, giving high solute concentrations and thereby minimizing the amount of solvent needed.
- They can be optimized for specific reactions by varying cation and anion structures.
- They are nonflammable.
- They are thermally stable.
- They have negligible vapor pressures and do not evaporate.
- They are generally recoverable and can be reused many times.

As an example of their use in organic chemistry, the analgesic drug pravadoline has been synthesized in two steps using 1-butyl-3-methylimidazolium hexafluorophosphate, abbreviated [bmim][PF_6], as the solvent for both steps. The first step is a base-induced S_N2 reaction of 2-methylindole with a primary alkyl halide, and the second is a Friedel–Crafts acylation. Both steps take place with 95% yield, and the ionic solvent is recovered simply by washing the reaction mixture, first with toluene and then with water.



Pravadoline

The first commercial process using an ionic liquid catalyst was introduced by PetroChina in 2008, when they opened a plant producing 65,000 tons per year of alkylate gasoline from isobutane. The aluminum-based ionic liquid catalyst replaced the sulfuric acid and hydrofluoric acid catalysts that had previously been used.



52% **20%** **18%**

This page titled 8.13.1.12: Chemistry Matters - Green Chemistry II- Ionic Liquids is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.11: Chemistry Matters - Green Chemistry II- Ionic Liquids** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.13.1.13: Key Terms

- alkylamine
- amine
- arylamine
- azo compound ($\mathrm{R–N=N–R'}$)
- Curtius rearrangement
- Gabriel amine synthesis
- heterocyclic amine
- Hofmann elimination reaction
- Hofmann rearrangement
- imide ($\mathrm{O=C–N–C=O}$)
- primary amine ($\mathrm{RNH_2}$)
- quaternary ammonium salt
- reductive amination
- Sandmeyer reaction
- secondary amine ($\mathrm{R_2NH}$)
- tertiary amine ($\mathrm{R_3N}$)

This page titled 8.13.1.13: Key Terms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.12: Key Terms** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.13.1.14: Summary

We've now seen all the common functional groups that occur in organic and biological chemistry. Of those groups, amines are among the most abundant and have among the richest chemistry. In addition to proteins and nucleic acids, the majority of pharmaceutical agents contain amine functional groups and many of the common coenzymes necessary for biological reactions are amines.

Amines are organic derivatives of ammonia. They are named in the IUPAC system either by adding the suffix *-amine* to the name of the alkyl substituent or by considering the amino group as a substituent on a more complex parent molecule.

The chemistry of amines is dominated by the lone-pair electrons on nitrogen, which makes amines both basic and nucleophilic. The basicity of **arylamines** is generally lower than that of **alkylamines** because the nitrogen lone-pair electrons are delocalized by interaction with the aromatic π system. Electron-withdrawing substituents on the aromatic ring further weaken the basicity of a substituted aniline, while electron-donating substituents increase basicity. Alkylamines are sufficiently basic that they exist almost entirely in their protonated form at the physiological pH of 7.3.

Heterocyclic amines are compounds that contain one or more nitrogen atoms as part of a ring. Saturated heterocyclic amines usually have the same chemistry as their open-chain analogs, but unsaturated heterocycles such as pyrrole, imidazole, pyridine, and pyrimidine are aromatic. All four are unusually stable, and all undergo aromatic substitution on reaction with electrophiles. Pyrrole is nonbasic because its nitrogen lone-pair electrons are part of the aromatic π system. Fused-ring heterocycles such as quinoline, isoquinoline, indole, and purine are also commonly found in biological molecules.

Arylamines are prepared by nitration of an aromatic ring followed by reduction. Alkylamines are prepared by S_N2 reaction of ammonia or an amine with an alkyl halide or by the **Gabriel amine synthesis**. Amines can also be prepared by a number of reductive methods, including $LiAlH_4$ reduction of amides, nitriles, and azides. Also important is the **reductive amination** reaction in which a ketone or an aldehyde is treated with an amine in the presence of a reducing agent such as $NaBH_4$. In addition, amines result from **Hofmann** and **Curtius rearrangements** of carboxylic acid derivatives. Both methods involve migration of the –R group bonded to the carbonyl carbon and yield a product that has one less carbon atom than the starting material.

Many of the reactions of amines are familiar from past chapters. Thus, amines react with alkyl halides in S_N2 reactions and with acid chlorides in nucleophilic acyl substitution reactions. Amines also undergo E2 elimination to yield alkenes if they are first quaternized by treatment with iodomethane and then heated with silver oxide, a process called the **Hofmann elimination**.

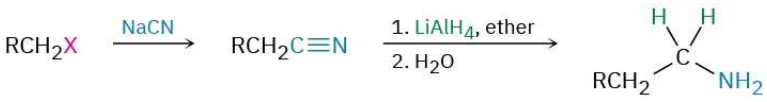
Arylamines are converted by diazotization with nitrous acid into **arenediazonium salts**, $ArN_2^+ X^-$. The diazonio group can then be replaced by many other substituents by the **Sandmeyer reaction** to give a wide variety of substituted aromatic compounds. Aryl chlorides, bromides, iodides, and nitriles can be prepared from arenediazonium salts, as can arenes and phenols. In addition to their reactivity toward substitution reactions, diazonium salts undergo coupling with phenols and arylamines to give brightly colored **azo compounds**.

This page titled 8.13.1.14: Summary is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

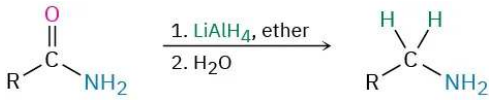
- **24.13: Summary** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.13.1.15: Summary of Reactions

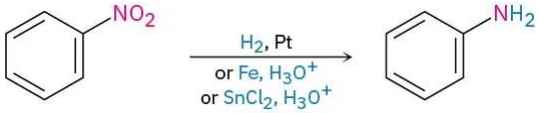
1. Synthesis of amines (Section 24.6)
   a. Reduction of nitriles



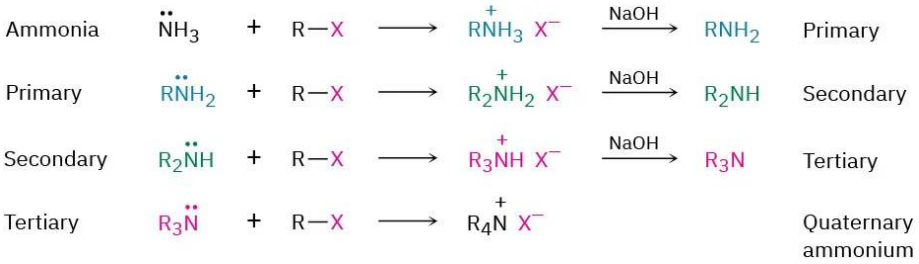
- Reduction of amides



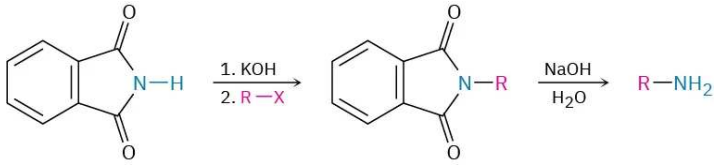
- Reduction of nitrobenzenes



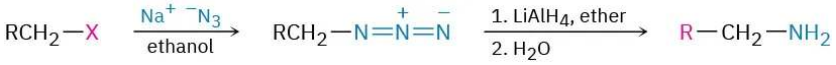
- S_N2 Alkylation of alkyl halides



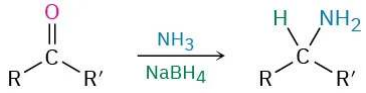
- Gabriel amine synthesis



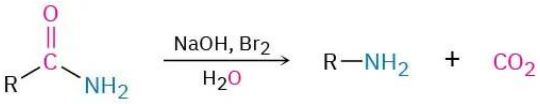
- Reduction of azides



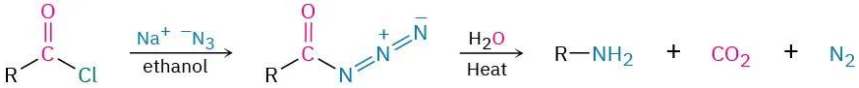
- Reductive amination of aldehydes/ketones



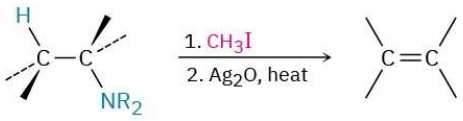
- Hofmann rearrangement of amides



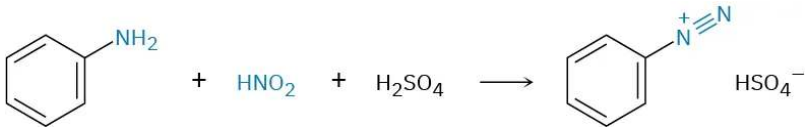
- Curtius rearrangement of acyl azides



- Reactions of amines
   a. Alkylation with alkyl halides; see reaction 1(d)
   b. Hofmann elimination (Section 24.7)

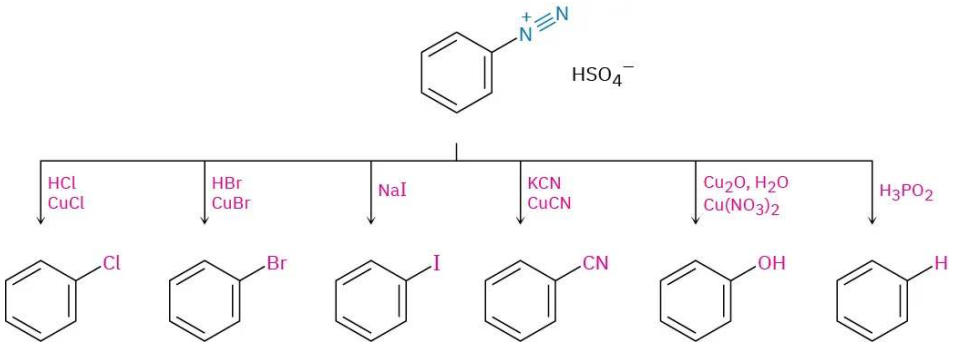


c. Diazotization (Section 24.8)

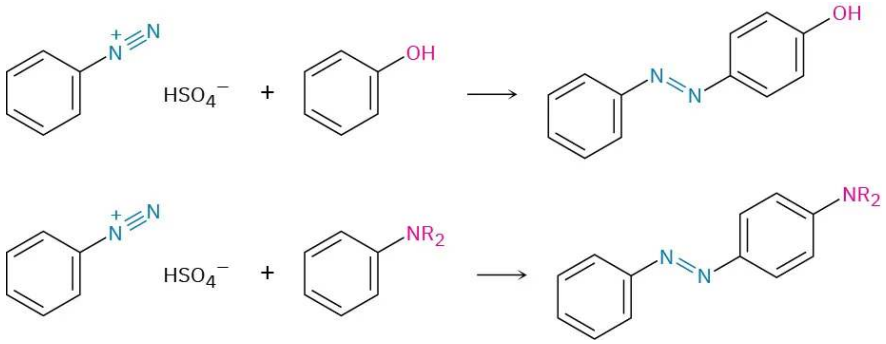


- Reactions of arenediazonium salts (Section 24.8)

a. Nucleophilic substitutions



b. Diazonium coupling



This page titled 8.13.1.15: Summary of Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

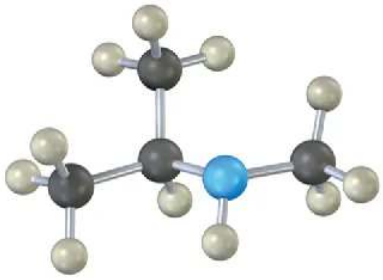
- **24.14: Summary of Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

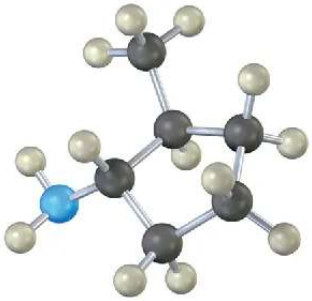
8.13.1.16: Additional Problems

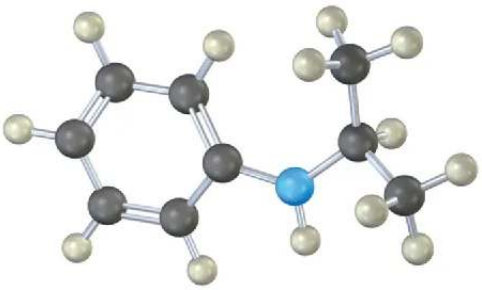
24 • Additional Problems

Visualizing Chemistry

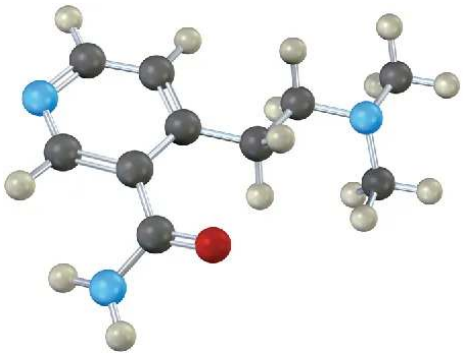
PROBLEM 24.26 Name the following amines, and identify each as primary, secondary, or tertiary:


(a)

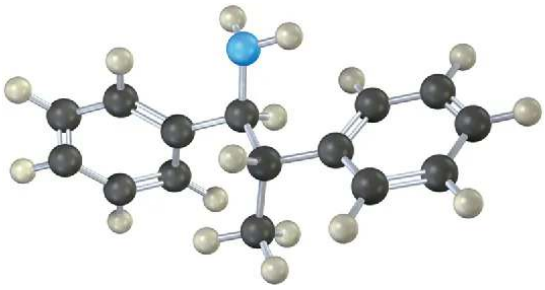

(b)


(c)

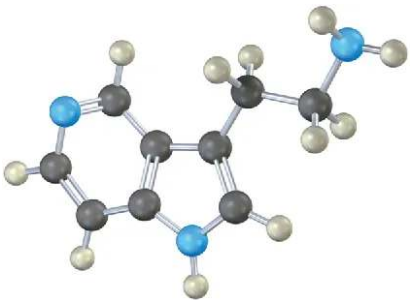
PROBLEM 24.27 The following compound contains three nitrogen atoms. Rank them in order of increasing basicity.



PROBLEM 24.28 Name the following amine, including *R*,*S* stereochemistry, and draw the product of its reaction with excess iodomethane followed by heating with Ag_2O (Hofmann elimination). Is the stereochemistry of the alkene product *Z* or *E*? Explain.

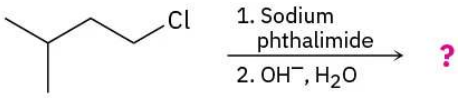


PROBLEM 24.29 Which nitrogen atom in the following compound is most basic? Explain.

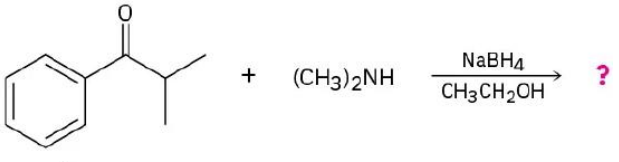


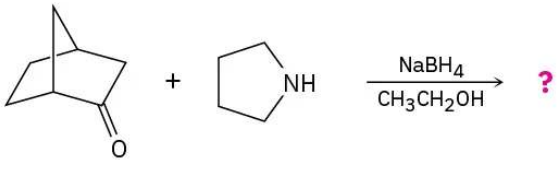
Mechanism Problems

PROBLEM 24.30

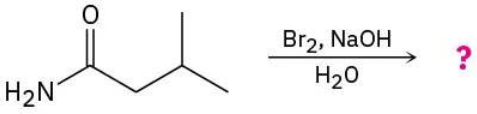
(a) (b) 

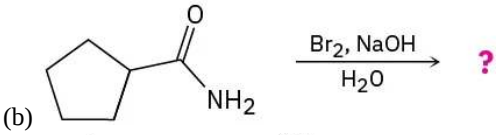
Problem 24-31 Predict the product(s) and write the mechanism for each of the following reactions:

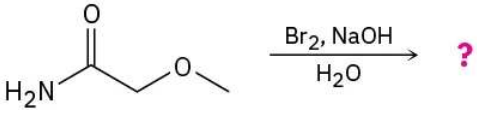
(a) 

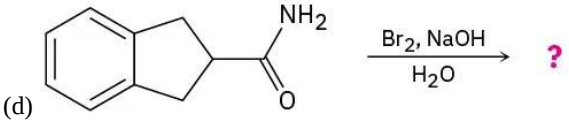
(b) 

Problem 24-32 Predict the product(s) and write the mechanism for each of the following reactions:

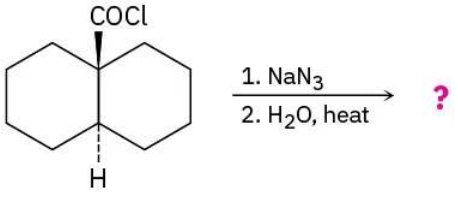
(a) 

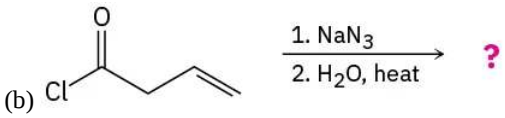
(b) 

(c) 

(d) 

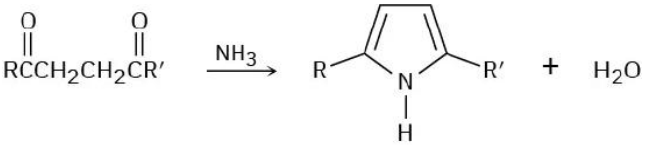
Problem 24-33 Predict the product(s) and write the mechanism for each of the following reactions:

(a) 

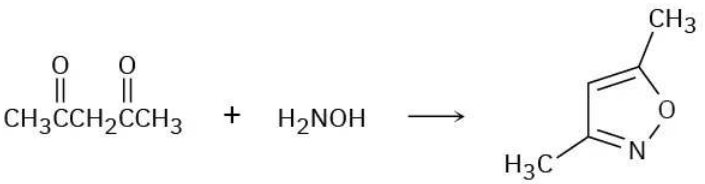
(b) 

Problem 24-34 The diazotization of aniline first involves the formation of NO^+ (nitrosonium ion) by the dehydration of nitrous acid with sulfuric acid. The aniline nitrogen then acts as a nucleophile and eventually loses water. Propose a mechanism for the formation of the dizaonium salt of aniline using curved arrows to show all electron movement.

Problem 24-35 Substituted pyrroles are often prepared by treatment of a 1,4-diketone with ammonia. Propose a mechanism.



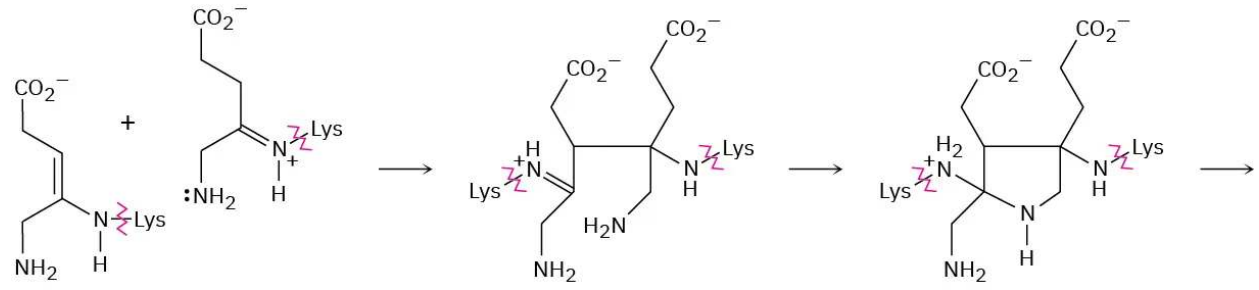
Problem 24-36 3,5-Dimethylisoxazole is prepared by reaction of 2,4-pentanedione with hydroxylamine. Propose a mechanism.



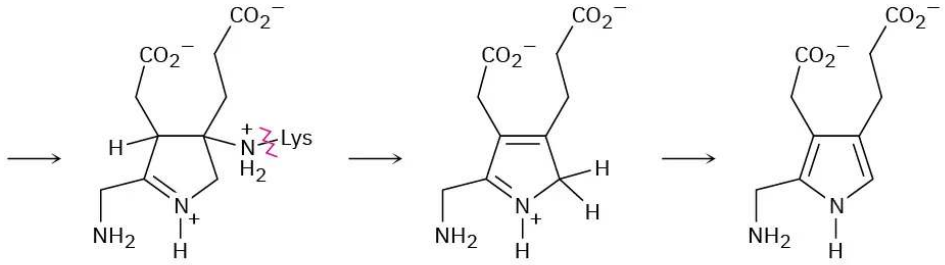
3,5-Dimethylisoxazole

Problem 24-37 One problem with reductive amination as a method of amine synthesis is that by-products are sometimes obtained. For example, reductive amination of benzaldehyde with methylamine leads to a mixture of *N*-methylbenzylamine and *N*-methyldibenzylamine. How do you suppose the tertiary amine by-product is formed? Propose a mechanism.

Problem 24-38 Chlorophyll, heme, vitamin B_{12}, and a host of other substances are biosynthesized from porphobilinogen (PBG), which is itself formed from condensation of two molecules of 5-aminolevulinate. The two 5-aminolevulinates are bound to lysine (Lys) amino acids in the enzyme, one in the enamine form and one in the imine form, and their condensation is thought to occur by the following steps. Use curved arrows to show the mechanism of each step.

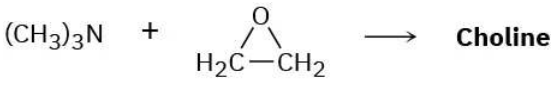


Enzyme-bound 5-aminolevulinate



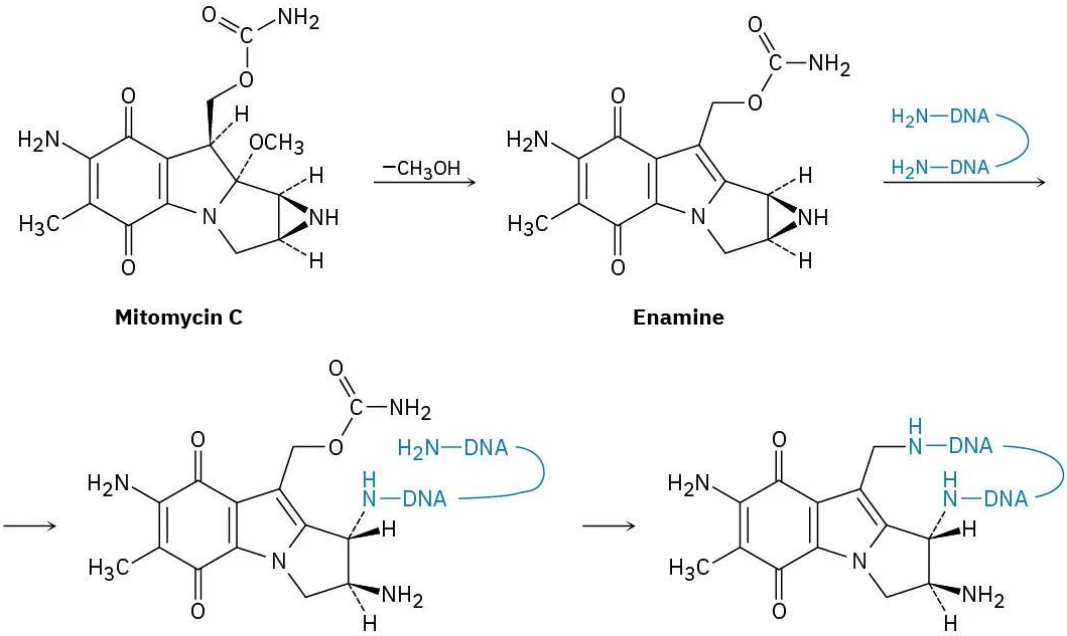
Porphobilinogen (PBG)

Problem 24-39 Choline, a component of the phospholipids in cell membranes, can be prepared by S_N2 reaction of trimethylamine with ethylene oxide. Show the structure of choline, and propose a mechanism for the reaction.



Choline

Problem 24-40 The antitumor antibiotic mitomycin C functions by forming cross-links in DNA chains.

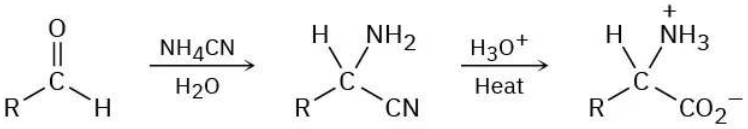


(a)The first step is loss of methoxide and formation of an iminium ion intermediate that is deprotonated to give an enamine. Show the mechanism.

(b) The second step is reaction of the enamine with DNA to open the three-membered, nitrogen-containing (aziridine) ring. Show the mechanism.

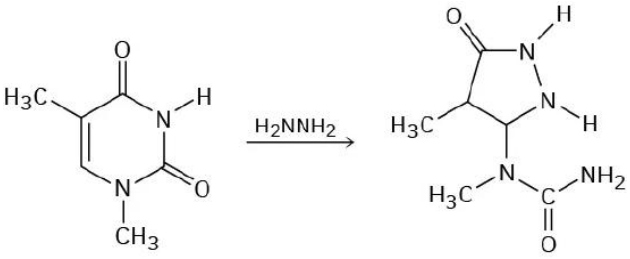
(c) The third step is loss of carbamate ($NH_2CO_2^-$) and formation of an unsaturated iminium ion, followed by a conjugate addition of another part of the DNA chain. Show the mechanism.

Problem 24-41 α-Amino acids can be prepared by the Strecker synthesis, a two-step process in which an aldehyde is treated with ammonium cyanide followed by hydrolysis of the amino nitrile intermediate with aqueous acid. Propose a mechanism for the reaction.

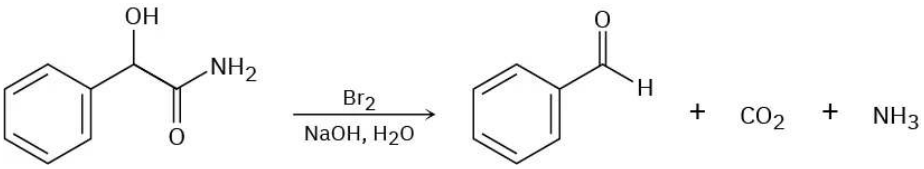


An α-amino acid

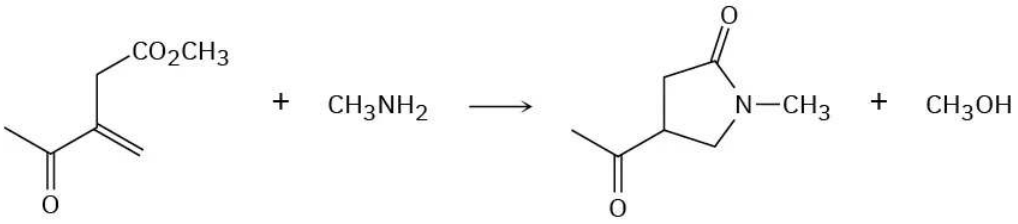
Problem 24-42 One of the reactions used in determining the sequence of nucleotides in a strand of DNA is reaction with hydrazine. Propose a mechanism for the following reaction, which occurs by an initial conjugate addition followed by internal amide formation.



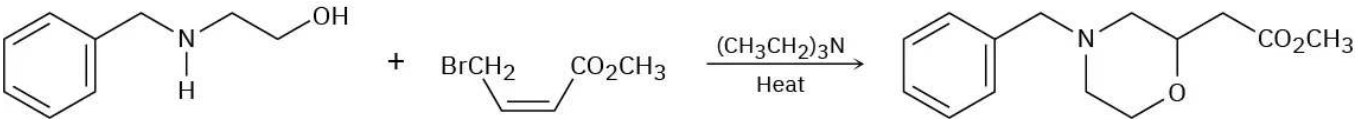
Problem 24-43 When an α-hydroxy amide is treated with Br_2 in aqueous NaOH under Hofmann rearrangement conditions, loss of CO_2 occurs and a chain-shortened aldehyde is formed. Propose a mechanism.



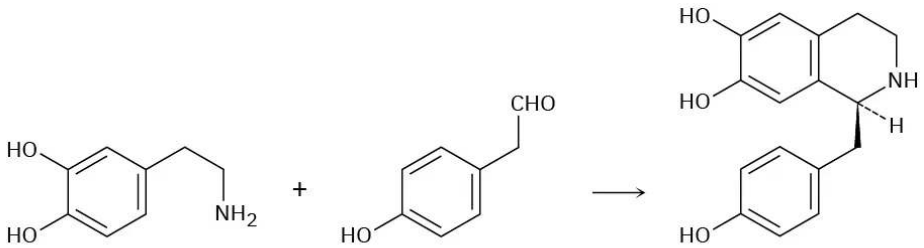
Problem 24-44 The following transformation involves a conjugate nucleophilic addition reaction (**Section 19.13**) followed by an intramolecular nucleophilic acyl substitution reaction (**Section 21.2**). Show the mechanism.



Problem 24-45 Propose a mechanism for the following reaction:



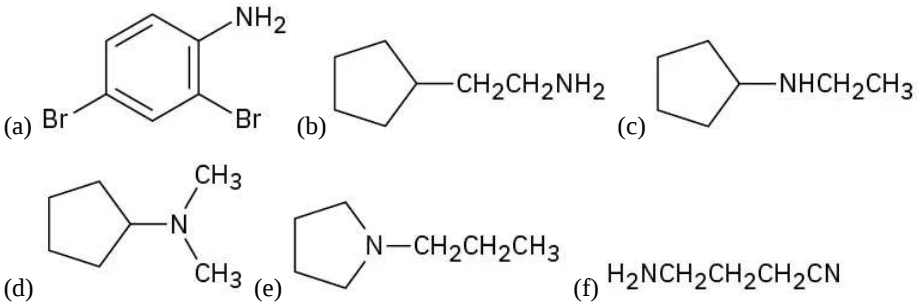
Problem 24-46 One step in the biosynthesis of morphine is the reaction of dopamine with *p*-hydroxyphenylacetaldehyde to give (*S*)-norcoclaurine. Assuming that the reaction is acid-catalyzed, propose a mechanism.



Dopamine | ***p*-Hydroxyphenyl-acetaldehyde** | **(*S*)-Norcoclaurine**

Naming Amines

Problem 24-47 Name the following compounds:

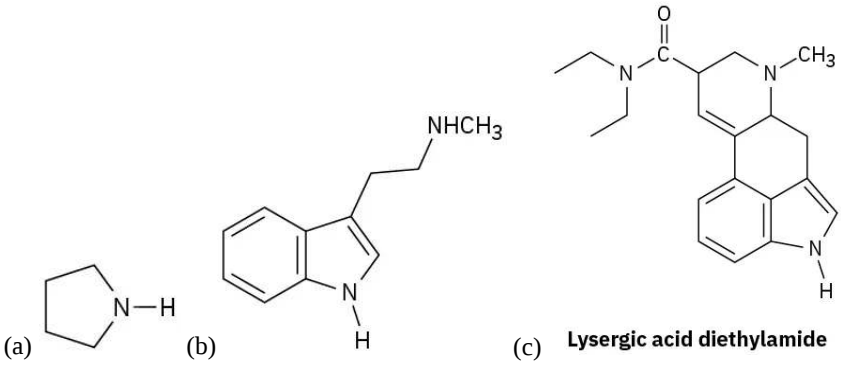


Problem 24-48 Draw structures corresponding to the following IUPAC names:

(a) *N*,*N*-Dimethylaniline **(b)** (Cyclohexylmethyl)amine **(c)** *N*-Methylcyclohexylamine

(d) (2-Methylcyclohexyl)amine **(e)** 3-(*N*,*N*-Dimethylamino)propanoic acid

Problem 24-49 Classify each of the amine nitrogen atoms in the following substances as primary, secondary, or tertiary:

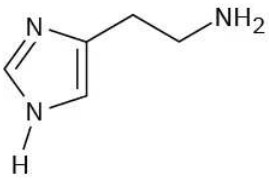


Lysergic acid diethylamide

Amine Basicity

Problem 24-50 Although pyrrole is a much weaker base than most other amines, it is a much stronger acid ($pK_a \approx 15$ for the pyrrole versus 35 for diethylamine). The N–H hydrogen is readily abstracted by base to yield the pyrrole anion, $C_4H_4N^-$. Explain.

Problem 24-51 Histamine, whose release in the body triggers nasal secretions and constricted airways, has three nitrogen atoms. List them in order of increasing basicity and explain your ordering.



Histamine

Problem 24-52 Account for the fact that *p*-nitroaniline ($pK_a = 1.0$) is less basic than *m*-nitroaniline ($pK_a = 2.5$) by a factor of 30. Draw resonance structures to support your argument. (The pK_a values refer to the corresponding ammonium ions.)

Synthesis of Amines

Problem 24-53 How would you prepare the following substances from 1-butanol?

(a) Butylamine (b) Dibutylamine (c) Propylamine (d) Pentylamine (e) *N*,*N*-Dimethylbutylamine (f) Propene

Problem 24-54 How would you prepare the following substances from pentanoic acid?

(a) Pentanamide (b) Butylamine (c) Pentylamine (d) 2-Bromopentanoic acid (e) Hexanenitrile (f) Hexylamine

Problem 24-55 How would you prepare aniline from the following starting materials?

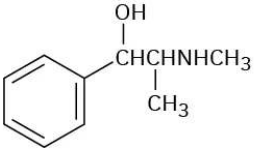
(a) Benzene (b) Benzamide (c) Toluene

Problem 24-56 How would you prepare benzylamine, $C_6H_5CH_2NH_2$, from benzene? More than one step is needed.

Problem 24-57 How might you prepare pentylamine from the following starting materials?

(a) Pentanamide (b) Pentanenitrile (c) 1-Butene (d) Hexanamide (e) 1-Butanol (f) 5-Decene (g) Pentanoic acid

Problem 24-58 How might a reductive amination be used to synthesize ephedrine, an amino alcohol that was widely used for the treatment of bronchial asthma?



Ephedrine

Reactions of Amines

Problem 24-59 How would you convert aniline into each of the following products?

(a) Benzene (b) Benzamide (c) Toluene

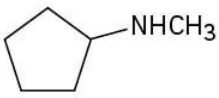
Problem 24-60 Write the structures of the major organic products you would expect from reaction of <i">m-toluidine (*m*-methylaniline) with the following reagents:

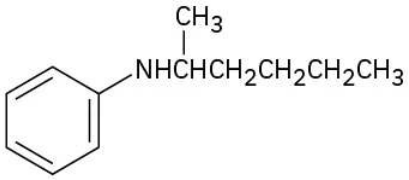
(a) Br_2 (1 equivalent) (b) CH_3I (excess) (c) CH_3COCl in pyridine (d) The product of (c), then HSO_3Cl

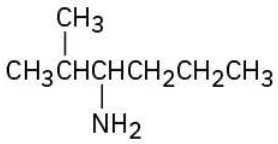
Problem 24-61 Show the products from reaction of *p*-bromoaniline with the following reagents:

(a) CH_3I (excess) (b) HCl (c) HNO_2, H_2SO_4 (d) CH_3COCl (e) CH_3MgBr (f) CH_3CH_2Cl, $AlCl_3$ (g) Product of (c) with CuCl, HCl (h) Product of (d) with CH_3CH_2Cl, $AlCl_3$

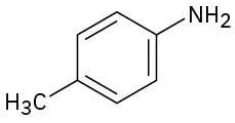
Problem 24-62 What are the major products you would expect from Hofmann elimination of the following amines?

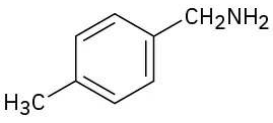
(a) 

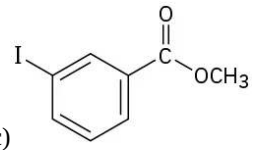
(b) 

(c) 

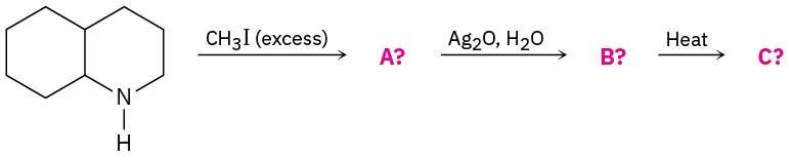
Problem 24-63 How would you prepare the following compounds from toluene? A diazonio replacement reaction is needed in some instances.

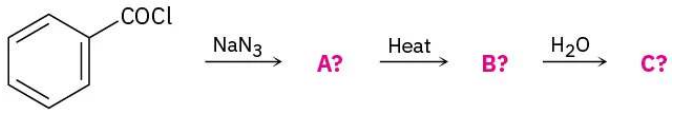
(a) 

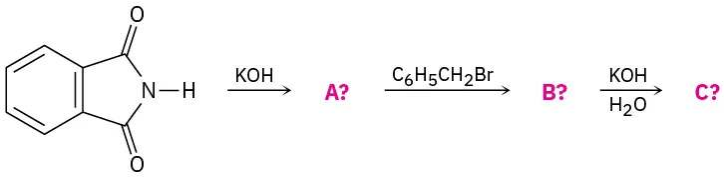
(b) 

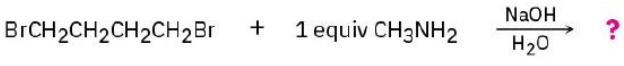
(c) 

Problem 24-64 Predict the product(s) of the following reactions. If more than one product is formed, tell which is major.

(a) 

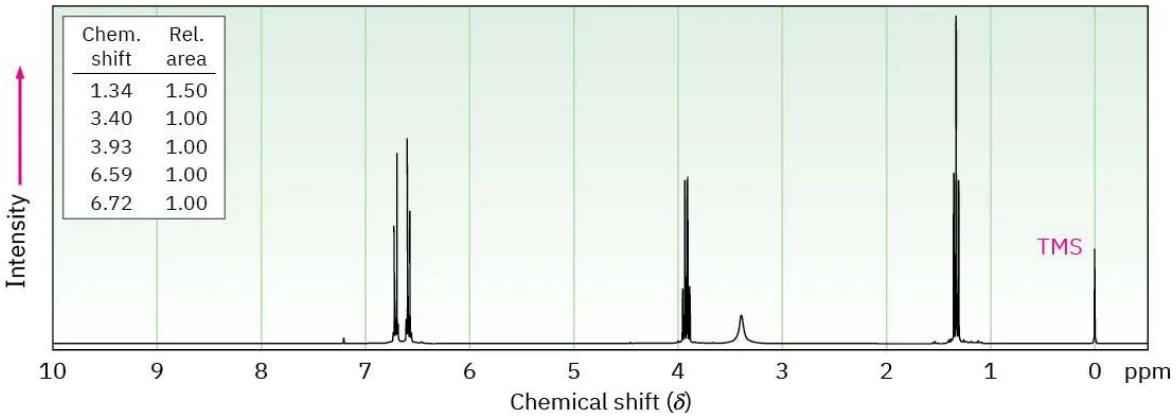
(b) 

(c) 

(d) 

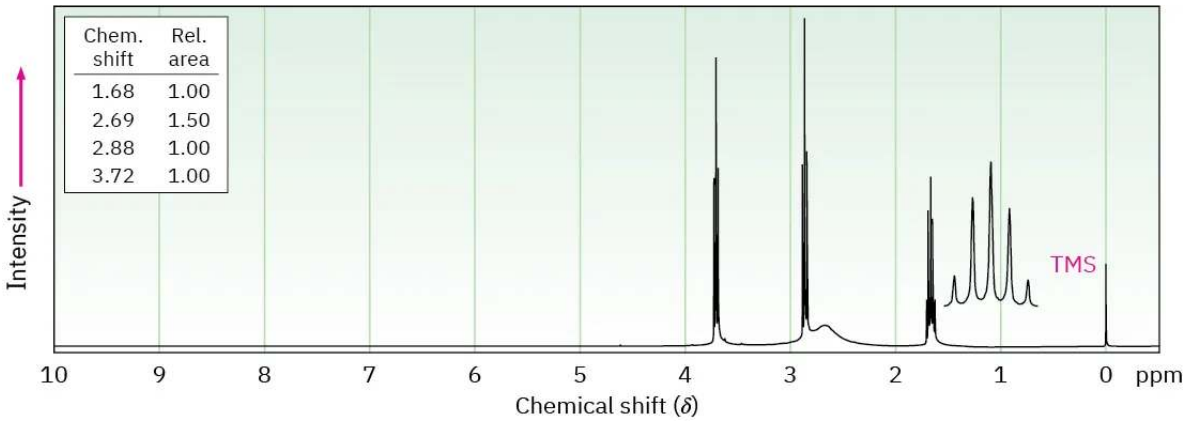
Spectroscopy

Problem 24-65 Phenacetin, a substance formerly used in over-the-counter headache remedies, has the formula $C_{10}H_{13}NO_2$. Phenacetin is neutral and does not dissolve in either acid or base. When warmed with aqueous NaOH, phenacetin yields an amine, $C_8H_{11}NO$, whose ^1H NMR spectrum is shown. When heated with HI, the amine is cleaved to an aminophenol, C_6H_7NO. What is the structure of phenacetin, and what are the structures of the amine and the aminophenol?

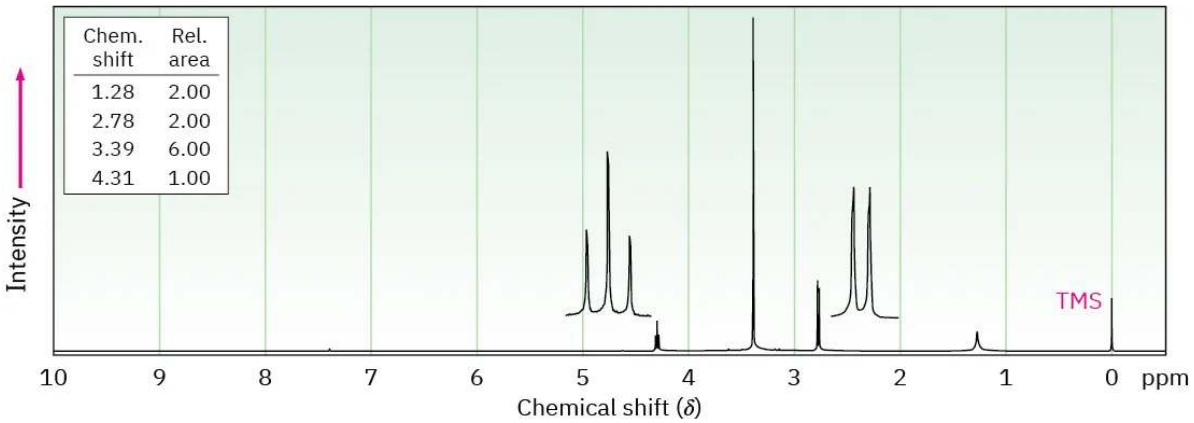


Problem 24-66 Propose structures for amines with the following 1H NMR spectra:

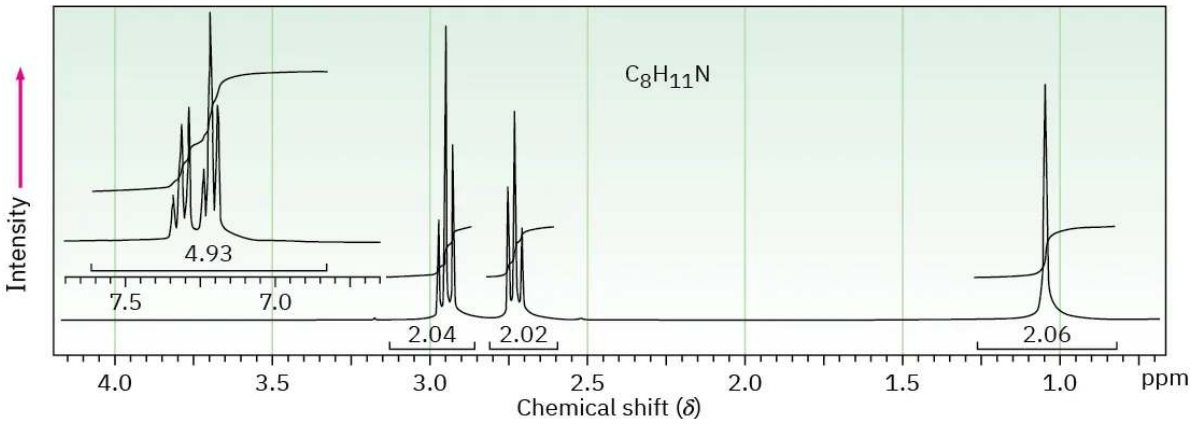
(a) C_3H_9NO



(b) $C_4H_{11}NO_2$



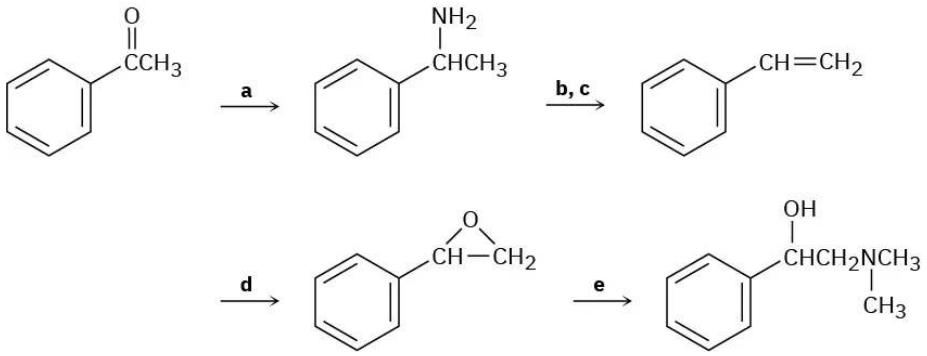
(c) $C_8H_{11}N$



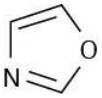
Problem 24-67 Draw the structure of the amine that produced the ^{1}H NMR spectrum shown in Problem 24-66(c). This compound has a single strong peak in its IR spectrum at 3280 cm^{-1}.

General Problems

Problem 24-68 Fill in the missing reagents **a**–**e** in the following scheme:

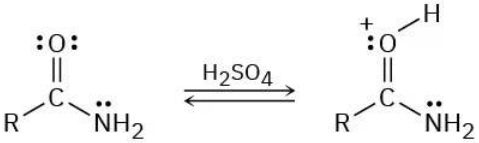


Problem 24-69 Oxazole is a five-membered aromatic heterocycle. Would you expect oxazole to be more basic or less basic than pyrrole? Explain.

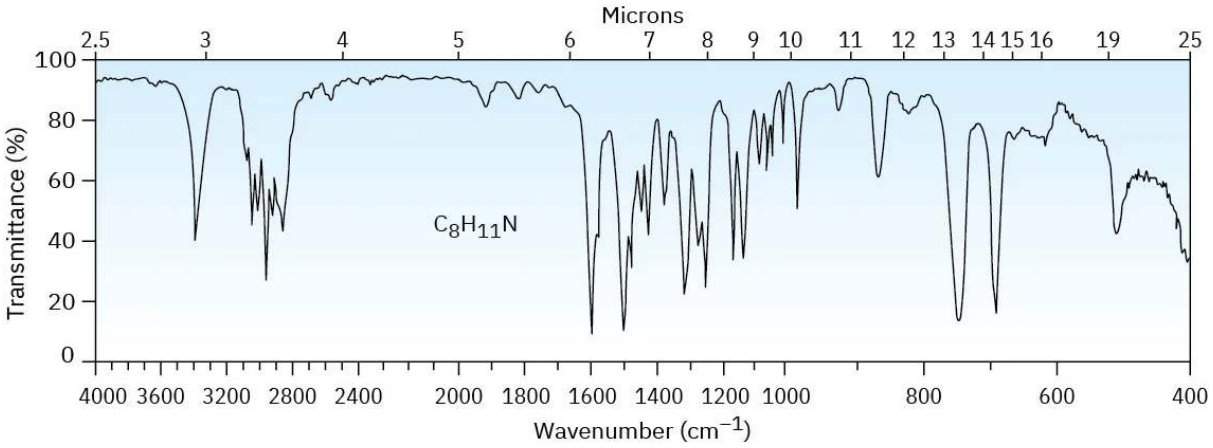


Oxazole

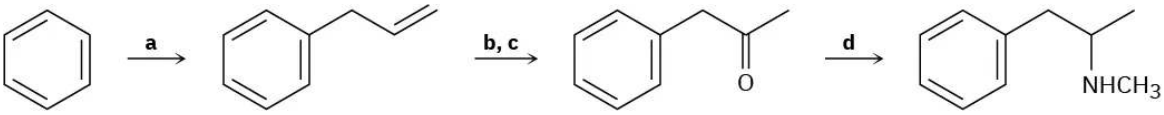
Problem 24-70 Protonation of an amide using strong acid occurs on oxygen rather than on nitrogen. Suggest a reason for this behavior, taking resonance into account.



Problem 24-71 What is the structure of the compound with formula $C_8H_{11}N$ that produced the following IR spectrum?

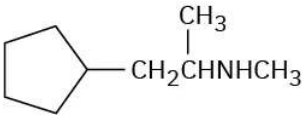


Problem 24-72 Fill in the missing reagents a–d in the following synthesis of racemic methamphetamine from benzene.



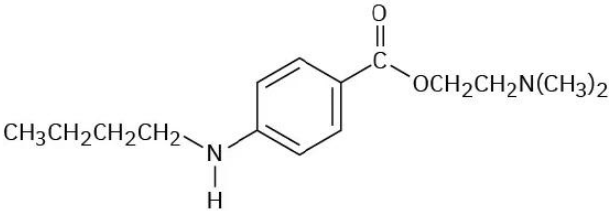
(*R*,*S*)-Methamphetamine

Problem 24-73 Cyclopentamine is an amphetamine-like central nervous system stimulant. Propose a synthesis of cyclopentamine from materials of five carbons or less.



Cyclopentamine

Problem 24-74 Tetracaine is a substance used as a spinal anesthetic.



Tetracaine

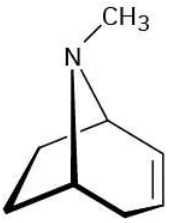
(a) How would you prepare tetracaine from the corresponding aniline derivative, $ArNH_2$?

(b) How would you prepare tetracaine from *p*-nitrobenzoic acid?

(c) How would you prepare tetracaine from benzene?

Problem 24-75 Atropine, $C_{17}H_{23}NO_3$, is a poisonous alkaloid isolated from the leaves and roots of *Atropa belladonna*, the deadly nightshade. In small doses, atropine acts as a muscle relaxant; 0.5 ng (nanogram, 10^{-9} g) is sufficient to cause pupil dilation. On basic hydrolysis, atropine yields tropic acid, $C_6H_5CH(CH_2OH)CO_2H$, and tropine, $C_8H_{15}NO$. Tropine is an optically inactive alcohol that yields tropidene on dehydration with H_2SO_4. Propose a structure for atropine.

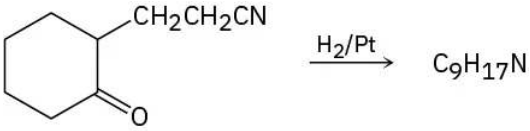
https://chem.libretexts.org/@go/page/564268



Tropidene

Problem 24-76 Tropidene (Problem 24-75) can be converted by a series of steps into tropilidene (1,3,5-cycloheptatriene). How would you accomplish this conversion?

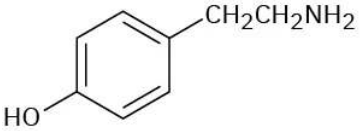
Problem 24-77 Propose a structure for the product with formula $C_9H_{17}N$ that results when 2-(2-cyanoethyl)cyclohexanone is reduced catalytically.



Problem 24-78 Coniine, $C_8H_{17}N$, is the toxic principle of the poison hemlock drunk by Socrates. When subjected to Hofmann elimination, coniine yields 5-(*N*,*N*-dimethylamino)-1-octene. If coniine is a secondary amine, what is its structure?

Problem 24-79 How would you synthesize coniine (Problem 24-78) from acrylonitrile ($H_2C{=}CHCN$) and ethyl 3-oxohexanoate ($CH_3CH_2CH_2COCH_2CO_2Et$)? (See Problem 24-77.)

Problem 24-80 Tyramine is an alkaloid found, among other places, in mistletoe and ripe cheese. How would you synthesize tyramine from benzene? From toluene?

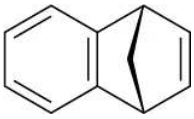


Tyramine

Problem 24-81 Reaction of anthranilic acid (*o*-aminobenzoic acid) with HNO_2 and H_2SO_4 yields a diazonium salt that can be treated with base to yield a neutral diazonium carboxylate.

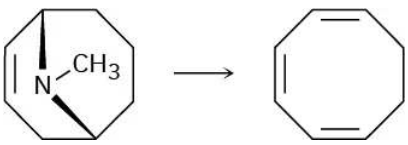
(a) What is the structure of the neutral diazonium carboxylate?

(b) Heating the diazonium carboxylate results in the formation of CO_2, N_2, and an intermediate that reacts with 1,3-cyclopentadiene to yield the following product:



What is the structure of the intermediate, and what kind of reaction does it undergo with cyclopentadiene?

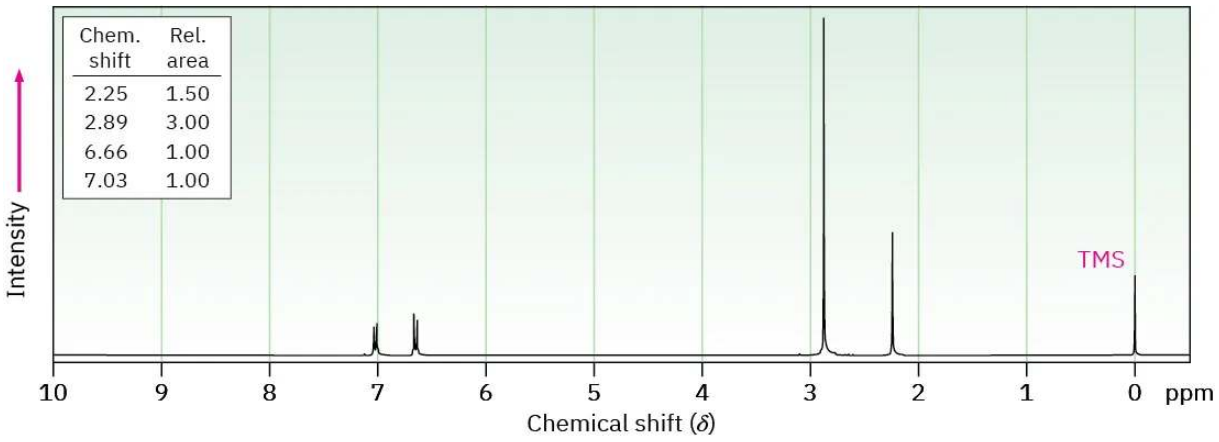
Problem 24-82 Cyclooctatetraene was first synthesized in 1911 by a route that involved the following transformation:



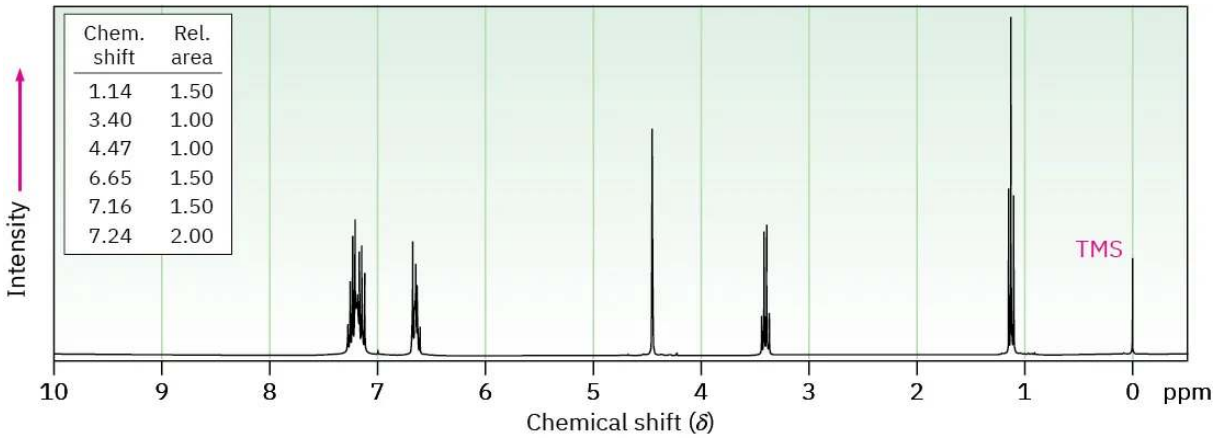
How might you use the Hofmann elimination to accomplish this reaction? How would you finish the synthesis by converting cyclooctatriene into cyclooctatetraene?

Problem 24-83 Propose structures for compounds that show the following ^1H NMR spectra.

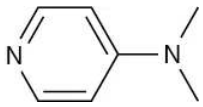
(a) $C_9H_{13}N$



(b) $C_{15}H_{17}N$



Problem 24-844-Dimethylaminopyridine (DMAP) acts as a catalyst in acyl transfer reactions. DMAP's catalytic activity stems from its nucleophilic character at the pyridine nitrogen, not the dimethylamino group. Explain this behavior, taking resonance into account.



This page titled 8.13.1.16: Additional Problems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.15: Additional Problems** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.14: Conjugate Nucleophilic Addition to α,β-Unsaturated Aldehydes and Ketones

All the reactions we've been discussing to this point have involved the addition of a nucleophile directly to the carbonyl group, a so-called **1,2-addition**. Closely related to this direct addition is the **conjugate addition**, or **1,4-addition**, of a nucleophile to the C=C bond of an α,β-unsaturated aldehyde or ketone. (The carbon atom next to a carbonyl group is often called the α carbon, the next carbon is the β carbon, and so on. Thus, an α,β-unsaturated aldehyde or ketone has a double bond conjugated with the carbonyl group.) The initial product of conjugate addition is a resonance-stabilized enolate ion, which typically undergoes protonation on the α carbon to give a saturated aldehyde or ketone product (Figure 8.14.1).

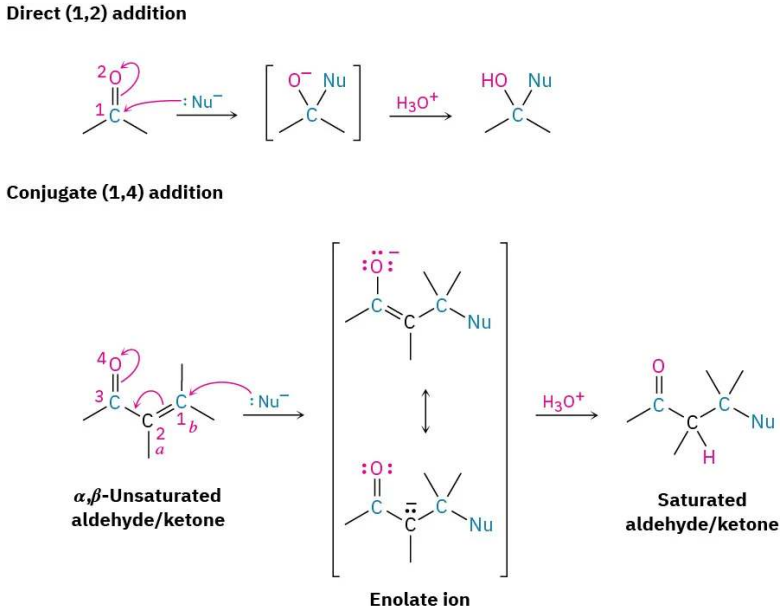
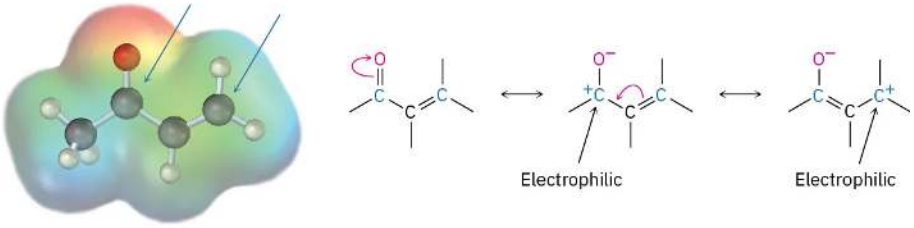
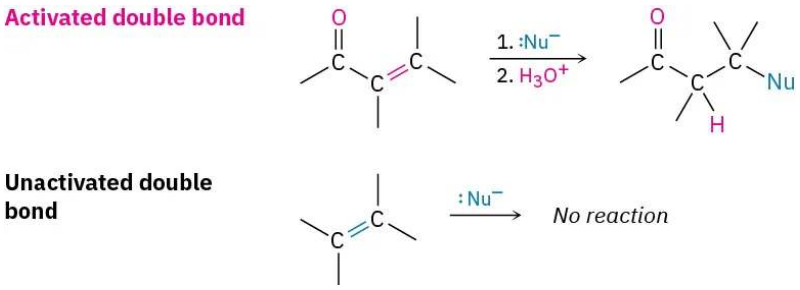


Figure 8.14.1: A comparison of direct (1,2) and conjugate (1,4) nucleophilic addition reactions. In conjugate addition, a nucleophile adds to the *β* carbon of an *α*,*β*-unsaturated aldehyde or ketone and protonation occurs on the *α* carbon.

The conjugate addition of a nucleophile to an *α*,*β*-unsaturated aldehyde or ketone is caused by the same electronic factors that are responsible for direct addition. The electronegative oxygen atom of the *α*,*β*-unsaturated carbonyl compound withdraws electrons from the *β* carbon, thereby making it electron-poor and more electrophilic than a typical alkene carbon.

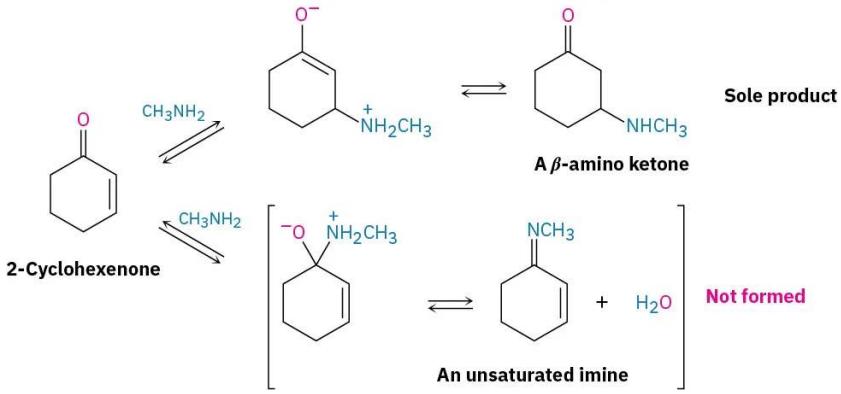


As noted, conjugate addition of a nucleophile to the *β* carbon of an *α*,*β*-unsaturated aldehyde or ketone leads to an enolate ion intermediate, which is protonated on the *α* carbon to give the saturated product (Figure 8.14.1). The net effect is addition of the nucleophile to the C=C bond, with the carbonyl group itself unchanged. In fact, of course, the carbonyl group is crucial to the success of the reaction. Without the carbonyl group, the C=C bond would not be activated for addition, and no reaction would occur.



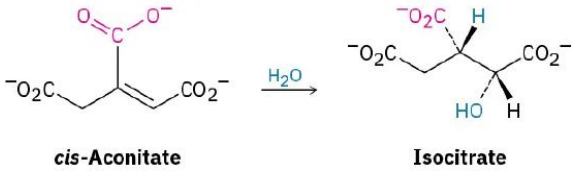
Conjugate Addition of Amines

Both primary and secondary amines add to α,β-unsaturated aldehydes and ketones to yield β-amino aldehydes and ketones rather than the alternative imines. Under typical reaction conditions, both modes of addition occur rapidly. But because the reactions are reversible, they generally proceed with thermodynamic control rather than kinetic control (Section 14.3), so the more stable conjugate addition product is often obtained with the complete exclusion of the less stable direct addition product.



Conjugate Addition of Water

Water can add reversibly to α,β-unsaturated aldehydes and ketones to yield β-hydroxy aldehydes and ketones, although the position of the equilibrium generally favors unsaturated reactant rather than saturated adduct. Related additions to α,β-unsaturated carboxylic acids occur in numerous biological pathways, such as the citric acid cycle of food metabolism in which *cis*-aconitate is converted into isocitrate by conjugate addition of water to a double bond.



? Exercise 8.14.1

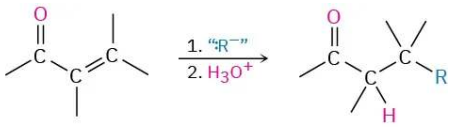
Assign *R* or *S* stereochemistry to the two chirality centers in isocitrate, and tell whether OH and H add to the Si face or the Re face of the double bond.

Answer

The −OH group adds to the Re face at C2, and −H adds to the Re face at C3, to yield (2*R*,3*S*)-isocitrate.

Conjugate Addition of Alkyl Groups: Organocopper Reactions

The conjugate addition of an alkyl or other organic group to an α,β-unsaturated ketone (but not aldehyde) is one of the more useful 1,4-addition reactions, just as direct addition of a Grignard reagent is one of the more useful 1,2-additions.

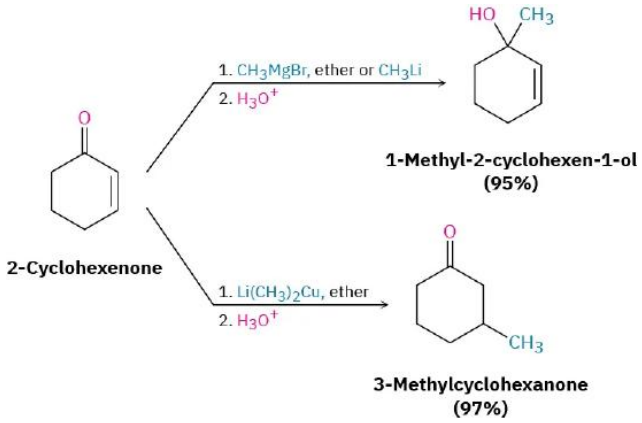


α,β-Unsaturated ketone

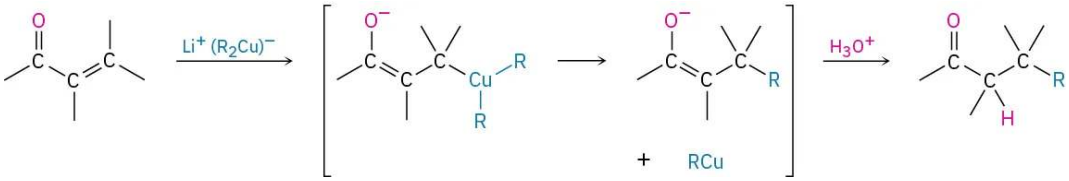
Conjugate addition of an organic group is carried out by treating the α,β-unsaturated ketone with a lithium diorganocopper reagent, R_2CuLi. As we saw in Section 10.7, lithium diorganocopper (Gilman) reagents are prepared by reaction between 1 equivalent of copper(I) iodide and 2 equivalents of an organolithium regent, RLi. The organolithium reagent, in turn, is formed by reaction of lithium metal with an organohalide in the same way that a Grignard reagent is prepared by reaction of magnesium metal with an organohalide.

A lithium diorganocopper (Gilman reagent)

Primary, secondary, and even tertiary alkyl groups undergo the conjugate addition reaction, as do aryl and alkenyl groups. Alkynyl groups, however, react poorly in the conjugate addition process. Diorganocopper reagents are unique in their ability to give conjugate addition products. Other organometallic reagents, such as Grignard reagents and organolithiums, normally result in direct carbonyl addition on reaction with α,β-unsaturated ketones.



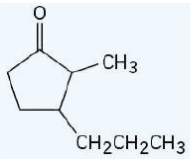
The mechanism of this reaction is thought to involve conjugate nucleophilic addition of the diorganocopper anion, R_2Cu^-, to the unsaturated ketone to give a copper-containing intermediate. Transfer of an R group from copper to carbon, followed by elimination of a neutral organocopper species, RCu, gives the final product.



? Worked Example 8.14.1: Using a Conjugate Addition Reaction

How might you use a conjugate addition reaction to prepare 2-methyl-3-propylcyclopentanone?

https://chem.libretexts.org/@go/page/564269

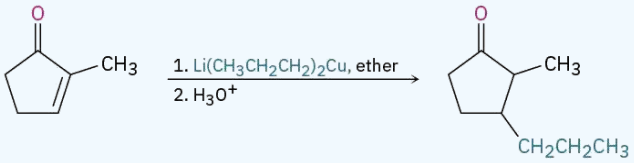


2-Methyl-3-propylcyclopentanone

Strategy

A ketone with a substituent group in its β position might be prepared by a conjugate addition of that group to an α,β-unsaturated ketone. In the present instance, the target molecule has a propyl substituent on the β carbon and might therefore be prepared from 2-methyl-2-cyclopentenone by reaction with lithium dipropylcopper.

Solution

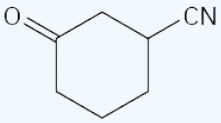


2-Methyl-2-cyclopentenone **2-Methyl-3-propylcyclopentanone**

Exercise 8.14.2

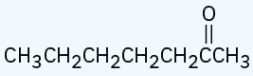
Treatment of 2-cyclohexenone with HCN/KCN yields a saturated keto nitrile rather than an unsaturated cyanohydrin. Show the structure of the product, and propose a mechanism for the reaction.

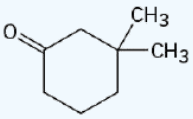
Answer

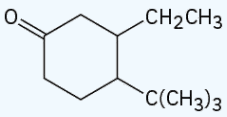


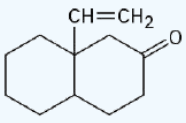
Exercise 8.14.3

How might conjugate addition reactions of lithium diorganocopper reagents be used to synthesize the following compounds?

a. 

b. 

c. 

d. 

Answer

a. 3-Buten-2-one + $(CH_3CH_2CH_2)_2CuLi$

b. 3-Methyl-2-cyclohexenone + $(CH_3)_2CuLi$

c. 4-tert-Butyl-2-cyclohexenone + $(CH_3CH_2)_2CuLi$

d. Unsaturated ketone + $(H_2C=CH)_2CuLi$

This page titled 8.14: Conjugate Nucleophilic Addition to α,β-Unsaturated Aldehydes and Ketones is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **19.13: Conjugate Nucleophilic Addition to α,β-Unsaturated Aldehydes and Ketones** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.15: Spectroscopy of Aldehydes and Ketones

Infrared Spectroscopy

Aldehydes and ketones show a strong C=O bond absorption in the IR region from 1660 to 1770 cm^{-1}, as the spectra of benzaldehyde and cyclohexanone demonstrate (Figure 8.15.1). In addition, aldehydes show two characteristic C–H absorptions between 2700–2760 and 2800–2860 cm^{-1}. These absorbances are important for distinguishing between aldehydes and ketones. The higher-frequency absorbance is sometimes obscured in cases where the compound has numerous saturated C–H groups, but the lower-frequency peak is almost always visible.

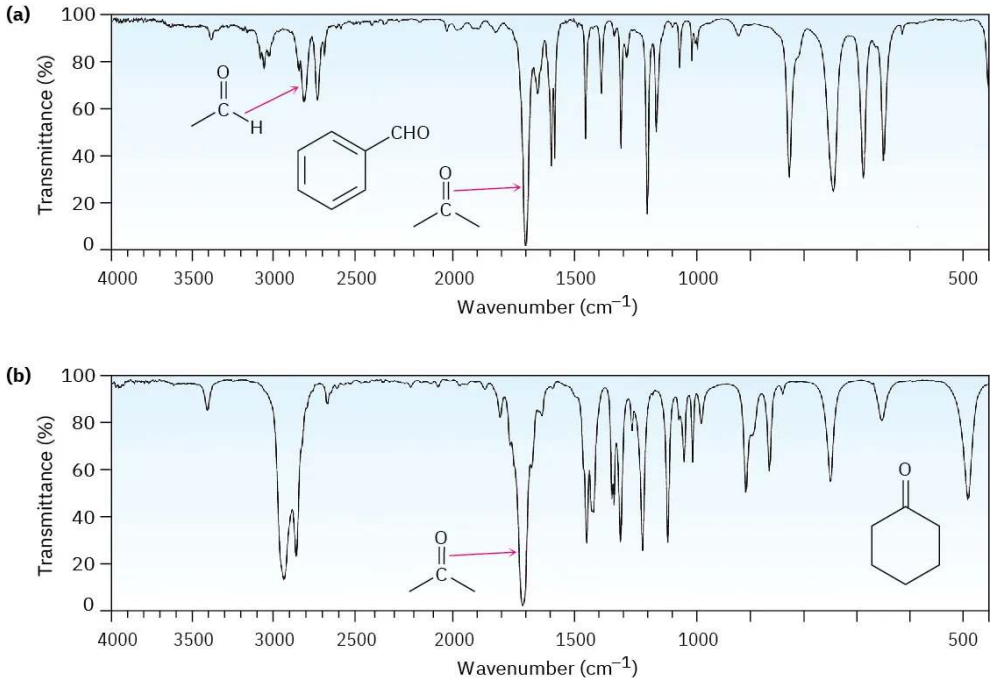


Figure 8.15.1: Infrared spectra of (a) benzaldehyde and (b) cyclohexanone.

The exact position of the C=O absorption is diagnostic of the nature of the carbonyl group. As the data in Table 8.15.1 indicate, saturated aldehydes usually show carbonyl absorptions near 1730 cm^{-1} in the IR spectrum, but conjugation of the aldehyde to an aromatic ring or a double bond lowers the absorption by 25 cm^{-1} to near 1705 cm^{-1}. Saturated aliphatic ketones and cyclohexanones both absorb near 1715 cm^{-1}, and conjugation with a double bond or an aromatic ring again lowers the absorption by 30 cm^{-1} to 1685–1690 cm^{-1}. Angle strain in the carbonyl group, caused by reducing the ring size of cyclic ketones to four or five, raises the absorption position. Cyclohexanone has its C=O stretch absorbance at 1715 cm^{-1} while cyclopentanone's carbonyl stretch is at 1750 cm^{-1} and cyclobutanone's is at 1785 cm^{-1}.

Table 8.15.1: Infrared Absorptions of Some Aldehydes and Ketones

Carbonyl type	Example	Absorption (cm^{-1})
Saturated aldehyde	CH_3CHO	1730
Aromatic aldehyde	PhCHO	1705
α,β-Unsaturated aldehyde	$H_2C{=}CHCHO$	1705
Saturated ketone	CH_3COCH_3	1715
Cyclohexanone		1715
Cyclopentanone		1750
Cyclobutanone		1785
Aromatic ketone	$PhCOCH_3$	1690
α,β-Unsaturated ketone	$H_2C{=}CHCOCH_3$	1685

The values given in Table 8.15.1 are remarkably constant from one aldehyde or ketone to another. As a result, IR spectroscopy is a powerful tool for identifying the kind of a carbonyl group in a molecule of unknown structure. An unknown that shows an IR absorption at 1730 cm^{-1} is almost certainly an aldehyde rather than a ketone; an unknown that shows an IR absorption at 1750 cm^{-1} is almost certainly a cyclopentanone, and so on.

? Exercise 8.15.1

How might you use IR spectroscopy to determine whether reaction between 2-cyclohexenone and lithium dimethylcopper gives the direct addition product or the conjugate addition product?

a. 4-Penten-2-one
b. 3-Penten-2-one
c. 2,2-Dimethylcyclopentanone
d. m-Chlorobenzaldehyde
e. 3-Cyclohexenone
f. 2-Hexenal

Answer

a. 1715 cm^{-1}
b. 1685 cm^{-1}
c. 1750 cm^{-1}
d. 1705 cm^{-1}
e. 1715 cm^{-1}
f. 1705 cm^{-1}

Nuclear Magnetic Resonance Spectroscopy

Aldehyde protons (RC**HO**) absorb near 10 δ in the ^1H NMR spectrum and are very distinctive because no other absorptions occur in this region. The aldehyde proton shows spin–spin coupling with protons on the neighboring carbon, with coupling constant $J \approx 3$ Hz. Acetaldehyde, for example, shows a quartet at 9.79 δ for the aldehyde proton, indicating that there are three protons neighboring the –CHO group (Figure 8.15.2).

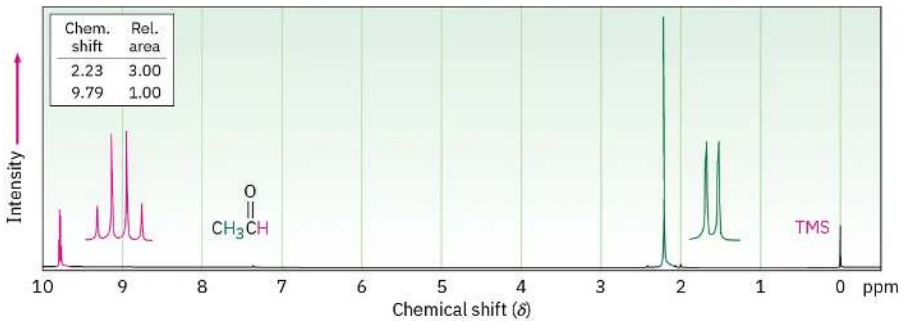
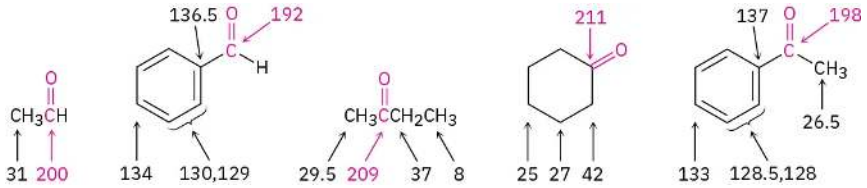


Figure 8.15.2: ^{1}H NMR spectrum of acetaldehyde. The absorption of the aldehyde proton appears at 9.79 δ and is split into a quartet.

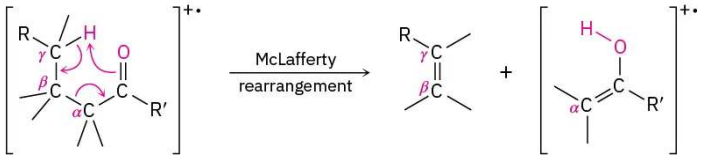
Hydrogens on the carbon next to a carbonyl group are slightly deshielded and usually absorb near 2.0 to 2.3 δ. The acetaldehyde methyl group in Figure 8.15.2, for instance, absorbs at 2.20 δ. Methyl ketones are particularly distinctive because they always show a sharp three-proton singlet near 2.1 δ.

The carbonyl-group carbon atoms of aldehydes and ketones have characteristic ^{13}C NMR resonances in the range 190 to 215 δ. Since no other kinds of carbons absorb in this range, the presence of an NMR absorption near 200 δ is clear evidence for a carbonyl group. Saturated aldehyde or ketone carbons usually absorb in the region from 200 to 215 δ, while aromatic and α,β-unsaturated carbonyl carbons absorb in the 190 to 200 δ region.

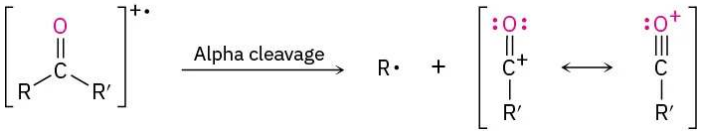


Mass Spectrometry

As discussed in Section 12.3, aliphatic aldehydes and ketones that have hydrogens on their gamma (γ) carbon atoms undergo a characteristic mass spectral cleavage called the **McLafferty rearrangement**. A hydrogen atom is transferred from the γ carbon to the carbonyl oxygen, the bond between the α and β carbons is broken, and a neutral alkene fragment is produced. The charge remains with the oxygen-containing fragment.



In addition to fragmentation by the McLafferty rearrangement, aldehydes and ketones also undergo cleavage of the bond between the carbonyl group and the α carbon, called an *α cleavage*. Alpha cleavage yields a neutral radical and a resonance-stabilized acyl cation.



Fragment ions from both McLafferty rearrangement and α cleavage are visible in the mass spectrum of 5-methyl-2-hexanone shown in Figure 8.15.3. McLafferty rearrangement with loss of 2-methylpropene yields a fragment with m/z = 58. Alpha cleavage occurs primarily at the more substituted side of the carbonyl group, leading to a $[CH_3CO]^+$ fragment with m/z = 43.

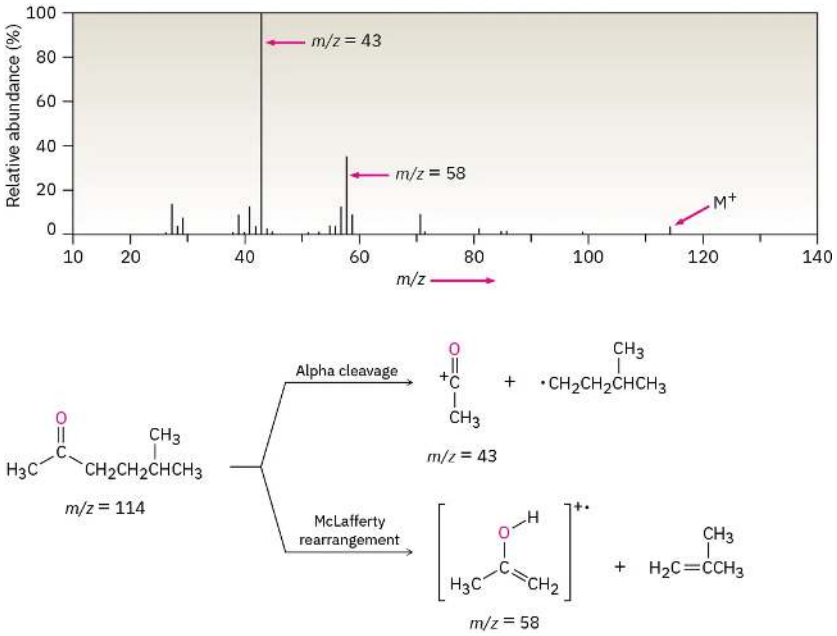


Figure 8.15.3: Mass spectrum and the related reactions of 5-methyl-2-hexanone. The peak at m/z = 58 is due to McLafferty rearrangement. The abundant peak at m/z = 43 is due to α cleavage at the more highly substituted side of the carbonyl group. Note that the peak due to the molecular ion is very small.

Exercise 8.15.2

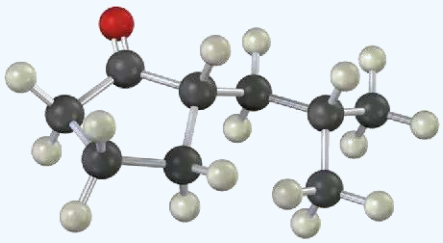
a. 3-Methyl-2-hexanone and 4-methyl-2-hexanone
b. 3-Heptanone and 4-heptanone
c. 2-Methylpentanal and 3-methylpentanal

Answer

a. Different peaks due to McLafferty rearrangement
b. Different peaks due to α cleavage and McLafferty rearrangement
c. Different peaks due to McLafferty rearrangement

Exercise 8.15.3

Describe the prominent IR absorptions and mass spectral peaks you would expect for the following compound:



Answer

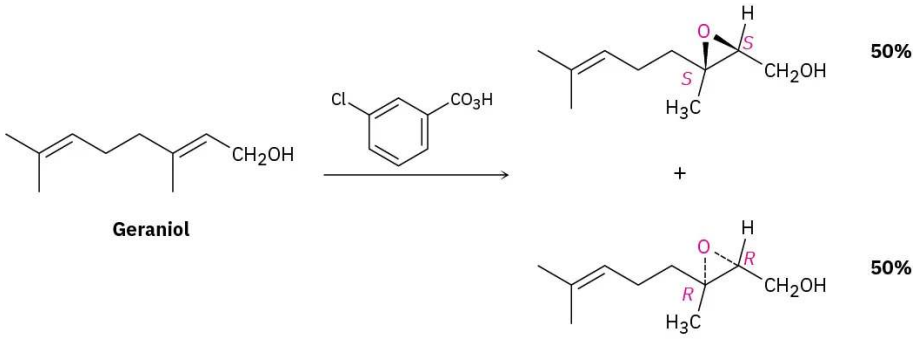
- IR: 1750 cm^{-1}
- MS: 140, 84

This page titled 8.15: Spectroscopy of Aldehydes and Ketones is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **19.14: Spectroscopy of Aldehydes and Ketones** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.16: Chemistry Matters—Enantioselective Synthesis

Whenever a chiral product is formed by reaction between achiral reagents, the product is racemic; that is, both enantiomers of the product are formed in equal amounts. The epoxidation reaction of geraniol with *m*-chloroperoxybenzoic acid, for instance, gives a racemic mixture of (2*S*,3*S*) and (2*R*,3*R*) epoxides.

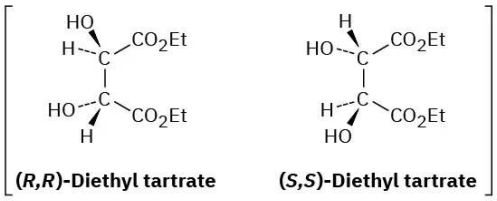


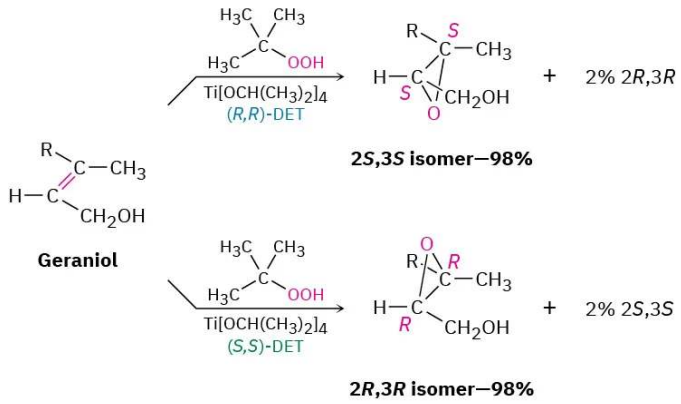
Unfortunately, it's usually the case that only one enantiomer of a given drug or other important substance has the desired biological properties. The other enantiomer might be inactive or even dangerous. Thus, much work is currently being done on developing *enantioselective* methods of synthesis, which yield only one of the two possible enantiomers. So important has enantioselective synthesis become that the 2001 Nobel Prize in Chemistry was awarded to three pioneers in the field: William S. Knowles of the Monsanto Co., K. Barry Sharpless of the Scripps Research Institute, and Ryoji Noyori of Nagoya University.

Several approaches to enantioselective synthesis have been developed, but the most efficient are those that use chiral catalysts to temporarily hold a substrate molecule in an unsymmetrical environment—the same strategy that nature uses when catalyzing reactions with chiral enzymes. While in that unsymmetrical environment, the substrate may be more open to reaction on one side than on another, leading to an excess of one enantiomeric product over another. As an analogy, think about picking up a coffee mug in your right hand to take a drink. The mug by itself is achiral, but as soon as you pick it up by the handle, it becomes chiral. One side of the mug now faces toward you so you can drink from it, but the other side faces away. The two sides are different, with one side much more accessible to you than the other.

Figure 8.16.1: A substance made from the tartaric acid found at the bottom of this wine vat catalyzes enantioselective reactions. (credit: "Pinot Noir fermentation in open vat" by Pipers Brook Vineyard Media/Flickr, CC BY 2.0)

Among the thousands of enantioselective reactions now known, one of the most useful is the so-called **Sharpless epoxidation**, in which an allylic alcohol, such as geraniol, is treated with *tert*-butyl hydroperoxide, $(CH_3)_3C–OOH$, in the presence of titanium tetraisopropoxide and diethyl tartrate (DET) as a chiral auxiliary reagent. When (*R*,*R*) tartrate is used, geraniol is converted into its 2*S*,3*S* epoxide with 98% selectivity, whereas the use of (*S*,*S*) tartrate gives the 2*R*,3*R* epoxide enantiomer. We say that the major product in each case is formed with an *enantiomeric excess* of 96%, meaning that 4% of the product is racemic (2% 2*S*,3*S* plus 2% 2*R*,3*R*) and an extra 96% of a single enantiomer is formed. The mechanistic details by which the chiral catalyst works are a bit complex, although it appears that a chiral complex of two tartrate molecules with one titanium is involved.





This page titled 8.16: Chemistry Matters—Enantioselective Synthesis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **19.15: Chemistry Matters—Enantioselective Synthesis** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.17: Key Terms

- acetal, $R_2C(OR')_2$
- acyl group
- 1,2-addition
- 1,4-addition
- aldehyde (RCHO)
- Cannizzaro reaction
- carbinolamine
- conjugate addition
- cyanohydrin
- enamine msub$R_2N–CR═CR_2$)
- hemiacetal
- imine msub$R_2C═NR$)
- ketal
- ketone (R_2CO)
- McLafferty rearrangement
- nucleophilic addition reaction
- phosphorane
- Schiff bases
- Wittig reaction
- Wolff–Kishner reaction
- ylide

This page titled 8.17: Key Terms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **19.16: Key Terms** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.18: Summary

Aldehydes and ketones are among the most important of all functional groups, both in the chemical industry and in biological pathways. In this chapter, we've looked at some of their typical reactions. Aldehydes are normally prepared in the laboratory by oxidation of primary alcohols or by partial reduction of esters. Ketones are similarly prepared by oxidation of secondary alcohols.

The **nucleophilic addition reaction** is the most common general reaction type for aldehydes and ketones. Many different kinds of products can be prepared by nucleophilic additions. Aldehydes and ketones are reduced by $NaBH_4$ or $LiAlH_4$ to yield primary and secondary alcohols, respectively. Addition of Grignard reagents to aldehydes and ketones also gives alcohols (secondary and tertiary, respectively), and addition of HCN yields **cyanohydrins**. Primary amines add to carbonyl compounds yielding **imines**, or **Schiff bases**, and secondary amines yield **enamines**. Reaction of an aldehyde or ketone with hydrazine and base gives an alkane (the **Wolff–Kishner reaction**). Alcohols add to carbonyl groups to yield **acetals**, which are valuable as protecting groups. Phosphorus **ylides** add to aldehydes and ketones in the **Wittig reaction** to give alkenes.

α,β-Unsaturated aldehydes and ketones often react with nucleophiles to give the product of **conjugate addition**, or **1,4-addition**. Particularly useful are the conjugate addition of an amine and the conjugate addition of an organic group by reaction with a diorganocopper reagent.

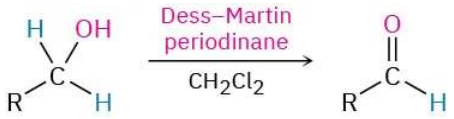
IR spectroscopy is helpful for identifying aldehydes and ketones. Carbonyl groups absorb in the IR range 1660 to 1770 cm^{-1}, with the exact position highly diagnostic of the kind of carbonyl group present in the molecule. ^{13}C NMR spectroscopy is also useful for aldehydes and ketones because their carbonyl carbons show resonances in the 190 to 215 δ range. ^{1}H NMR is useful for aldehyde –CHO protons, which absorb near 10 δ. Aldehydes and ketones undergo two characteristic kinds of fragmentation in the mass spectrometer: α cleavage and McLafferty rearrangement.

This page titled 8.18: Summary is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

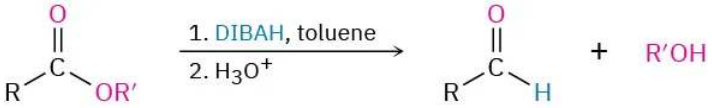
- **19.17: Summary** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

8.19: Summary of Reactions

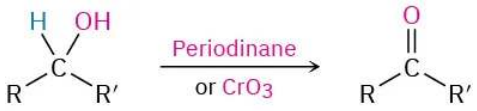
1. Preparation of aldehydes (Section 19.2)
   a. Oxidation of primary alcohols (Section 17.7)



- Partial reduction of esters (Section 19.2)

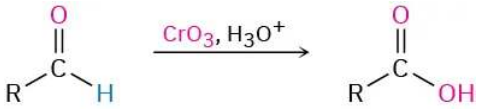


- Preparation of ketones
   a. Oxidation of secondary alcohols (Section 17.7)

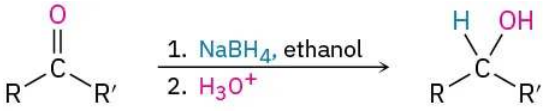


- Diorganocopper reaction with acid chlorides (Section 19.2)

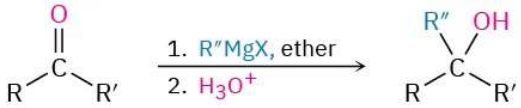
- Oxidation of aldehydes (Section 19.3)



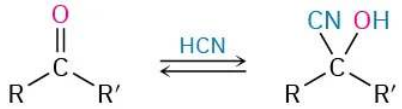
- Nucleophilic addition reactions of aldehydes and ketones
   a. Addition of hydride to give alcohols: reduction (Section 19.7)



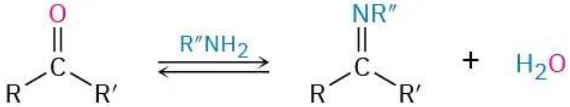
   b. Addition of Grignard reagents to give alcohols (Section 19.7)



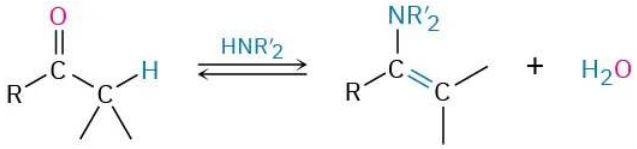
   c. Addition of HCN to give cyanohydrins (Section 19.6)



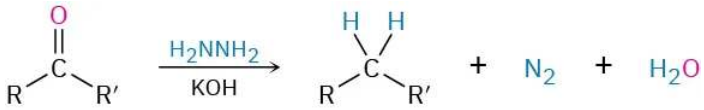
   d. Addition of primary amines to give imines (Section 19.8)



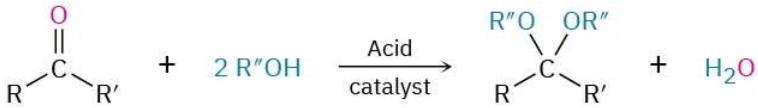
   e. Addition of secondary amines to give enamines (Section 19.8)



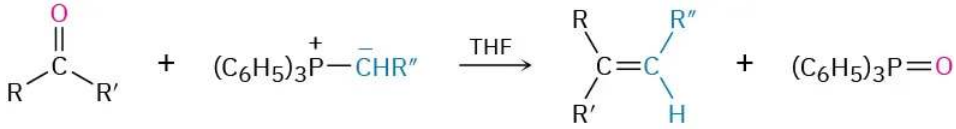
f. Wolff–Kishner reaction to give alkanes (Section 19.9)



g. Addition of alcohols to give acetals (Section 19.10)

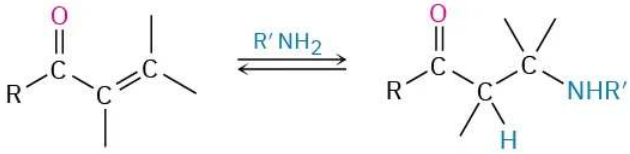


h. Addition of phosphorus ylides to give alkenes: Wittig reaction (Section 19.11)

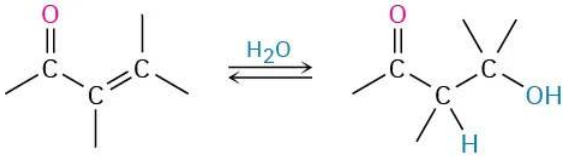


- Conjugate additions to α,β-unsaturated aldehydes and ketones (Section 19.13)

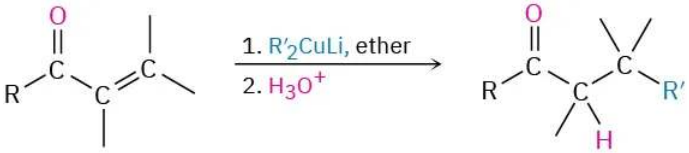
a. Conjugate addition of amines



b. Conjugate addition of water



c. Conjugate addition of alkyl groups by diorganocopper reaction



This page titled 8.19: Summary of Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

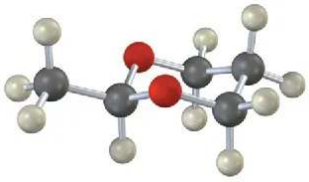
- **19.18: Summary of Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

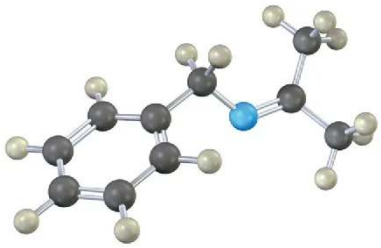
8.20: Additional Problems

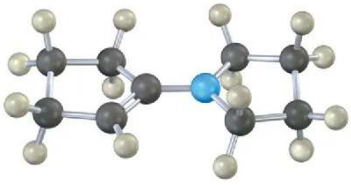
19 • Additional Problems

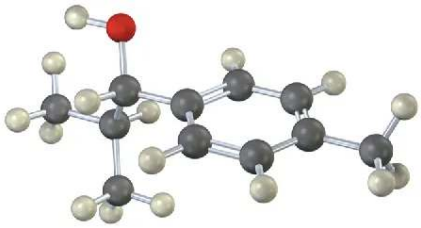
Visualizing Chemistry

PROBLEM 19-27 Each of the following substances can be prepared by a nucleophilic addition reaction between an aldehyde or ketone and a nucleophile. Identify the reactants from which each was prepared. If the substance is an acetal, identify the carbonyl compound and the alcohol; if it is an imine, identify the carbonyl compound and the amine; and so forth.

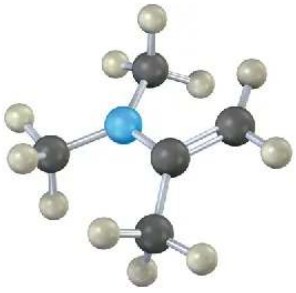
(a) 

(b) 

(c) 

(d) 

PROBLEM 19-28 The following molecular model represents a tetrahedral intermediate resulting from addition of a nucleophile to an aldehyde or ketone. Identify the reactants, and write the structure of the final product when the nucleophilic addition reaction is complete.



PROBLEM 19-29 The enamine prepared from acetone and dimethylamine is shown in its lowest-energy form.

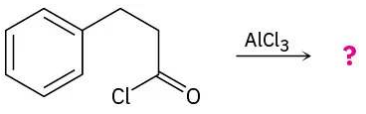
(a) What is the geometry and hybridization of the nitrogen atom?

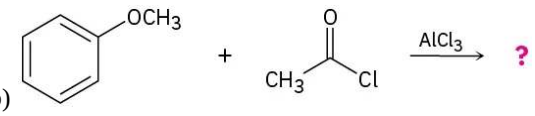
(b) What orbital on nitrogen holds the lone pair of electrons?

(c) What is the geometric relationship between the *p* orbitals of the double bond and the nitrogen orbital that holds the lone pair? Why do you think this geometry represents the minimum energy?

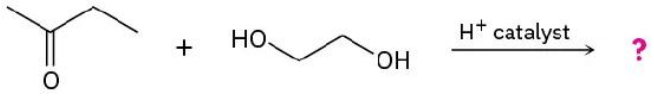
Mechanism Problems

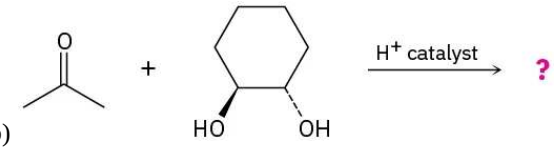
PROBLEM 19-30 Predict the product(s) and propose a mechanism for each of the following reactions:

(a) 

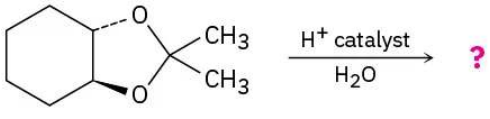
(b) 

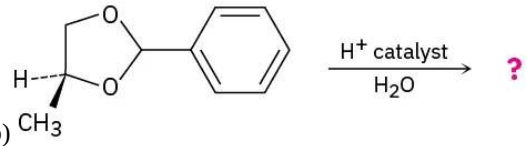
PROBLEM 19-31 Predict the product(s) and propose a mechanism for each of the following reactions:

(a) 

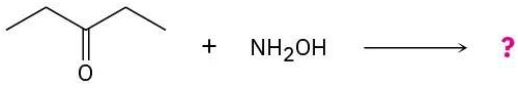
(b) 

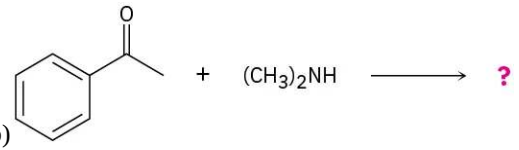
PROBLEM 19-32 Predict the product(s) and propose a mechanism for each of the following reactions:

(a) 

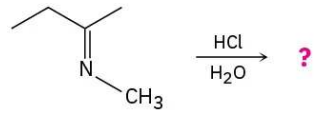
(b) 

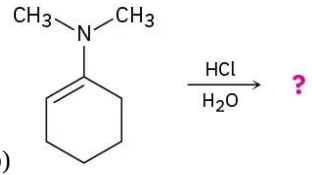
PROBLEM 19-33 Predict the product(s) and propose a mechanism for each of the following reactions:

(a) 

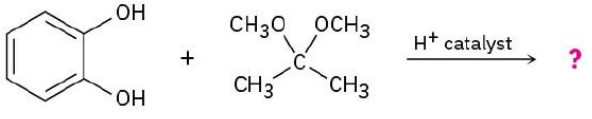
(b) 

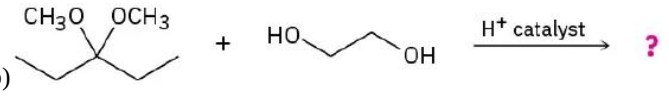
PROBLEM 19-34 Predict the product(s) and propose mechanisms for the following reactions:

(a) 

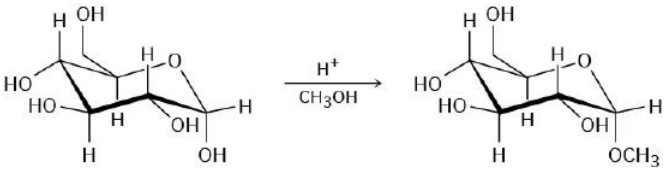
(b) 

PROBLEM 19-35 The following reaction begins with an acetal and converts it into a different acetal. Predict the product(s) and propose a mechanism.

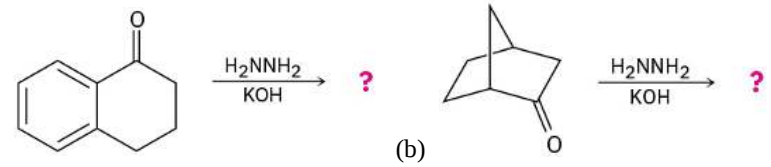
(a) 

(b) 

PROBLEM 19-36 When α-glucose is treated with an acid catalyst in the presence of an alcohol, an acetal is formed. Propose a mechanism for this process and give the structure of the stereoisomeric acetal that you would also expect as a product.

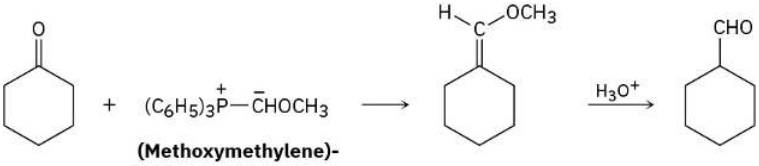


PROBLEM 19-37 Predict the products of the following Wolff–Kishner reactions. Write the mechanism for each, beginning from the hydrazone intermediate.

(a) 

(b)

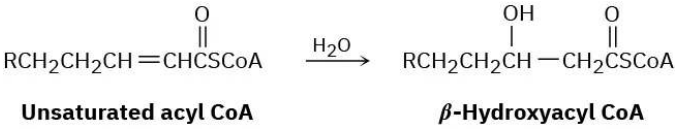
PROBLEM 19-38 Aldehydes can be prepared by the Wittig reaction using (methoxymethylene)triphenylphosphorane as the Wittig reagent and then hydrolyzing the product with acid. For example,



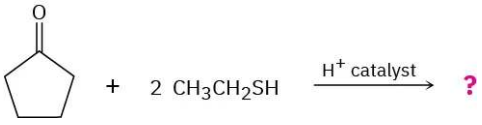
(a) How would you prepare the necessary phosphorane?

(b) Propose a mechanism for the hydrolysis step.

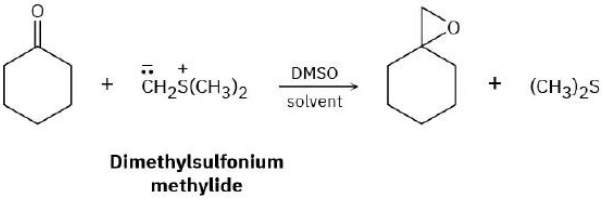
PROBLEM 19-39 One of the steps in the metabolism of fats is the reaction of an unsaturated acyl CoA with water to give a β-hydroxyacyl CoA. Propose a mechanism.



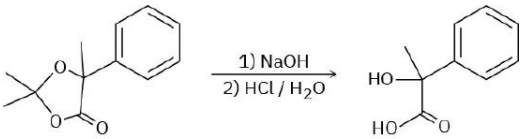
PROBLEM 19-40 Aldehydes and ketones react with thiols to yield *thioacetals* just as they react with alcohols to yield acetals. Predict the product of the following reaction, and propose a mechanism:



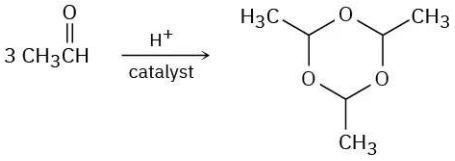
PROBLEM 19-41 Ketones react with dimethylsulfonium methylide to yield epoxides. Suggest a mechanism for the reaction.



PROBLEM 19-42 Propose a mechanism for the following reaction.

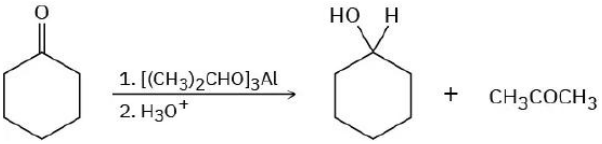


PROBLEM 19-43 Paraldehyde, a sedative and hypnotic agent, is prepared by treatment of acetaldehyde with an acidic catalyst. Propose a mechanism for the reaction.

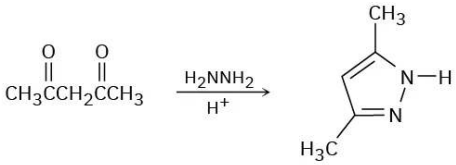


Paraldehyde

PROBLEM 19-44 The Meerwein–Ponndorf–Verley reaction involves reduction of a ketone by treatment with an excess of aluminum triisopropoxide, $[(CH_3)_2CHO]_3Al$. The mechanism of the process is closely related to the Cannizzaro reaction in that a hydride ion acts as a leaving group. Propose a mechanism.

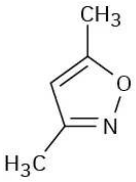


PROBLEM 19-45 Propose a mechanism to account for the formation of 3,5-dimethylpyrazole from hydrazine and 2,4-pentanedione. What has happened to each carbonyl carbon in going from starting material to product.



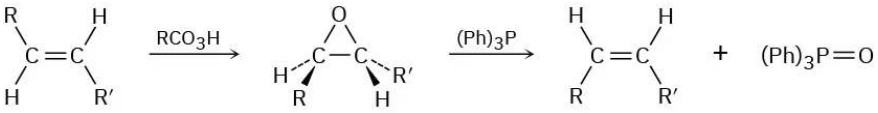
2,4-Pentanedione **3,5-Dimethylpyrazole**

PROBLEM 19-46 In light of your answer to Problem 19-45, propose a mechanism for the formation of 3,5-dimethylisoxazole from hydroxylamine and 2,4-pentanedione.

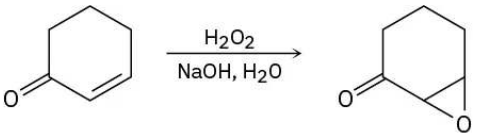


3,5-Dimethylisoxazole

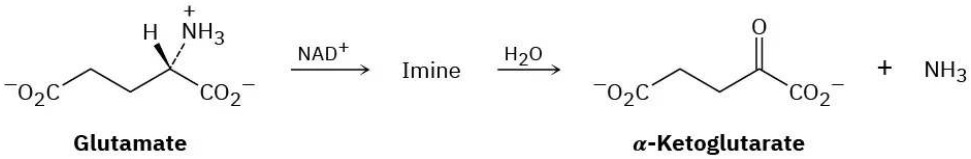
PROBLEM 19-47 Trans alkenes are converted into their cis isomers and vice versa on epoxidation followed by treatment of the epoxide with triphenylphosphine. Propose a mechanism for the reaction.



PROBLEM 19-48 Treatment of an α,β-unsaturated ketone with basic aqueous hydrogen peroxide yields an epoxy ketone. The reaction is specific to unsaturated ketones; isolated alkene double bonds do not react. Propose a mechanism.

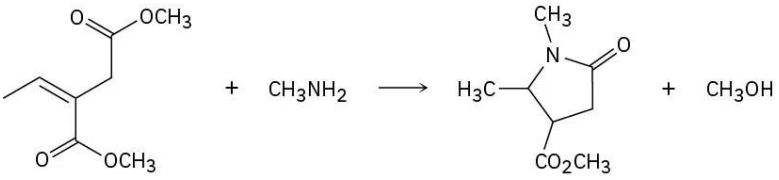


PROBLEM 19-49 One of the biological pathways by which an amine is converted to a ketone involves two steps: (1) oxidation of the amine by NAD^+ to give an imine and (2) hydrolysis of the imine to give a ketone plus ammonia. Glutamate, for instance, is converted by this process into α-ketoglutarate. Show the structure of the imine intermediate, and propose mechanisms for both steps.

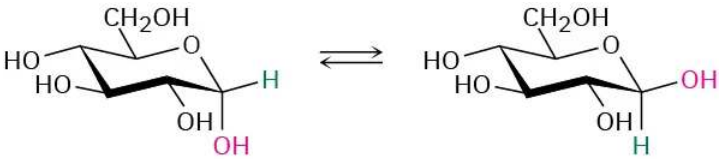


Glutamate **α-Ketoglutarate**

PROBLEM 19-50 Primary amines react with esters to yield amides: $RCO_2R' + R''NH_2 \rightarrow RCONHR'' + R'OH$. Propose a mechanism for the following reaction of an α,β-unsaturated ester.

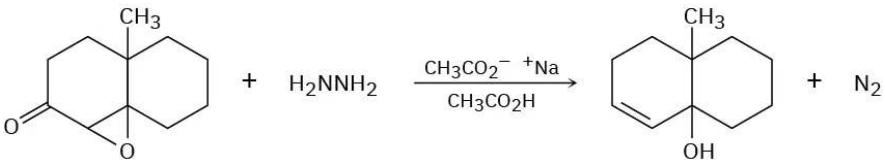


PROBLEM 19-51 When crystals of pure α-glucose are dissolved in water, isomerization occurs slowly to produce β-glucose. Propose a mechanism for the isomerization.



α-Glucose **β-Glucose**

PROBLEM 19-52 The Wharton reaction converts an epoxy ketone to an allylic alcohol by reaction with hydrazine. Review the Wolff–Kishner reaction in Section 19.9 and then propose a mechanism.



Naming Aldehydes and Ketones

PROBLEM 19-53 Draw structures corresponding to the following names:

(a) Bromoacetone

(b) (*S*)-2-Hydroxypropanal

(c) 2-Methyl-3-heptanone

(d) (2*S*,3*R*)-2,3,4-Trihydroxybutanal

(e) 2,2,4,4-Tetramethyl-3-pentanone

https://chem.libretexts.org/@go/page/564275

(f) 4-Methyl-3-penten-2-one

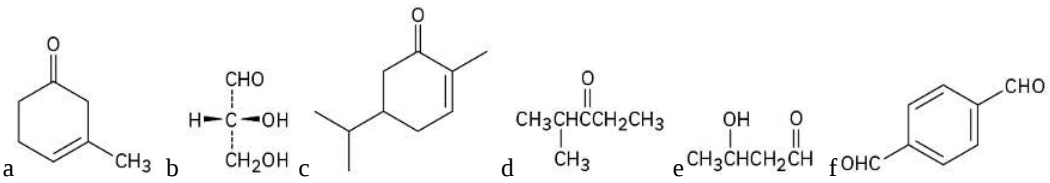
(g) Butanedial

(h) 3-Phenyl-2-propenal

(i) 6,6-Dimethyl-2,4-cyclohexadienone (j) *p*-Nitroacetophenone

PROBLEM 19-54 Draw and name the seven aldehydes and ketones with the formula $C_5H_{10}O$. Which are chiral?

PROBLEM 19-55 Give IUPAC names for the following compounds:



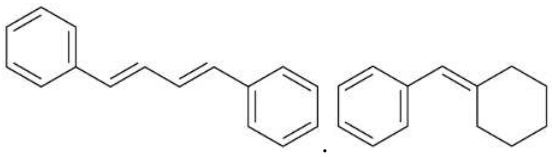
PROBLEM 19-56 Draw structures of compounds that fit the following descriptions:

(a)An α,β-unsaturated ketone, C6H8O (b) An *α*-diketone (c) An aromatic ketone, $C_9H_{10}O$ (d) A diene aldehyde, C_7H_8O

PROBLEM 19-57 Predict the products of the reaction of (1) phenylacetaldehyde and (2) acetophenone with the following reagents:

(a) NaBH4, then H3O+, (b) Dess–Martin reagent (c) NH_2OH, HCl catalyst (d) CH_3MgBr, then H_3O^+ (e) 2 CH_3OH, HCl catalyst (f) H_2NNH_2, KOH (g) $(C_6H_5)_3P$=Math input error$_2$ (h) HCN, KCN

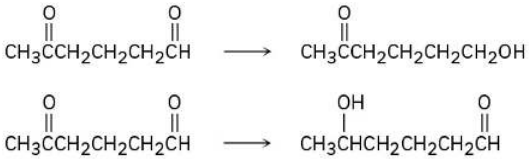
PROBLEM 19-58 Show how you might use a Wittig reaction to prepare the following alkenes. Identify the alkyl halide and the carbonyl components.



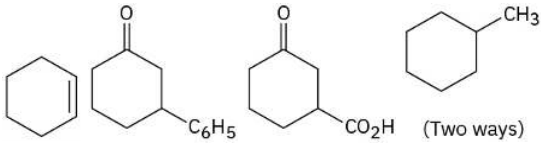
PROBLEM 19-59 How would you use a Grignard reaction on an aldehyde or ketone to synthesize the following compounds?

(a) 2-Pentanol. (b) 1-Butanol (c) 1-Phenylcyclohexanol (d) Diphenylmethanol

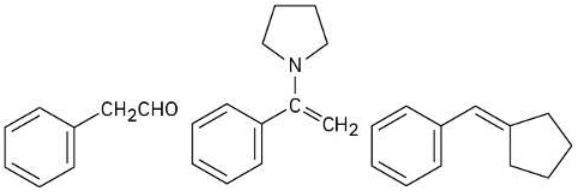
PROBLEM 19-60 How might you carry out the following selective transformations? One of the two schemes requires a protection step. (Recall from Section 19.4 that aldehydes are more reactive than ketones toward nucleophilic addition.)



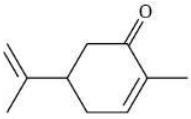
PROBLEM 19-61 How would you prepare the following substances from 2-cyclohexenone? More than one step may be needed.



PROBLEM 19-62 How would you synthesize the following substances from benzaldehyde and any other reagents needed?



PROBLEM 19-63 Carvone is the major constituent of spearmint oil. What products would you expect from the reaction of carvone with the following reagents?



Carvone

(a) (CH3)2Cu–Li+, then H_3O^+

(b) $LiAlH_4$, then H_3O^+

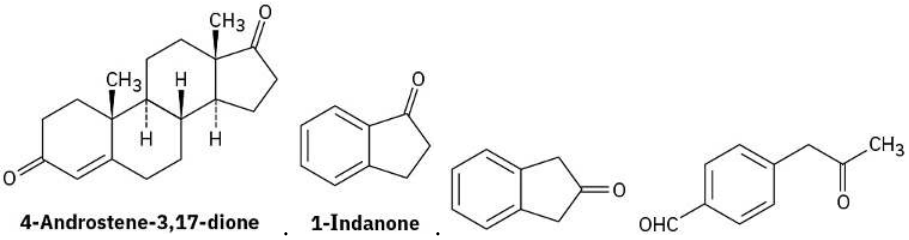
(c) CH_3NH_2 (d) C_6H_5MgBr, then H_3O^+ (e) H_2/Pd (f) $HOCH_2CH_2OH$, HCl (g) $(C_6H_5)_3\overset{+}{T}eXAtom\overset{-}{T}eXAtomHCH_3$

PROBLEM 19-64 How would you synthesize the following compounds from cyclohexanone?

(a)1-Methylcyclohexene (b) 2-Phenylcyclohexanone (c) *cis*-1,2-Cyclohexanediol (d) 1-Cyclohexylcyclohexanol

Spectroscopy

PROBLEM 19-65 At what position would you expect to observe IR absorptions for the following molecules?

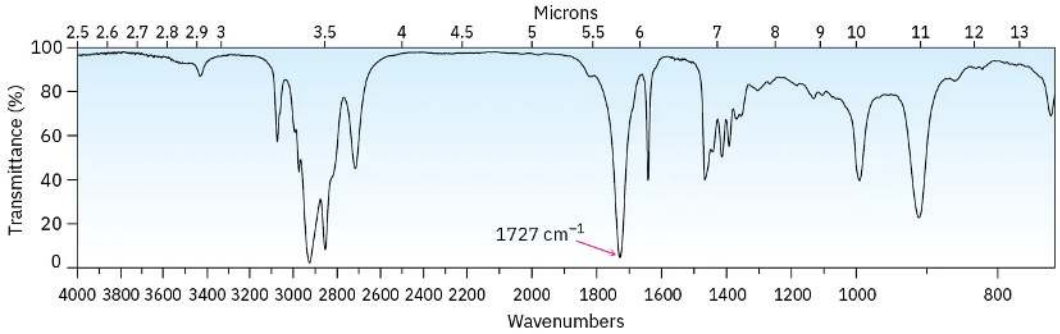


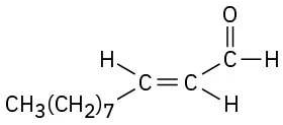
4-Androstene-3,17-dione

1-Indanone

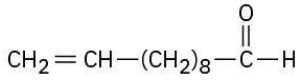
PROBLEM 19-66 Acid-catalyzed dehydration of 3-hydroxy-3-phenylcyclohexanone leads to an unsaturated ketone. What possible structures are there for the product? At what position in the IR spectrum would you expect each to absorb? If the actual product has an absorption at 1670 cm^{–1}, what is its structure?

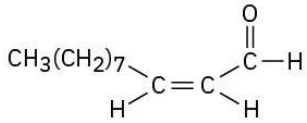
PROBLEM 19-67 Choose the structure that best fits the IR spectrum shown.

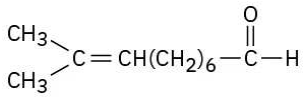


1. 

https://chem.libretexts.org/@go/page/564275

2. 

3. 

4. 

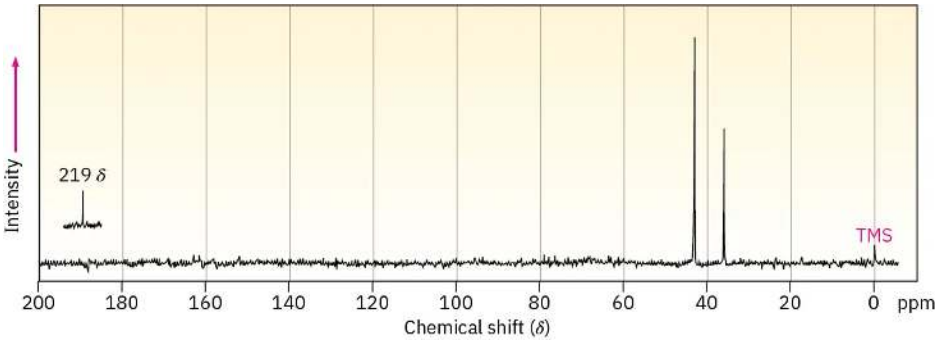
PROBLEM 19-68 Propose structures for molecules that meet the following descriptions. Assume that the kinds of carbons (1°, 2°, 3°, or 4°) have been assigned by DEPT–NMR.

$C_6H_{12}O$; IR: 1715 cm^{-1}; ^{13}C NMR: 8.0 δ (1°), 18.5 δ (1°), 33.5 δ (2°), 40.6 δ (3°), 214.0 δ (4°)

$C_5H_{10}O$; IR: 1730 cm^{-1}; ^{13}C NMR: 22.6 δ (1°), 23.6 δ (3°), 52.8 δ (2°), 202.4 δ (3°)

C_6H_8O; IR: 1680 cm^{-1}; ^{13}C NMR: 22.9 δ (2°), 25.8 δ (2°), 38.2 δ (2°), 129.8 δ (3°), 150.6 δ (3°), 198.7 δ (4°)

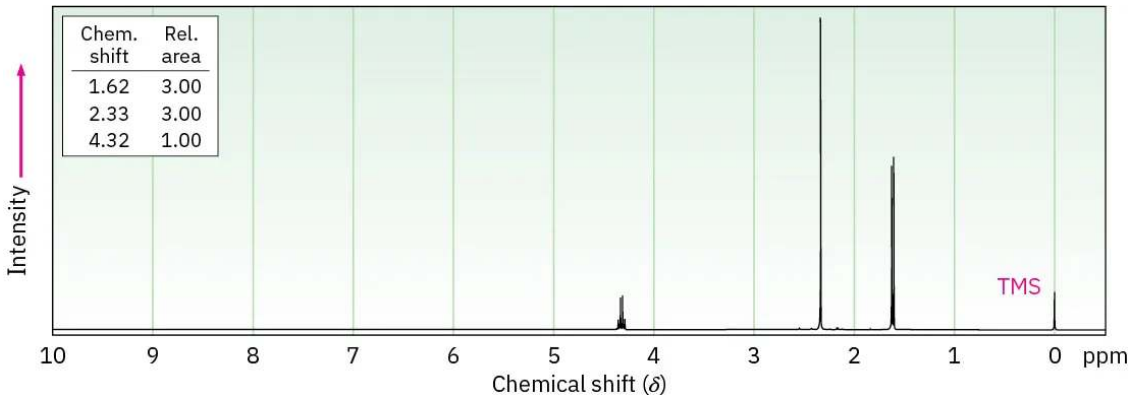
PROBLEM 19-69 Compound A, $C_8H_{10}O_2$, has an intense IR absorption at 1750 cm^{-1} and gives the ^{13}C NMR spectrum shown. Propose a structure for A.



PROBLEM 19-70 Propose structures for ketones or aldehydes that have the following ^1H NMR spectra:

(a) C_4H_7ClO

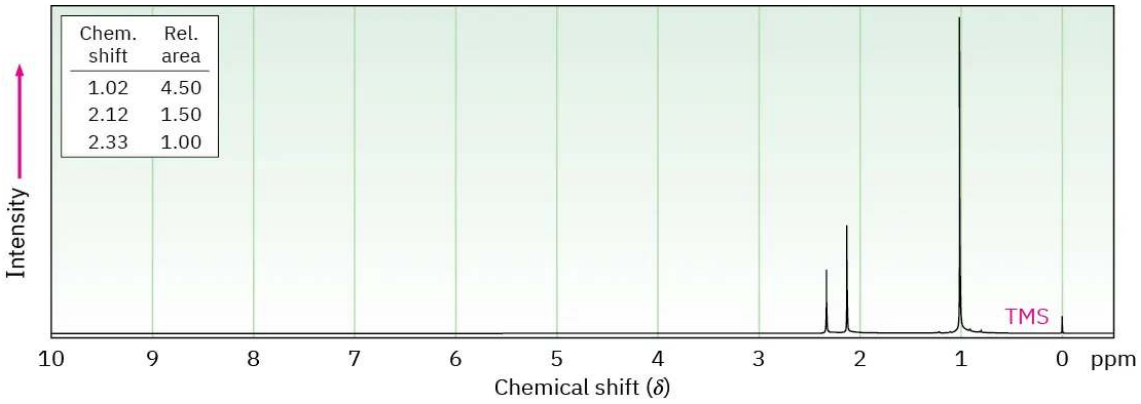
IR: 1715 cm^{-1}



(b) $C_7H_{14}O$

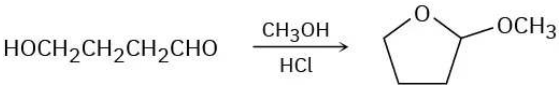
IR: 1710 cm^{-1}

https://chem.libretexts.org/@go/page/564275



General Problems

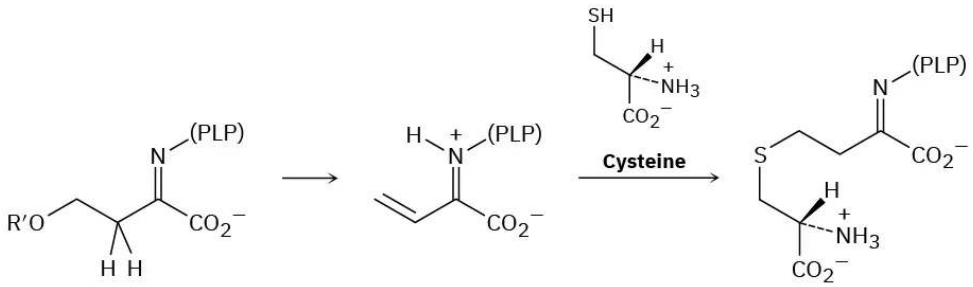
PROBLEM 19-71 When 4-hydroxybutanal is treated with methanol in the presence of an acid catalyst, 2-methoxytetrahydrofuran is formed. Explain.



PROBLEM 19-72 The S_N2 reaction of (dibromomethyl)benzene, $C_6H_5CHBr_2$, with NaOH yields benzaldehyde rather than (dihydroxymethyl)benzene, $C_6H_5CH(OH)_2$. Explain.

PROBLEM 19-73 Reaction of 2-butanone with HCN yields a chiral product. What stereochemistry does the product have? Is it optically active?

PROBLEM 19-74 The amino acid methionine is biosynthesized by a multistep route that includes reaction of an imine of pyridoxal phosphate (PLP) to give an unsaturated imine, which then reacts with cysteine. What kinds of reactions are occurring in the two steps?

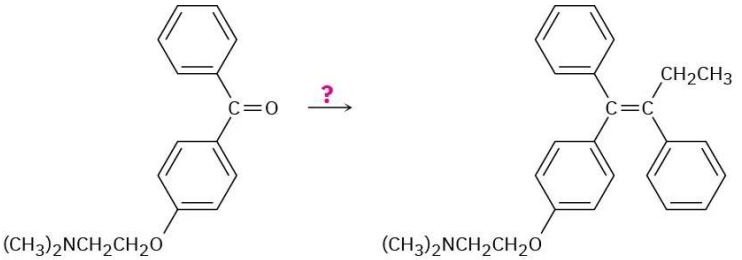


***O*-Succinylhomoserine–PLP imine** **Unsaturated imine**

PROBLEM 19-75 Each of the following reaction schemes has one or more flaws. What is wrong in each case? How would you correct each scheme?

PROBLEM 19-76 6-Methyl-5-hepten-2-one is a constituent of lemongrass oil. How could you synthesize this substance from methyl 4-oxopentanoate?

PROBLEM 19-77 Tamoxifen is a drug used in the treatment of breast cancer. How would you prepare tamoxifen from benzene, the following ketone, and any other reagents needed?

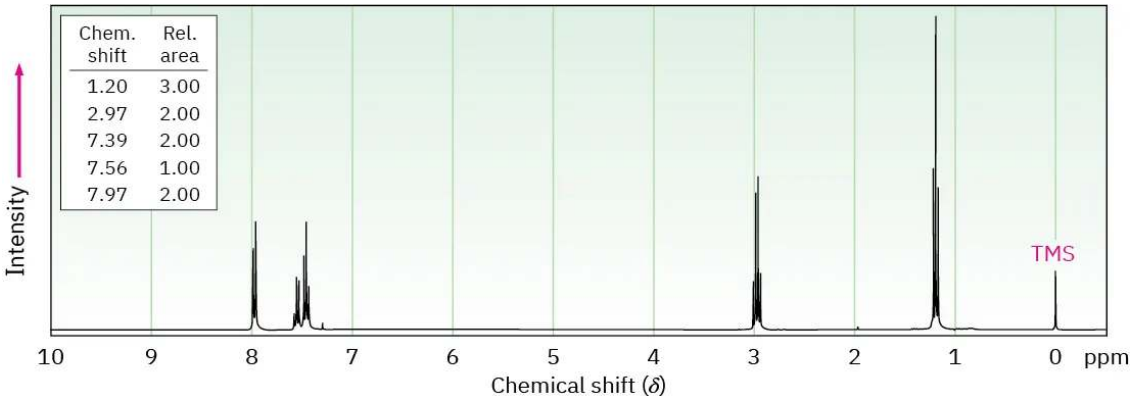


Tamoxifen

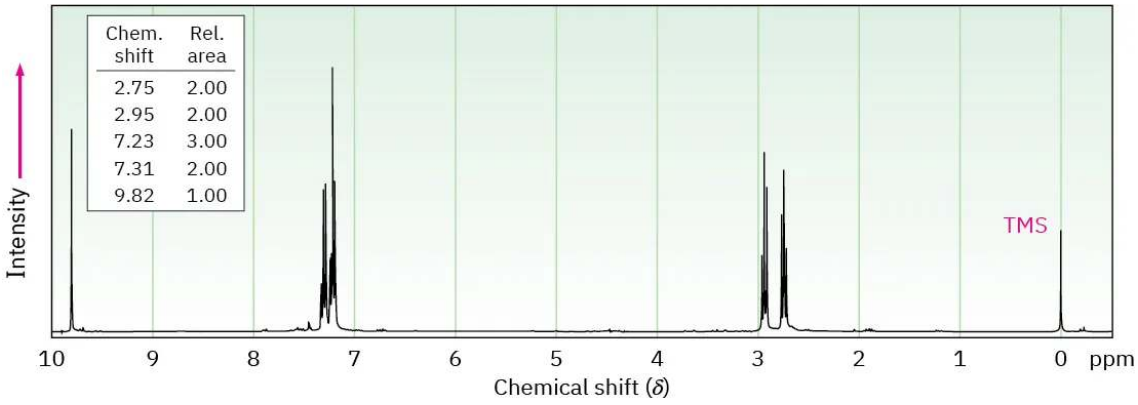
PROBLEM 19-78 Compound A, MW = 86, shows an IR absorption at 1730 cm^{-1} and a very simple ^1H NMR spectrum with peaks at 9.7 δ (1 H, singlet) and 1.2 δ (9 H, singlet). Propose a structure for A.

PROBLEM 19-79 Compound B is isomeric with A (Problem 19-78) and shows an IR peak at 1715 cm^{-1}. The ^1H NMR spectrum of B has peaks at 2.4 δ (1 H, septet, J = 7 Hz), 2.1 δ (3 H, singlet), and 1.2 δ (6 H, doublet, J = 7 Hz). What is the structure of B?

PROBLEM 19-80 The ^1H NMR spectrum shown is that of a compound with the formula $C_9H_{10}O$. How many double bonds and/or rings does this compound contain? If the unknown compound has an IR absorption at 1690 cm^{-1}, what is a likely structure?



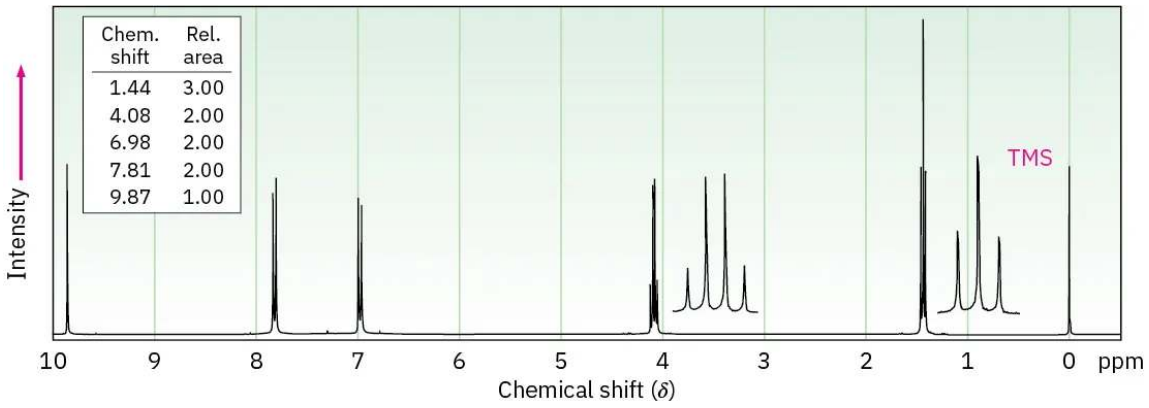
PROBLEM 19-81 The ^1H NMR spectrum shown is that of a compound isomeric with the one in Problem 19-80. This isomer has an IR absorption at 1730 cm^{-1}. Propose a structure. [*Note:* Aldehyde protons (CHO) often show low coupling constants to adjacent hydrogens, so the splitting of aldehyde signals is not always apparent.]



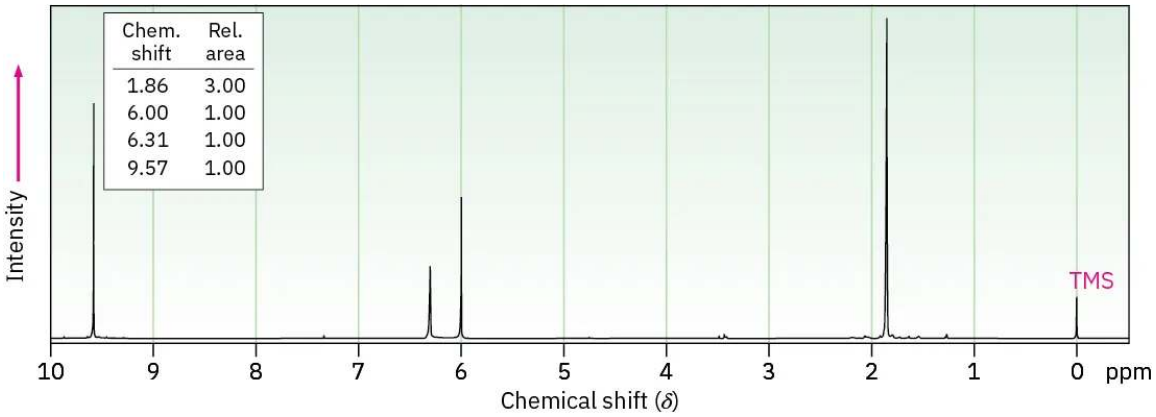
PROBLEM 19-82

Propose structures for ketones or aldehydes that have the following ^1H NMR spectra:

(a) $C_9H_{10}O_2$- IR: 1695 cm^{-1}

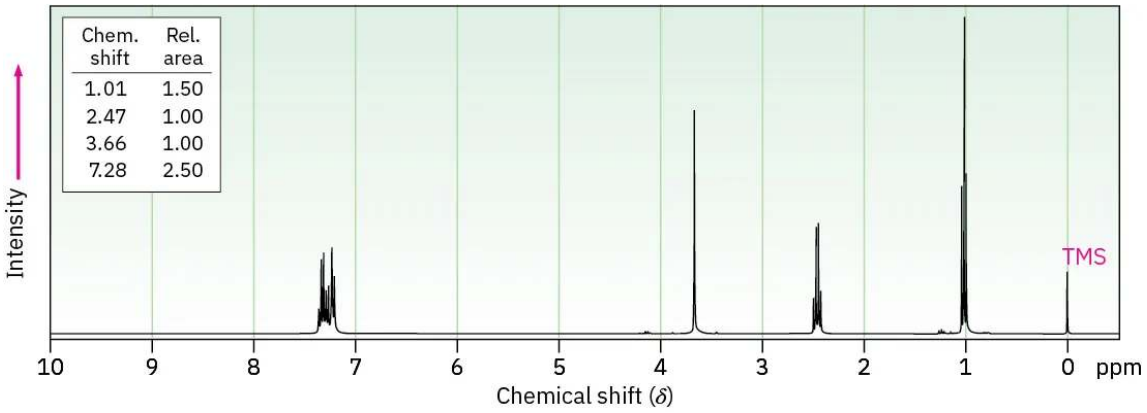


(b) C_4H_6O - IR: 1690 cm^{-1}



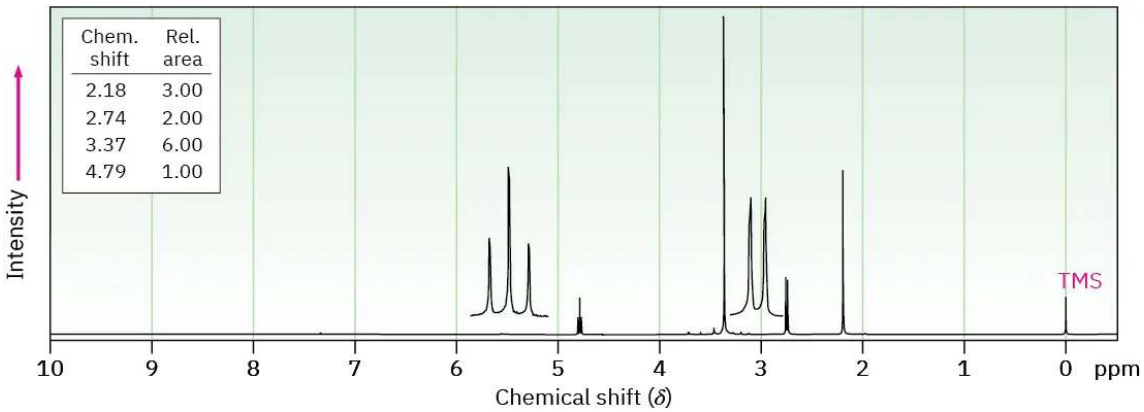
PROBLEM 19-83 Propose structures for ketones or aldehydes that have the following ^1H NMR spectra.

(a) $C_{10}H_{12}O$: IR: 1710 cm^{-1}

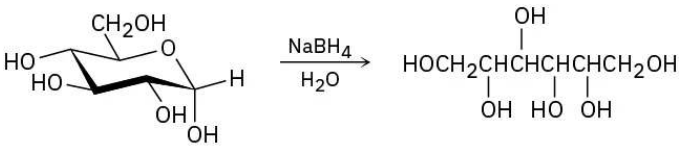


(b) $C_6H_{12}O_3$: IR: 1715 cm^{-1}

https://chem.libretexts.org/@go/page/564275

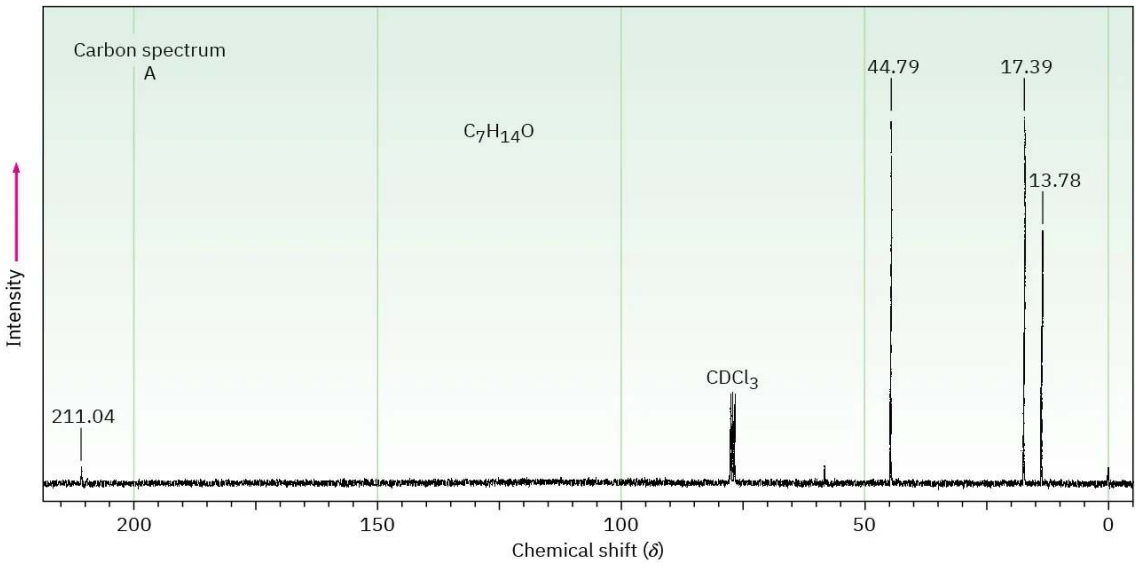


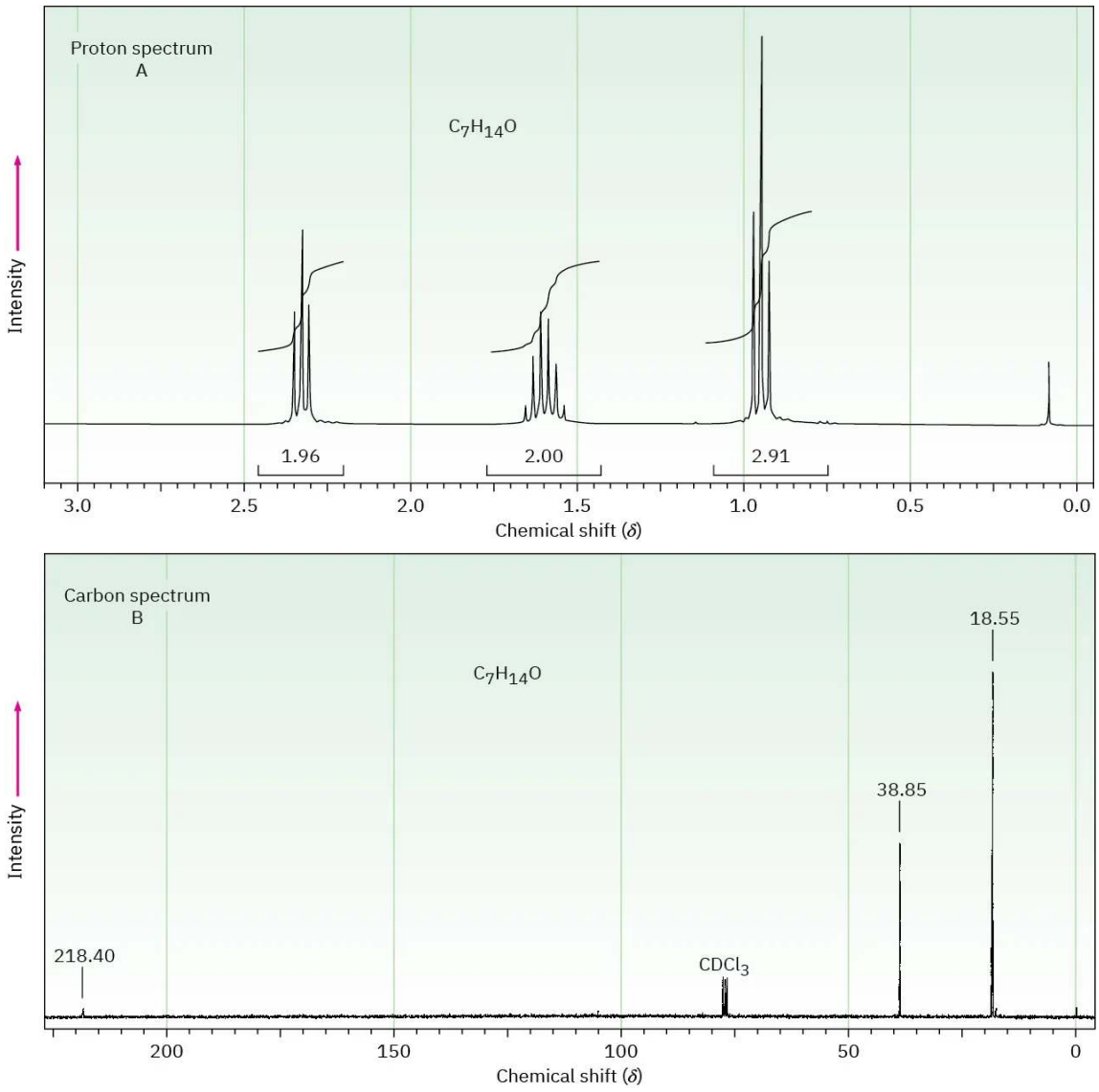
PROBLEM 19-84 When glucose (Problem 19-51) is treated with $NaBH_4$, reaction occurs to yield *sorbitol*, a polyalcohol commonly used as a food additive. Show how this reduction occurs.



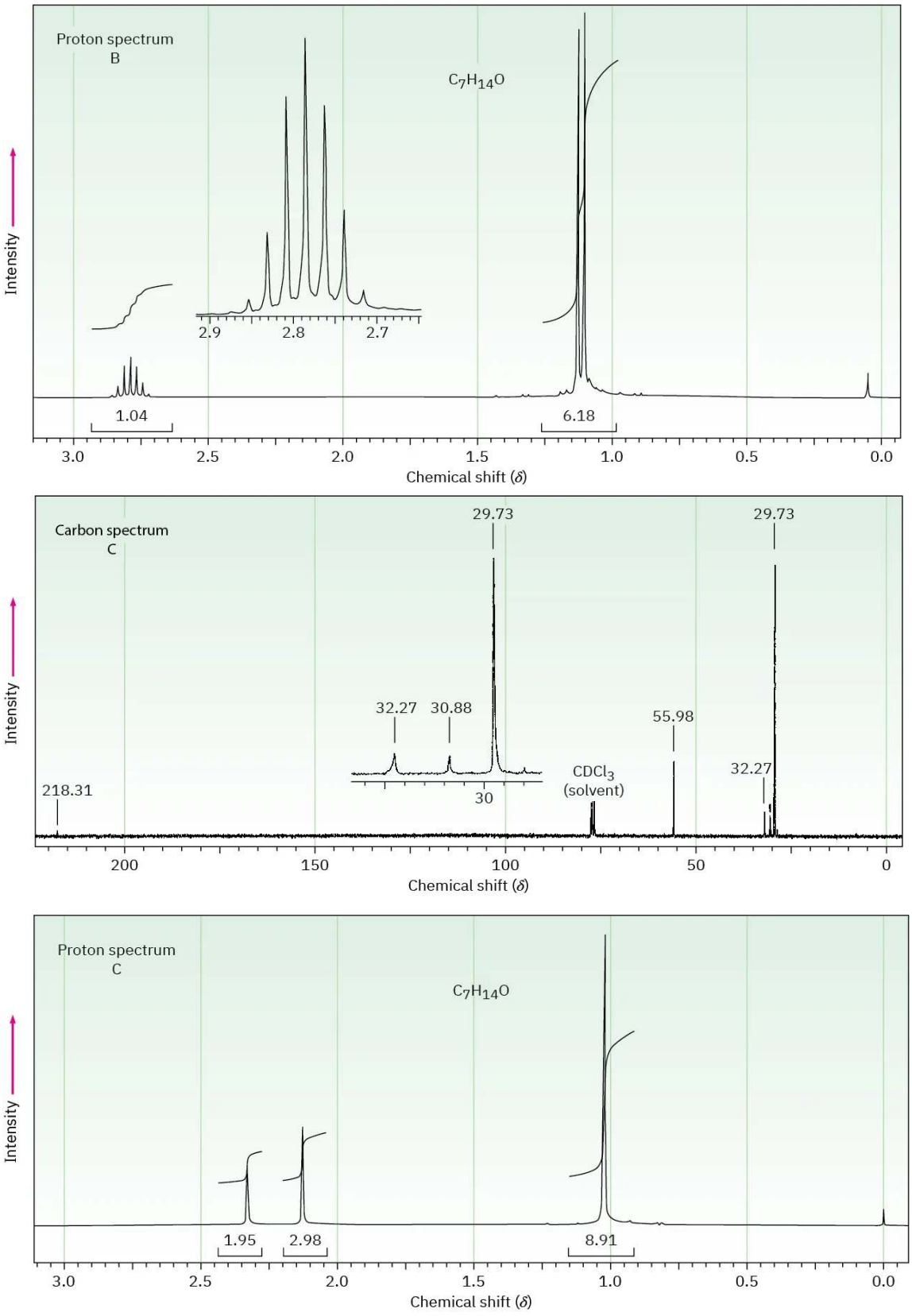
Glucose **Sorbitol**

PROBLEM 19-85 The proton and carbon NMR spectra for each of the three isomeric ketones with the formula $C_7H_{14}O$ are shown. Assign a structure to each pair of spectra.



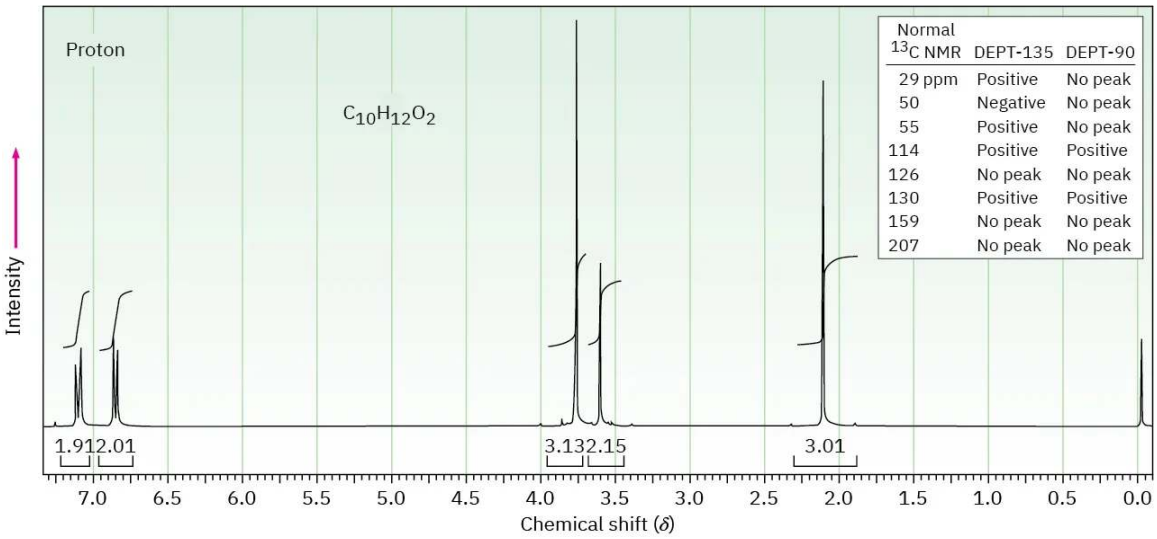


https://chem.libretexts.org/@go/page/564275



PROBLEM 19-86 The proton NMR spectrum for a compound with formula $C_{10}H_{12}O_2$ is shown below. The infrared spectrum has a strong band at 1711 cm^{-1}. The broadband-decoupled 13C NMR spectral results are tabulated along with the DEPT-135 and DEPT-90 information. Draw the structure of this compound.

https://chem.libretexts.org/@go/page/564275



This page titled 8.20: Additional Problems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **19.19: Additional Problems** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

SECTION OVERVIEW

8.21: Carbonyl Condensation Reactions

Learning Objectives

When you have completed Chapter 23, you should be able to

- fulfill all of the detailed objectives listed under each individual section.
- design multi-step syntheses in which the reactions introduced in this unit are used in conjunction with any of the reactions described in previous units.
- solve road-map problems that require a knowledge of carbonyl condensation reactions.
- define, and use in context, any of the key terms introduced.

In this chapter, we consider the fourth and final general type of reaction that carbonyl compounds undergo—the carbonyl condensation reaction. Carbonyl condensation reactions take place between two carbonyl-containing reactants, one of which must possess an alpha-hydrogen atom. The first step of the reaction involves the removal of an alpha-hydrogen atom by a base. In the second step, the enolate anion that results from this removal attacks the carbonyl-carbon of the second reacting molecule. In the final step of the reaction, a proton is transferred to the tetrahedral intermediate formed in the second step, although in some cases the product that results may subsequently be dehydrated.

This page titled 8.21: Carbonyl Condensation Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

CHAPTER OVERVIEW

9: Carboxylic Acids and Nitriles

This chapter presents a straightforward discussion of the chemistry of carboxylic acids (formerly called “fatty acids”) and nitriles. As usual, we begin with a description of how the compounds are named. We then consider the subtleties of their structure, and how these structural features influence physical properties, such as boiling point. We place considerable emphasis on the dissociation of carboxylic acids and the effect of substituents on acid strength.

We have already encountered a number of methods for preparing carboxylic acids. We shall review these methods, and learn about two additional procedures. The only reactions of carboxylic acids that we study in detail in this chapter are reduction and decarboxylation, although two other common reactions of carboxylic acids, alpha substitution and nucleophilic acyl substitution, will be described in later chapters.

We will then look at the formation of nitriles and their chemical reactivity; and our discussion of carboxylic acid and nitrile chemistry concludes with a look at the infrared and NMR spectra of these compounds, with emphasis on the characterization of carboxylic acids.

9.1: Why This Chapter?
9.2: Naming Carboxylic Acids and Nitriles
9.3: Structure and Properties of Carboxylic Acids
9.4: Biological Acids and the Henderson-Hasselbalch Equation
9.5: Substituent Effects on Acidity
9.6: Preparing Carboxylic Acids
9.7: Reactions of Carboxylic Acids - An Overview
9.8: Chemistry of Nitriles
9.9: Spectroscopy of Carboxylic Acids and Nitriles
9.10: Chemistry Matters—Vitamin C
9.11: Key Terms
9.12: Summary
9.13: Summary of Reactions
9.14: Additional Problems

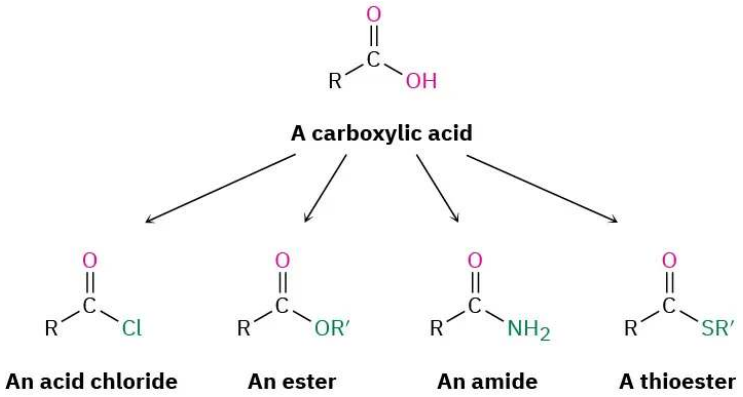
This page titled 9: Carboxylic Acids and Nitriles is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

9.1: Why This Chapter?

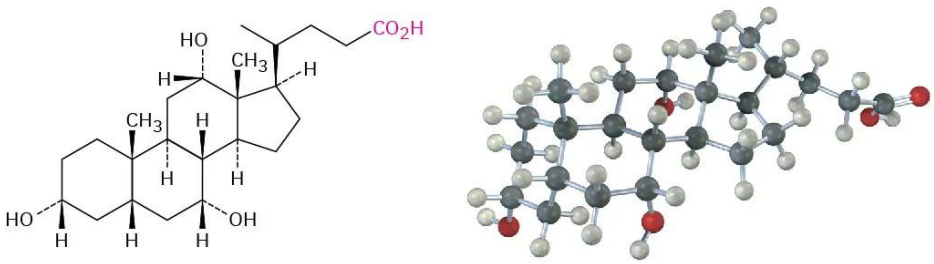
Carboxylic acids are present in many industrial processes and most biological pathways and are the starting materials from which other acyl derivatives are made. Thus, an understanding of their properties and reactions is fundamental to understanding organic chemistry. We'll look both at acids and at their close relatives, nitriles ($RC{\equiv}N$), in this chapter and at carboxylic acid derivatives in the next chapter.

Figure 9.1.1: The burning sensation produced by touching or eating chili peppers is due to capsaicin, a carboxylic acid derivative called an amide. (credit: modification of "Chillis" by Lucas Cobb/Flickr, CC BY 2.0)

Carboxylic acids, RCO_2H, occupy a central place among carbonyl compounds. Not only are they valuable in themselves, they also serve as starting materials for preparing numerous carboxylic acid derivatives such as acid chlorides, esters, amides, and thioesters. In addition, carboxylic acids are present in the majority of biological pathways.

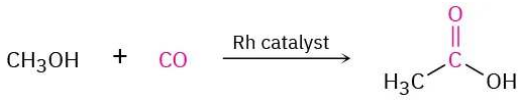


A great many carboxylic acids are found in nature: acetic acid, CH_3CO_2H, is the chief organic component of vinegar; butanoic acid, $CH_3CH_2CH_2CO_2H$, is responsible for the rancid odor of sour butter; and hexanoic acid (caproic acid), $CH_3(CH_2)_4CO_2H$, is responsible for the unmistakable aroma of goats and dirty gym socks (the name comes from the Latin *caper*, meaning "goat"). Other examples are cholic acid, a major component of human bile, and long-chain aliphatic acids such as palmitic acid, $CH_3(CH_2)_{14}CO_2H$, a biological precursor of fats and vegetable oils.



Cholic acid

Approximately 20 million tons of acetic acid is produced worldwide each year for a variety of purposes, including preparation of the vinyl acetate polymer used in paints and adhesives. About 20% of the acetic acid synthesized industrially is obtained by oxidation of acetaldehyde. Much of the remaining 80% is prepared by the rhodium-catalyzed reaction of methanol with carbon monoxide.



This page titled 9.1: Why This Chapter? is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **20.0: Why This Chapter?** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

9.2: Naming Carboxylic Acids and Nitriles

Carboxylic Acids, RCO_2H

Simple carboxylic acids derived from open-chain alkanes are systematically named by replacing the terminal *–e* of the corresponding alkane name with *-oic acid*. The $–CO_2H$ carbon atom is numbered C1.

Propanoic acid **4-Methylpentanoic acid** **3-Ethyl-6-methyloctanedioic acid**

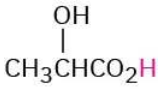
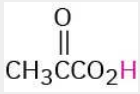
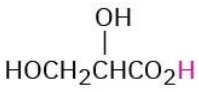
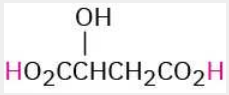
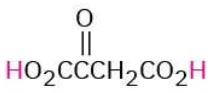
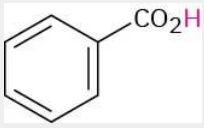
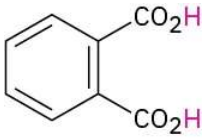
Compounds that have a $–CO_2H$ group bonded to a ring are named using the suffix *-carboxylic acid*. The CO_2H carbon is attached to C1 in this system and is not itself numbered. As a substituent, the CO_2H group is called a carboxyl group.

***trans*-4-Hydroxycyclohexanecarboxylic acid** **1-Cyclopentenecarboxylic acid**

Because many carboxylic acids were among the first organic compounds to be isolated and purified, quite a few common names exist (Table 9.2.1). Biological chemists, in particular, make frequent use of these names, so you may find yourself referring back to this list on occasion. We'll use systematic names in this book, with a few exceptions such as formic (methanoic) acid and acetic (ethanoic) acid, whose names are accepted by IUPAC and are so well known that it makes little sense to refer to them any other way.

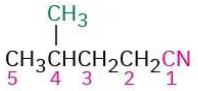
Also listed in Table 9.2.1 are the names of acyl groups $\left(R{-}\overset{\overset{O}{\|}}{C}{-}\right)$ derived from the parent acids. Except for the eight entries at the top of Table 9.2.1, whose names have a *-yl* ending, all other acyl groups are named using an *-oyl* ending.

Table 9.2.1 Common Names of Some Carboxylic Acids and Acyl Groups

Structure	Name	Acyl group
HCO_2H	Formic	Formyl
CH_3CO_2H	Acetic	Acetyl
$CH_3CH_2CO_2H$	Propionic	Propionyl
$CH_3CH_2CH_2CO_2H$	Butyric	Butyryl
HO_2CCO_2H	Oxalic	Oxalyl
$HO_2CCH_2CO_2H$	Malonic	Malonyl
$HO_2CCH_2CH_2CO_2H$	Succinic	Succinyl
$HO_2CCH_2CH_2CH_2CO_2H$	Glutaric	Glutaryl
$HO_2CCH_2CH_2CH_2CH_2CO_2H$	Adipic	Adipoyl
$H_2C{=}CHCO_2H$	Acrylic	Acryloyl
$HO_2CCH{=}CHCO_2H$	Maleic (cis) Fumaric (trans)	Maleoyl Fumaroyl
$HOCH_2CO_2H$	Glycolic	Glycoloyl
	Lactic	Lactoyl
	Pyruvic	Pyruvoyl
	Glyceric	Glyceroyl
	Malic	Maloyl
	Oxaloacetic	Oxaloacetyl
	Benzoic	Benzoyl
	Phthalic	Phthaloyl

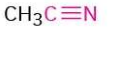
Nitriles, RC≡N

Compounds containing the –C≡N functional group are called nitriles and can undergo some chemistry similar to that of carboxylic acids. Simple open-chain nitriles are named by adding *-nitrile* as a suffix to the alkane name, with the nitrile carbon numbered C1.

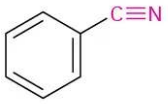


4-Methylpentanenitrile

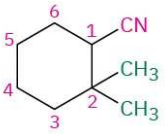
Nitriles can also be named as derivatives of carboxylic acids by replacing the *-ic acid* or *-oic acid* ending with *-onitrile*, or by replacing the *-carboxylic acid* ending with *-carbonitrile*. The nitrile carbon atom is attached to C1 but is not itself numbered.



Acetonitrile (from acetic acid)

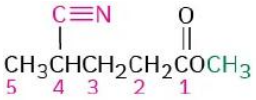


Benzonitrile (from benzoic acid)



2,2-Dimethylcyclohexanecarbonitrile (from 2,2-dimethylcyclohexane-carboxylic acid)

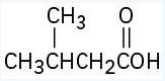
If another carboxylic acid derivative is present in the same molecule, the prefix *cyano-* is used for the C≡N group.

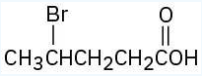


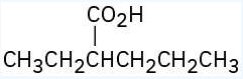
Methyl 4-cyanopentanoate

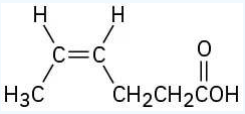
Exercise 9.2.1

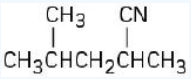
Give IUPAC names for the following compounds:

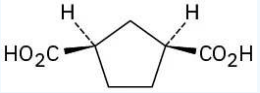
a. 

b. 

c. 

d. 

e. 

f. 

Answer

a. 3-Methylbutanoic acid
b. 4-Bromopentanoic acid
c. 2-Ethylpentanoic acid
d. cis-4-Hexenoic acid
e. 2,4-Dimethylpentanenitrile
f. cis-1,3-Cyclopentanedicarboxylic acid

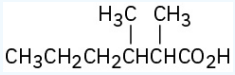
Exercise 9.2.2

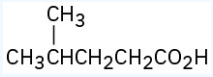
Draw structures corresponding to the following IUPAC names:

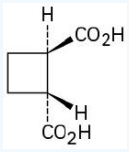
a. 2,3-Dimethylhexanoic acid
b. 4-Methylpentanoic acid

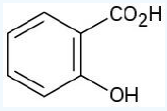
c. trans-1,2-Cyclobutanedicarboxylic acid
d. o-Hydroxybenzoic acid
e. (9Z,12Z)-9,12-Octadecadienoic acid
f. 2-Pentenenitrile

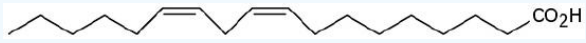
Answer

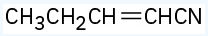
a. 

b. 

c. 

d. 

e. 

f. 

This page titled 9.2: Naming Carboxylic Acids and Nitriles is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **20.1: Naming Carboxylic Acids and Nitriles** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

9.3: Structure and Properties of Carboxylic Acids

Carboxylic acids are similar in some respects to both ketones and alcohols. Like ketones, the carboxyl carbon is sp^2-hybridized, and carboxylic acid groups are therefore planar with C–C=O and O=C–O bond angles of approximately 120° (Table 9.3.1).

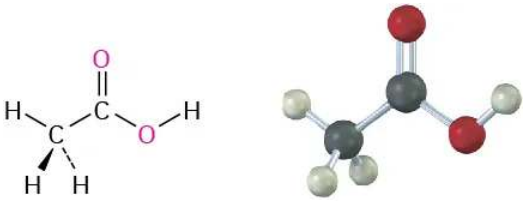
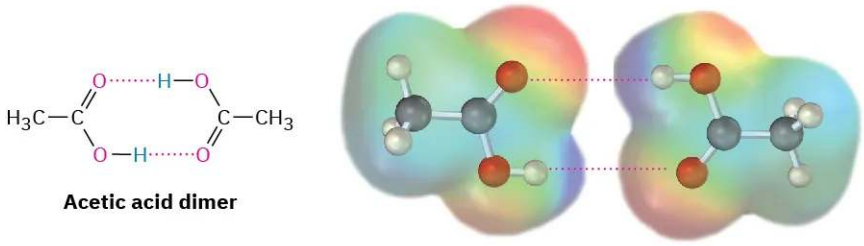


Table 9.3.1: Physical Parameters for Acetic Acid

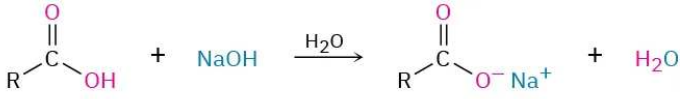
Bond angle	(degrees)	Bond length	(pm)
C–C=O	119	C–C	152
C–C–OH	119	C=O	125
O=C–OH	122	C–OH	131

Like alcohols, carboxylic acids are strongly associated because of hydrogen-bonding. Most carboxylic acids exist as cyclic dimers held together by two hydrogen bonds. This strong hydrogen-bonding has a noticeable effect on boiling points, making carboxylic acids boil far less easily than their corresponding alcohols. Acetic acid, for instance, has a boiling point of 117.9 °C, versus 78.3 °C for ethanol, even though both compounds have two carbons.



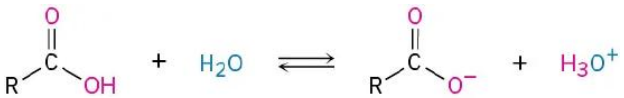
Acetic acid dimer

The most obvious property of carboxylic acids is implied by their name: carboxylic acids are *acidic*. They therefore react with bases such as NaOH and $NaHCO_3$ to give metal carboxylate salts, RCO_2^- M^+. Carboxylic acids with more than six carbons are only slightly soluble in water, but the alkali metal salts of carboxylic acids are often highly water-soluble. In fact, it's often possible to purify an acid by extracting its salt into aqueous base, then reacidifying and extracting the pure acid back into an organic solvent.



A carboxylic acid (water-insoluble) **A carboxylic acid salt (water-soluble)**

Like other Brønsted–Lowry acids discussed in Section 2.7, carboxylic acids dissociate slightly in dilute aqueous solution to give H_3O^+ and the corresponding carboxylate anions, RCO_2^-. The extent of dissociation is given by an acidity constant, K_a.



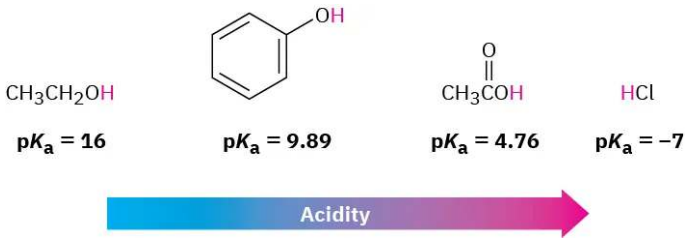
$$K_a = \frac{[RCO_2^-][H_3O^+]}{[RCO_2H]} \quad \text{and} \quad pK_a = -\log K_a$$

A list of K_a values for various carboxylic acids is given in Table 9.3.2. For most, K_a is approximately 10^{-4} to 10^{-5}. Acetic acid, for instance, has $K_a = 1.75 \times 10^{-5}$ at 25 °C, which corresponds to a pK_a of 4.76. In practical terms, a K_a value near 10^{-5} means that only about 0.1% of the molecules in a 0.1 M solution are dissociated, as opposed to the 100% dissociation found with strong mineral acids like HCl.

Table 9.3.2: Acidity of Some Carboxylic Acids

Structure	K_a	pK_a	
CF_3CO_2H	0.59	0.23	Stronger acid
HCO_2H	1.77×10^{-4}	3.75	
$HOCH_2CO_2H$	1.5×10^{-4}	3.84	
$C_6H_5CO_2H$	6.46×10^{-5}	4.19	
H2C═CHCO2HH2C═CHCO2H	5.6×10^{-5}	4.25	
CH_3CO_2H	1.75×10^{-5}	4.76	
$CH_3CH_2CO_2H$	1.34×10^{-5}	4.87	Weaker acid
CH_3CH_2OH (ethanol)	(1×10^{-16})	(16)	

Although much weaker than mineral acids, carboxylic acids are nevertheless much stronger acids than alcohols and phenols. The K_a of ethanol, for example, is approximately 10^{-16}, making it a weaker acid than acetic acid by a factor of 10^{11}.



Why are carboxylic acids so much more acidic than alcohols, even though both contain –OH groups? An alcohol dissociates to give an alkoxide ion, in which the negative charge is localized on a single electronegative atom. A carboxylic acid, however, gives a carboxylate ion, in which the negative charge is delocalized over two equivalent oxygen atoms (Figure 9.3.1). In resonance terms (Section 2.4), a carboxylate ion is a stabilized resonance hybrid of two equivalent structures. Since a carboxylate ion is more stable than an alkoxide ion, it is lower in energy and more favored in the dissociation equilibrium.

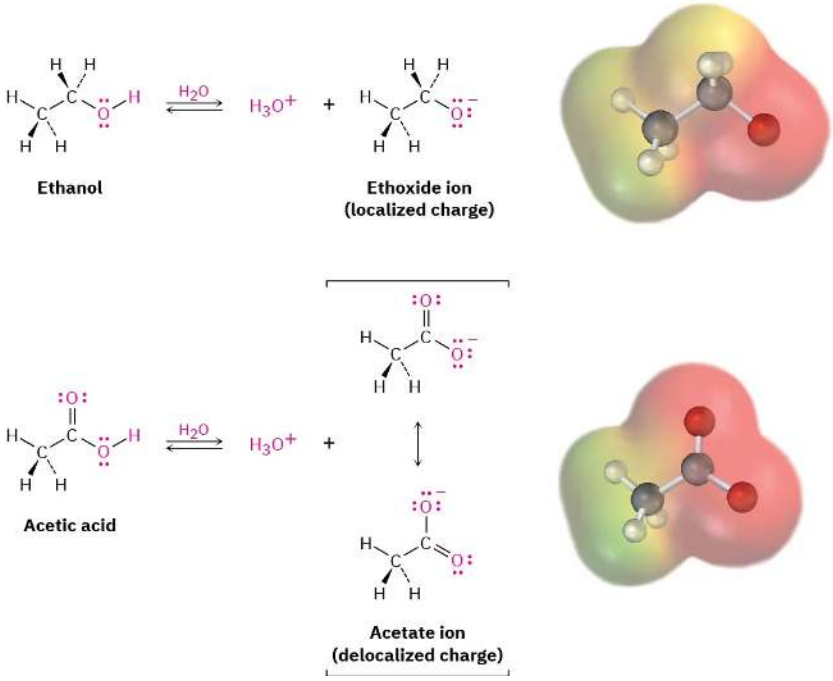
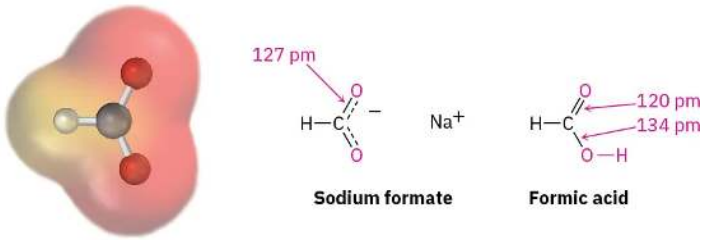


Figure 9.3.1: An alkoxide ion has its charge localized on one oxygen atom and is less stable, while a carboxylate ion has the charge spread equally over both oxygens and is therefore more stable.

Experimental evidence for the equivalence of the two carboxylate oxygens comes from X-ray crystallographic studies on sodium formate. Both carbon–oxygen bonds are 127 pm in length, midway between the C=O double bond (120 pm) and the C–O single bond (134 pm) of formic acid. An electrostatic potential map of the formate ion also shows how the negative charge (red) is spread equally over both oxygens.



? Exercise 9.3.1

Assume you have a mixture of naphthalene and benzoic acid that you want to separate. How might you take advantage of the acidity of one component in the mixture to effect a separation?

Answer

Dissolve the mixture in ether, extract with aqueous NaOH, separate and acidify the aqueous layer, and extract with ether.

? Exercise 9.3.2

The K_a for dichloroacetic acid is 3.32×10^{-2}. Approximately what percentage of the acid is dissociated in a 0.10 M aqueous solution?

Answer

43%

This page titled 9.3: Structure and Properties of Carboxylic Acids is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **20.2: Structure and Properties of Carboxylic Acids** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

9.4: Biological Acids and the Henderson-Hasselbalch Equation

In acidic solution, at low pH, a carboxylic acid is completely undissociated and exists entirely as RCOH. In basic solution, at high pH, a carboxylic acid is completely dissociated and exists entirely as RCO_2^-. Inside living cells, however, the pH is neither acidic nor basic but is instead buffered to a nearly neutral pH of 3.5–4.5 in humans, a value often referred to as *physiological pH*. In what form, then, do carboxylic acids exist inside cells? The question is an important one for understanding the acid catalysts so often found in biological reactions.

If the pK_a value of a given acid and the pH of the medium are known, the percentages of dissociated and undissociated forms can be calculated using the Henderson–Hasselbalch equation.

For any acid HA, we have

$$\begin{aligned} \mathrm{p}K_\mathrm{a} &= -\log \frac{[\mathrm{H_3O^+}]\,[\mathrm{A^-}]}{[\mathrm{HA}]} \\ &= -\log [\mathrm{H_3O^+}] - \log \frac{[\mathrm{A^-}]}{[\mathrm{HA}]} \\ &= \mathrm{pH} - \log \frac{[\mathrm{A^-}]}{[\mathrm{HA}]} \end{aligned}$$

which can be rearranged to give

$$\mathrm{pH} = +\log \frac{[\mathrm{A^-}]}{[\mathrm{HA}]} \qquad \text{(Henderson-Hasselbalch)}$$

so

$$\log \frac{[\mathrm{A^-}]}{[\mathrm{HA}]} = \mathrm{pH} - \mathrm{pK_a}$$

This equation says that the logarithm of the concentration of dissociated acid [A^-] divided by the concentration of undissociated acid [HA] is equal to the pH of the solution minus the pK_a of the acid. Thus, if we know both the pH of the solution and the pK_a of the acid, we can calculate the ratio of [A^-] to [HA]. Furthermore, when pH = pK_a, then HA and A^- are present in equal amounts because log 1 = 0.

As an example of how to use the Henderson–Hasselbalch equation, let's find out what species are present in a 0.0010 M solution of acetic acid at pH = 7.3. According to Table 20-3, the pK_a of acetic acid is 4.76. From the Henderson–Hasselbalch equation, we have

$$\begin{aligned} \log \frac{[\mathrm{A^-}]}{\mathrm{HA}} &= \mathrm{pH} - \mathrm{p}K_\mathrm{a} \\ &= 7.3 - 4.76 \\ &= 2.54 \\ \frac{[\mathrm{A^-}]}{\mathrm{HA}} &= \mathrm{antilog}(2.54) \\ &= 3.5 \times 10^2 \end{aligned}$$

so

$$[\mathrm{A^-}] = (3.5 \times 10^2)\,[\mathrm{HA}]$$

In addition, we know that

$$[\mathrm{A^-}] + [\mathrm{HA}] = 0.0010\mathrm{M}$$

Solving the two simultaneous equations gives [A^-] = 0.0010 M and [HA] = 3×10^{-6} M. In other words, at a physiological pH of 7.3, essentially 100% of acetic acid molecules in a 0.0010 M solution are dissociated to the acetate ion.

What is true for acetic acid is also true for other carboxylic acids: At the physiological pH that occurs inside cells, carboxylic acids are almost entirely dissociated. To reflect this fact, we always refer to cellular carboxylic acids by the name of their anion—acetate,

lactate, citrate, and so forth, rather than acetic acid, lactic acid, and citric acid.

Exercise 9.4.1

Calculate the percentages of dissociated and undissociated forms present in the following solutions:

a. 0.0010 M glycolic acid ($HOCH_2CO_2H$; pKa = 3.83) at pH = 4.50
b. 0.0020 M propanoic acid (pKa = 4.87) at pH = 5.30

Answer

a. 82% dissociation
b. 73% dissociation

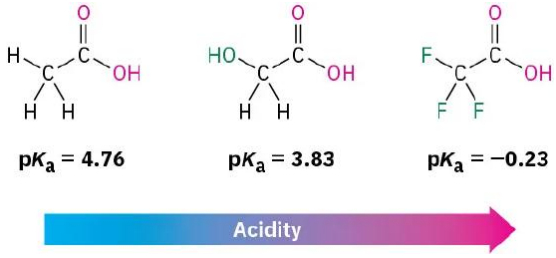
This page titled 9.4: Biological Acids and the Henderson-Hasselbalch Equation is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **20.3: Biological Acids and the Henderson-Hasselbalch Equation** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

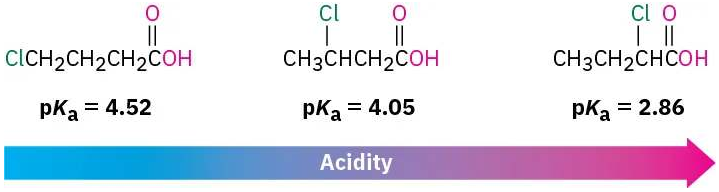
9.5: Substituent Effects on Acidity

The listing of pK_a values shown previously in Table 20.3 indicates that there are substantial differences in acidity from one carboxylic acid to another. For example, trifluoroacetic acid (K_a = 0.59) is 33,000 times as strong as acetic acid ($K_a = 1.75 \times 10^{-5}$). How can we account for such differences?

Because the dissociation of a carboxylic acid is an equilibrium process, any factor that stabilizes the carboxylate anion relative to undissociated carboxylic acid will drive the equilibrium toward increased dissociation and result in increased acidity. For instance, three electron-withdrawing fluorine atoms delocalize the negative charge in the trifluoroacetate anion, thereby stabilizing the ion and increasing the acidity of CF_3CO_2H. In the same way, glycolic acid ($HOCH_2CO_2H$; pK_a = 3.83) is stronger than acetic acid because of the electron-withdrawing effect of the electronegative oxygen atom.



Because inductive effects operate through σ bonds and are dependent on distance, the effect of halogen substitution decreases as the substituent moves farther from the carboxyl. Thus, 2-chlorobutanoic acid has pK_a = 2.86, 3-chlorobutanoic acid has pK_a = 4.05, and 4-chlorobutanoic acid has pK_a = 4.52, similar to that of butanoic acid itself.



Substituent effects on acidity are also found in substituted benzoic acids. We said during the discussion of electrophilic aromatic substitution in Section 16.4 that substituents on the aromatic ring strongly affect reactivity. Aromatic rings with electron-donating groups are activated toward further electrophilic substitution, and aromatic rings with electron-withdrawing groups are deactivated. Exactly the same effects can be observed on the acidity of substituted benzoic acids (Table 9.5.1).

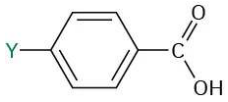
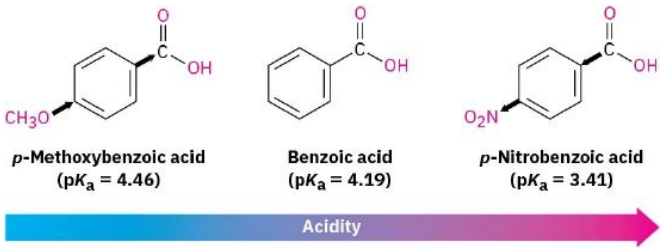


Table 9.5.1: Substituent Effects on the Acidity of *p*-Substituted Benzoic Acids

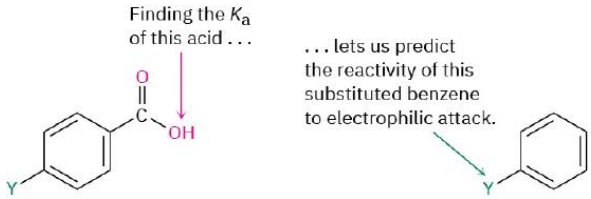
https://chem.libretexts.org/@go/page/564282

	Y	$K_a \times 10^{-5}$	pK_a	
Stronger acid	$-NO_2$	39	3.41	Deactivating groups
	–CN	28	3.55	
	–CHO	18	3.75	
	–Br	11	3.96	
	–Cl	10	4.0	
	–H	6.46	4.19	
	$-CH_3$	4.3	4.34	Activating groups
	$-OCH_3$	3.5	4.46	
Weaker acid	–OH	3.3	4.48	

As Table 9.5.1 shows, an electron-donating (activating) group such as methoxy decreases acidity by destabilizing the carboxylate anion, and an electron-withdrawing (deactivating) group such as nitro increases acidity by stabilizing the carboxylate anion.



Because it's much easier to measure the acidity of a substituted benzoic acid than it is to determine the relative reactivity of an aromatic ring toward electrophilic substitution, the correlation between the two effects is useful for predicting reactivity. If we want to know the effect of a certain substituent on electrophilic reactivity, we can simply find the acidity of the corresponding benzoic acid. Worked Example 9.5.1 gives an illustration.



✔ Worked Example 9.5.1: Predicting the Effect of a Substituent on the Reactivity of an Aromatic Ring toward Electrophilic Substitution

The pK_a of *p*-(trifluoromethyl)benzoic acid is 3.6. Is the trifluoromethyl substituent an activating or deactivating group in electrophilic aromatic substitution?

Strategy

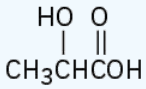
Decide whether *p*-(trifluoromethyl)benzoic acid is stronger or weaker than benzoic acid. A substituent that strengthens the acid is a deactivating group because it withdraws electrons, and a substituent that weakens the acid is an activating group because it donates electrons.

Solution

A pK_a of 3.6 means that *p*-(trifluoromethyl)benzoic acid is stronger than benzoic acid, whose pK_a is 4.19. Thus, the trifluoromethyl substituent favors dissociation by helping stabilize the negative charge. Trifluoromethyl must therefore be an electron-withdrawing, deactivating group.

Exercise 9.5.1

Which would you expect to be a stronger acid, the lactic acid found in tired muscles or acetic acid? Explain.



Lactic acid

Answer

Lactic acid is stronger because of the inductive effect of the −OH group.

Exercise 9.5.2

Dicarboxylic acids have two dissociation constants, one for the initial dissociation into a monoanion and one for the second dissociation into a dianion. For oxalic acid, $HO_2C–CO_2H$, the first ionization constant is pK_{a1} = 1.2 and the second ionization constant is pK_{a2} = 4.2. Why is the second carboxyl group far less acidic than the first?

Answer

The dianion is destabilized by repulsion between charges.

Exercise 9.5.3

The pK_a of *p*-cyclopropylbenzoic acid is 4.45. Is cyclopropylbenzene likely to be more reactive or less reactive than benzene toward electrophilic bromination? Explain.

Answer

More reactive

Exercise 9.5.4

Rank the following compounds in order of increasing acidity. Don't look at a table of pK_a data to help with your answer.

a. Benzoic acid, *p*-methylbenzoic acid, *p*-chlorobenzoic acid
b. *p*-Nitrobenzoic acid, acetic acid, benzoic acid

Answer

a. p-Methylbenzoic acid < Benzoic acid < p-Chlorobenzoic acid
b. Acetic acid < Benzoic acid < p-Nitrobenzoic acid

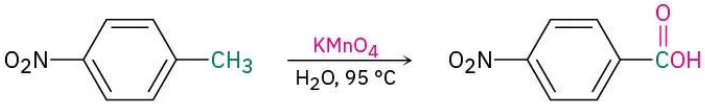
This page titled 9.5: Substituent Effects on Acidity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **20.4: Substituent Effects on Acidity** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

9.6: Preparing Carboxylic Acids

Let's review briefly some of the methods for preparing carboxylic acids that we've seen in previous chapters.

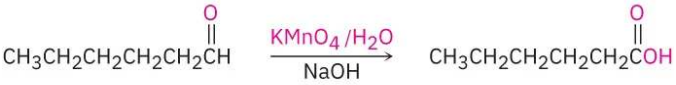
- Oxidation of a substituted alkylbenzene with $KMnO_4$ gives a substituted benzoic acid (Section 16.8). Both primary and secondary alkyl groups can be oxidized, but tertiary groups are not affected.



***p*-Nitrotoluene** ***p*-Nitrobenzoic acid (88%)**

- Oxidation of a primary alcohol or an aldehyde yields a carboxylic acid (Section 17.7 and Section 19.3). Primary alcohols are often oxidized with the Dess Martin periodinane, and aldehydes are similarly oxidized with alkaline $KMnO_4$.

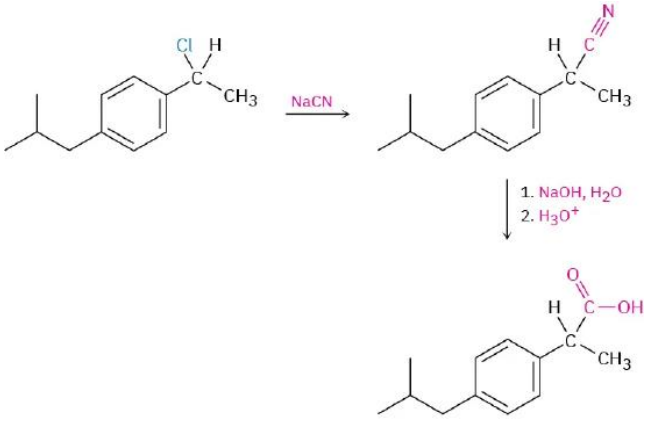
4-Methyl-1-pentanol **4-Methylpentanoic acid**



Hexanal **Hexanoic acid**

Hydrolysis of Nitriles

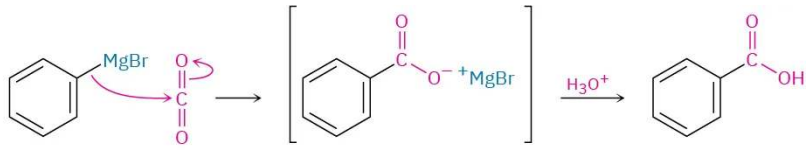
Carboxylic acids can be prepared from nitriles on heating with aqueous acid or base by a mechanism that we'll discuss in Section 20.7. Since nitriles themselves are usually made by S_N2 reaction of a primary or secondary alkyl halide with CN^-, the two-step sequence of cyanide displacement followed by nitrile hydrolysis is a good way to make a carboxylic acid from an alkyl halide ($RBr \longrightarrow RC{\equiv}N \rightarrow$ Chemistry Matters.)



Ibuprofen

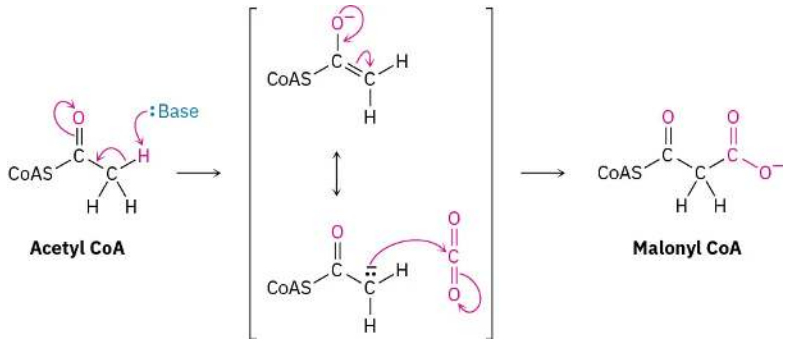
Carboxylation of Grignard Reagents

Another method for preparing carboxylic acids is by reaction of a Grignard reagent with CO_2 to yield a metal carboxylate, followed by protonation to give a carboxylic acid. This carboxylation reaction is usually carried out by bubbling a stream of dry CO_2 gas through a solution of the Grignard reagent. The organomagnesium halide adds to a C═O bond of carbon dioxide in a typical nucleophilic carbonyl addition reaction, and protonation of the carboxylate by addition of aqueous HCl in a separate step then gives the free carboxylic acid. For example:



Phenylmagnesium bromide **Benzoic acid**

As noted previously, there are no Grignard reagents inside living cells, but there are other types of stabilized carbanions that are often carboxylated. One of the initial steps in fatty-acid biosynthesis, for instance, involves the formation of a carbanion from acetyl CoA, followed by carboxylation to yield malonyl CoA.



Acetyl CoA **Malonyl CoA**

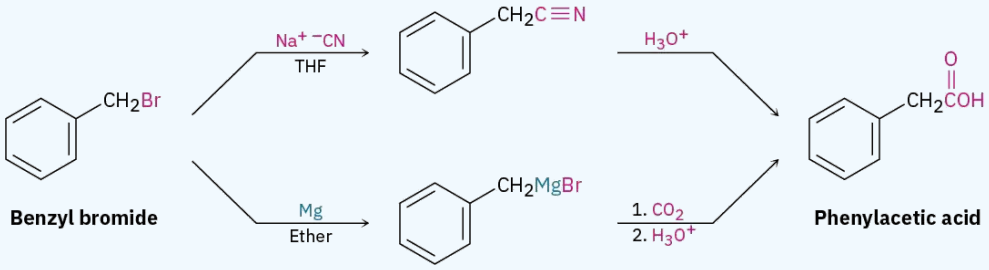
Worked Example 9.6.1: Devising a Synthesis Route for a Carboxylic Acid

How would you prepare phenylacetic acid ($PhCH_2CO_2H$) from benzyl bromide ($PhCH_2Br$)?

Strategy

We've seen two methods for preparing carboxylic acids from alkyl halides: (1) cyanide ion displacement followed by hydrolysis and (2) formation of a Grignard reagent followed by carboxylation. The first method involves an S_N2 reaction and is therefore limited to use with primary and some secondary alkyl halides. The second method involves formation of a Grignard reagent and is therefore limited to use with organic halides that have no acidic hydrogens or reactive functional groups elsewhere in the molecule. In the present instance, either method would work well.

Solution



Benzyl bromide **Phenylacetic acid**

Exercise 9.6.1

How would you prepare the following carboxylic acids?

a. $(CH_3)_3CCO_2H$ from $(CH_3)_3CCl$
b. $CH_3CH_2CH_2CO_2H$ from $CH_3CH_2CH_2Br$

Answer

a. 1. Mg; 2. CO_2; 3. H_3O^+
b. 1. Mg; 2. CO_2; 3. H_3O^+ or 1. NaCN; 2. H_3O^+

This page titled 9.6: Preparing Carboxylic Acids is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **20.5: Preparing Carboxylic Acids** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

9.7: Reactions of Carboxylic Acids - An Overview

We commented earlier in this chapter that carboxylic acids are similar in some respects to both alcohols and ketones. Like alcohols, carboxylic acids can be deprotonated to give anions, which are good nucleophiles in S_N2 reactions. Like ketones, carboxylic acids undergo addition of nucleophiles to the carbonyl group. However, carboxylic acids also undergo other reactions characteristic of neither alcohols nor ketones. Figure 9.7.1 shows some of the general reactions of carboxylic acids.

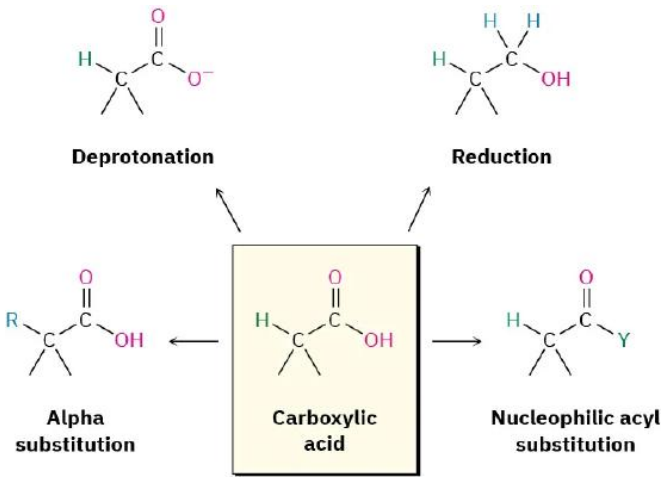
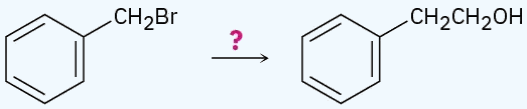


Figure 9.7.1: Some general reactions of carboxylic acids.

Reactions of carboxylic acids can be grouped into the four categories indicated in Figure 9.7.1. Of the four, we've already discussed the acidic behavior of carboxylic acids in Section 20.2 through Section 20.4, and we mentioned reduction by treatment with $LiAlH_4$ in Section 17.4. The remaining two categories are examples of fundamental carbonyl-group reaction mechanisms—nucleophilic acyl substitution and α substitution—that will be discussed in detail in Chapters 21 and 22.

? Exercise 9.7.1

How might you prepare 2-phenylethanol from benzyl bromide? More than one step is needed.



Answer

1. NaCN; 2. H_3O^+; 3. $LiAlH_4$

? Exercise 9.7.2

How might you carry out the following transformation? More than one step is needed.

Answer

1. PBr_3; 2. NaCN; 3. H_3O^+; 4. $LiAlH_4$

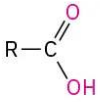
This page titled 9.7: Reactions of Carboxylic Acids - An Overview is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **20.6: Reactions of Carboxylic Acids - An Overview** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

9.8: Chemistry of Nitriles

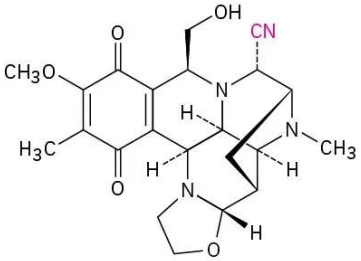
Nitriles are analogous to carboxylic acids in that both have a carbon atom with three bonds to an electronegative atom and both contain a π bond. Thus, some reactions of nitriles and carboxylic acids are similar. Both kinds of compounds are electrophiles, for instance, and both undergo nucleophilic addition reactions.

A nitrile—three bonds to nitrogen

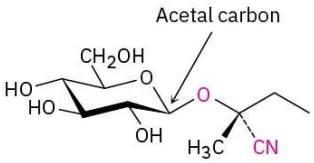


An acid—three bonds to two oxygens

Nitriles occur infrequently in living organisms, although several hundred examples are known. Cyanocycline A, for instance, has been isolated from the bacterium *Streptomyces lavendulae* and was found to have both antimicrobial and antitumor activity. In addition, more than 1000 compounds called *cyanogenic glycosides* are known. Derived primarily from plants, cyanogenic glycosides contain a sugar with an acetal carbon, one oxygen of which is bonded to a nitrile-bearing carbon (sugar–O–C–CN). On hydrolysis with aqueous acid, the acetal is cleaved (Section 19.10), generating a cyanohydrin (HO–C–CN), which releases hydrogen cyanide. It's thought that the primary function of cyanogenic glycosides is to protect the plant by poisoning any animal foolish enough to eat it. Lotaustralin from the cassava plant is an example.



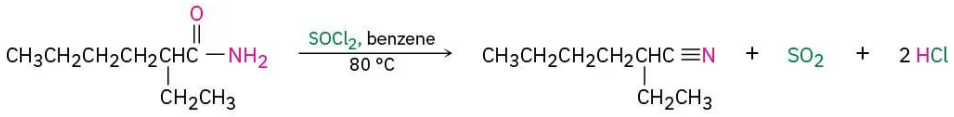
Cyanocycline A



Lotaustralin (a cyanogenic glycoside)

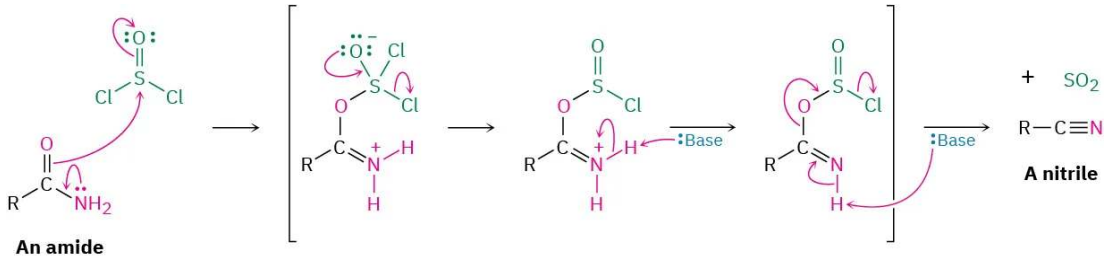
Preparation of Nitriles

The simplest method of nitrile preparation is the S_N2 reaction of CN^- with a primary or secondary alkyl halide, as discussed in Section 20.5. Another method for preparing nitriles is by dehydration of a primary amide, $RCONH_2$. Thionyl chloride is often used for this reaction, although other dehydrating agents such as $POCl_3$ also work.



2-Ethylhexanamide **2-Ethylhexanenitrile (94%)**

The dehydration occurs by initial reaction of $SOCl_2$ on the nucleophilic amide oxygen atom, followed by deprotonation and a subsequent E2-like elimination reaction.

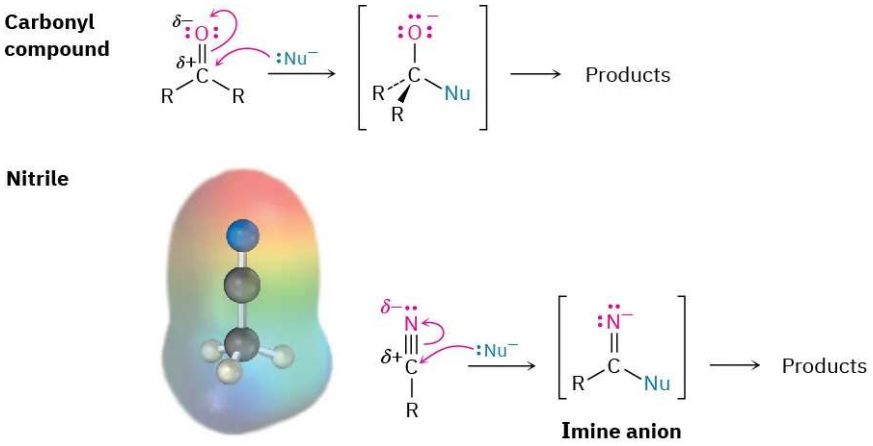


An amide **A nitrile**

Both methods of nitrile synthesis—S_N2 displacement by CN^- on an alkyl halide and amide dehydration—are useful, but the synthesis from amides is more general because it is not limited by steric hindrance.

Reactions of Nitriles

Like a carbonyl group, a nitrile group is strongly polarized and has an electrophilic carbon atom. Nitriles therefore react with nucleophiles to yield sp^2-hybridized imine anions in a reaction analogous to the formation of a sp^3-hybridized alkoxide ion by nucleophilic addition to a carbonyl group.



Some general reactions of nitriles are shown in Figure 9.8.1.

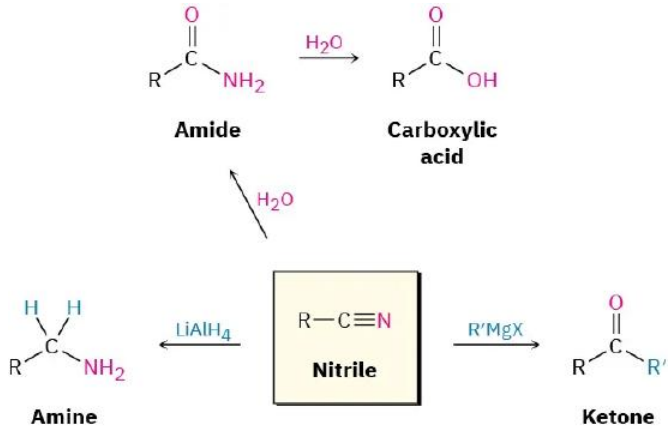
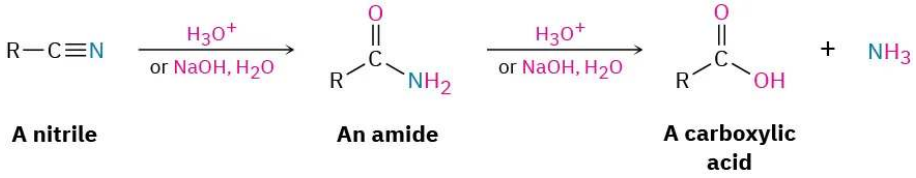


Figure 9.8.1: Some reactions of nitriles.

Hydrolysis: Conversion of Nitriles into Carboxylic Acids

Among the most useful reactions of nitriles is their hydrolysis to yield first an amide and then a carboxylic acid plus ammonia or an amine. The reaction occurs in either basic or acidic aqueous solution:



As shown in Figure 9.8.2, base-catalyzed nitrile hydrolysis involves nucleophilic addition of hydroxide ion to the polar C≡N bond to give an imine anion in a process similar to the nucleophilic addition to a polar C═O bond to give an alkoxide anion. Protonation then gives a hydroxy imine, which tautomerizes (Section 9.4) to an amide in a step similar to the tautomerization of an enol to a ketone. Further hydrolysis gives a carboxylate ion.

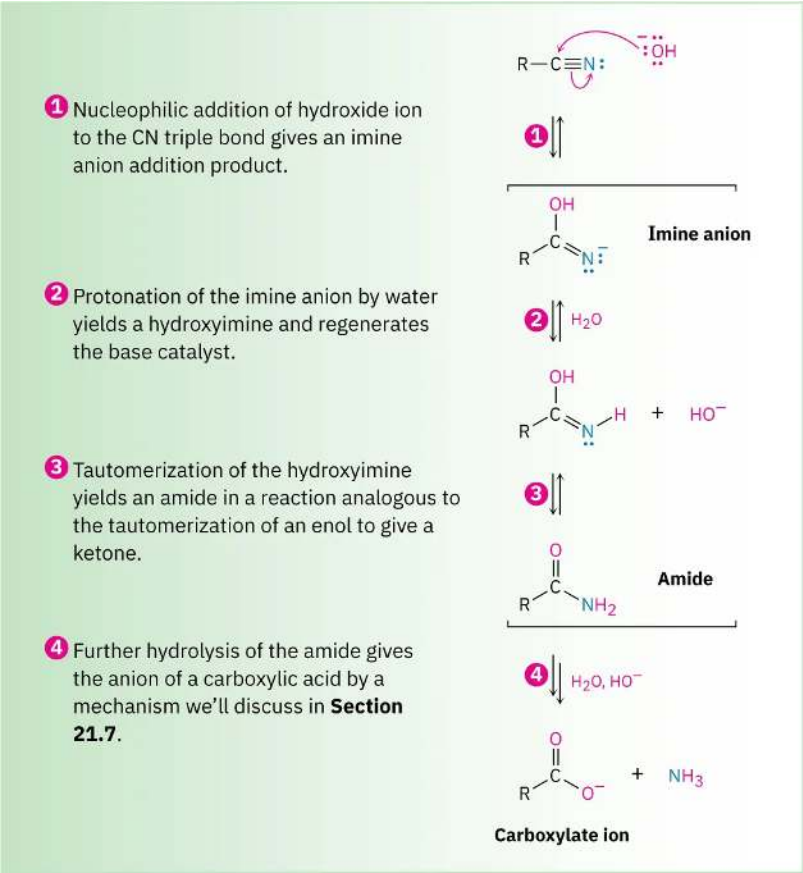
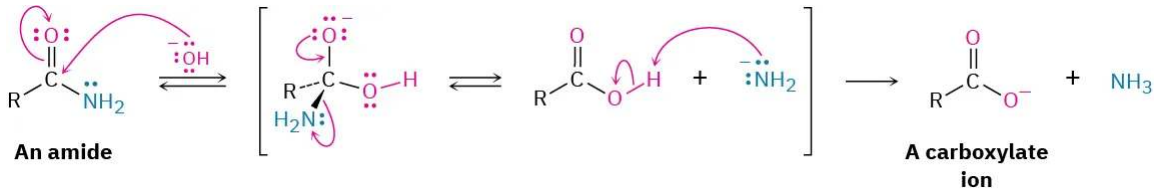


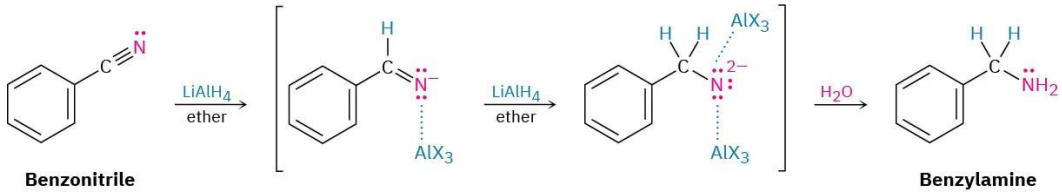
Figure 9.8.2: Mechanism for the basic hydrolysis of a nitrile to yield an amide, which is then hydrolyzed further to a carboxylic acid anion.

The further hydrolysis of the amide intermediate takes place by a nucleophilic addition of hydroxide ion to the amide carbonyl group, which yields a tetrahedral alkoxide ion. Expulsion of amide ion, NH_2^-, as leaving group gives the carboxylate ion, thereby driving the reaction toward the products. Subsequent acidification in a separate step yields the carboxylic acid. We'll look at this process in more detail in **Section 21.7**.



Reduction: Conversion of Nitriles into Amines

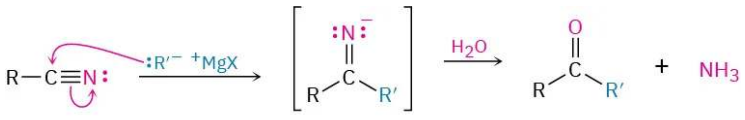
Reduction of a nitrile with $LiAlH_4$ gives a primary amine, RNH_2. The reaction occurs by nucleophilic addition of hydride ion to the polar C≡N bond, yielding an imine anion, which still contains a C=N bond and therefore undergoes a second nucleophilic addition of hydride to give a *dianion*. Both monoanion and dianion intermediates are undoubtedly stabilized by Lewis acid–base complexation to an aluminum species, facilitating the second addition that would otherwise be difficult. Protonation of the dianion by addition of water in a subsequent step gives the amine.



https://chem.libretexts.org/@go/page/564285

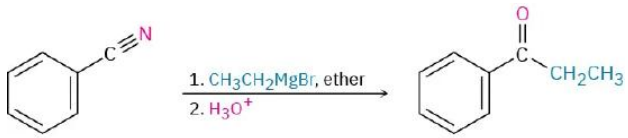
Reaction of Nitriles with Grignard Reagents

Grignard reagents add to a nitrile to give an intermediate imine anion that is hydrolyzed by addition of water to yield a ketone. The mechanism of the hydrolysis is the exact reverse of imine formation (see Figure 19.7).



Nitrile **Imine anion** **Ketone**

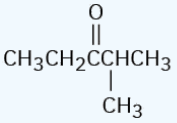
This reaction is similar to the reduction of a nitrile to an amine, except that only one nucleophilic addition occurs rather than two and the attacking nucleophile is a carbanion ($R:^-$) rather than a hydride ion. For example:



Benzonitrile **Propiophenone (89%)**

Worked Example 9.8.1: Synthesizing a Ketone from a Nitrile

How would you prepare 2-methyl-3-pentanone from a nitrile?



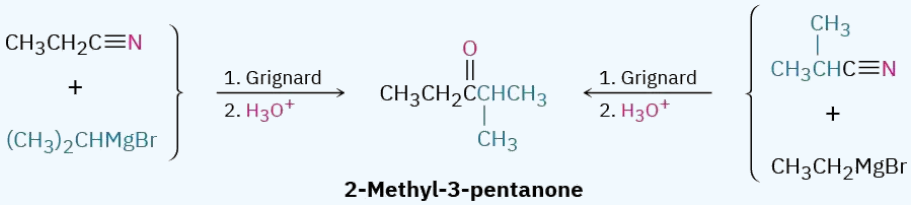
2-Methyl-3-pentanone

Strategy

A ketone results from the reaction between a Grignard reagent and a nitrile, with the C≡N carbon of the nitrile becoming the carbonyl carbon. Identify the two groups attached to the carbonyl carbon atom in the product. One will come from the Grignard reagent and the other will come from the nitrile.

Solution

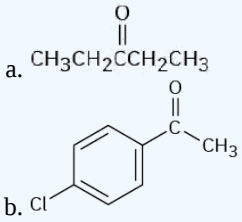
There are two possibilities.



2-Methyl-3-pentanone

Exercise 9.8.1

How would you prepare the following carbonyl compounds from a nitrile?



Answer

a. Propanenitrile + CH_3CH_2MgBr, then H_3O^+
b. *p*-Chlorobenzonitrile + CH_3MgBr, then H_3O^+

? Exercise 9.8.1

How would you prepare 1-phenyl-2-butanone, $C_6H_5CH_2COCH_2CH_3$, from benzyl bromide, $C_6H_5CH_2Br$? More than one step is needed.

Answer

1. NaCN; 2. CH_3CH_2MgBr, then H_3O^+

This page titled 9.8: Chemistry of Nitriles is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

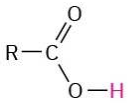
- **20.7: Chemistry of Nitriles** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

9.9: Spectroscopy of Carboxylic Acids and Nitriles

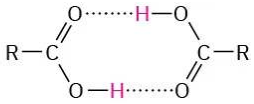
Infrared Spectroscopy

Carboxylic acids have two characteristic IR absorptions that make the $-CO_2H$ group easily identifiable. The O–H bond of the carboxyl group gives rise to a very broad absorption over the range 2500 to 3300 cm^{-1}. The C═O bond shows an absorption between 1710 and 1760 cm^{-1}. The exact position of C═O absorption depends both on the structure of the molecule and on whether the acid is free (monomeric) or hydrogen-bonded (dimeric). Free carboxyl groups absorb at 1760 cm^{-1}, but the more commonly encountered dimeric carboxyl groups absorb in a broad band centered around 1710 cm^{-1}. As with other carbonyl-containing functional groups, conjugation with an alkene or benzene ring lowers the frequency of the C═O stretch by 20 to 30 cm^{-1}.

Free carboxyl (uncommon), 1760 cm^{-1}



Associated carboxyl (usual case), 1710 cm^{-1}



Both the broad O–H absorption and the C═O absorption at 1710 cm^{-1} (dimeric) are identified in the IR spectrum of butanoic acid shown in Figure 9.9.1.

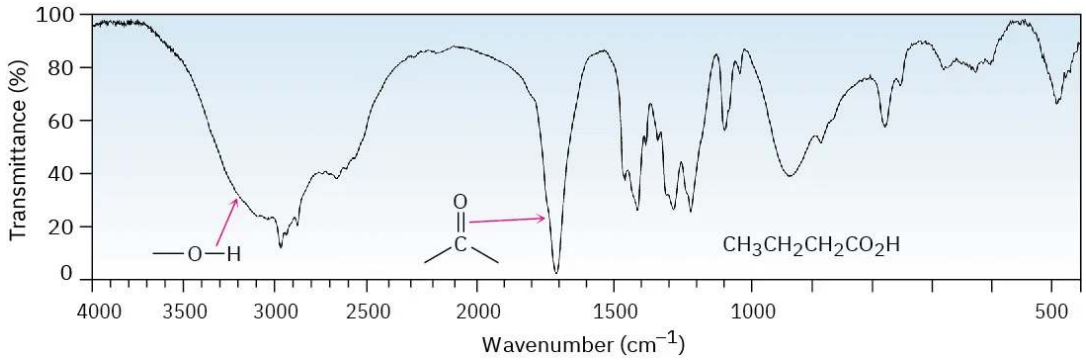


Figure 9.9.1: IR spectrum of butanoic acid, $CH_3CH_2CH_2CO_2H$.

Nitriles show an intense and easily recognizable C≡N bond absorption near 2250 cm^{-1} for saturated compounds and 2230 cm^{-1} for aromatic and conjugated molecules. Few other functional groups absorb in this region, so IR spectroscopy is highly diagnostic for nitriles.

? Exercise 9.9.1

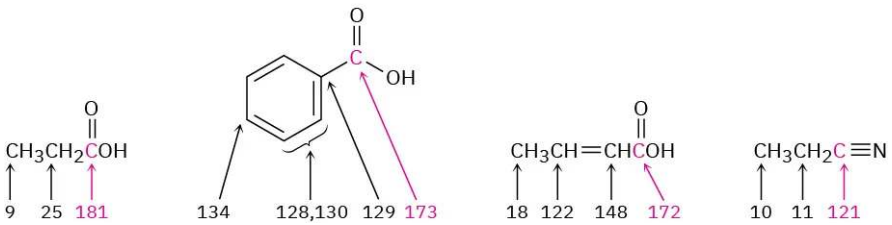
Cyclopentanecarboxylic acid and 4-hydroxycyclohexanone have the same formula ($C_6H_{10}O_2$), and both contain an –OH and a C═O group. How could you distinguish between them using IR spectroscopy?

Answer

A carboxylic acid has a very broad −OH absorption at 2500–3300 cm^{-1}.

Nuclear Magnetic Resonance Spectroscopy

Carboxyl carbon atoms absorb in the range 165 to 185 δ in the ^{13}C NMR spectrum, with aromatic and α,β-unsaturated acids near the upfield end of the range (∼165 δ) and saturated aliphatic acids near the downfield end (∼185 δ). Nitrile carbons absorb in the range 115 to 130 δ.



In the ^{1}H NMR spectrum, the acidic –CO_2**H** proton normally absorbs as a singlet near 12 δ. The chemical shift of the carboxyl proton is concentration and solvent dependent, as these variables can change the extent of hydrogen-bonding in the sample. In some cases, the carboxyl-proton resonance is broadened to the point of being nearly undetectable. Traces of water in the sample can exacerbate the situation. As with alcohols (Section 17.11), the –CO_2H proton can be replaced by deuterium when D_2O is added to the sample tube, causing the absorption to disappear from the NMR spectrum. Figure 9.9.2 shows the ^{1}H NMR spectrum of phenylacetic acid. Note that the –CO_2H absorption occurs at 12.0 δ.

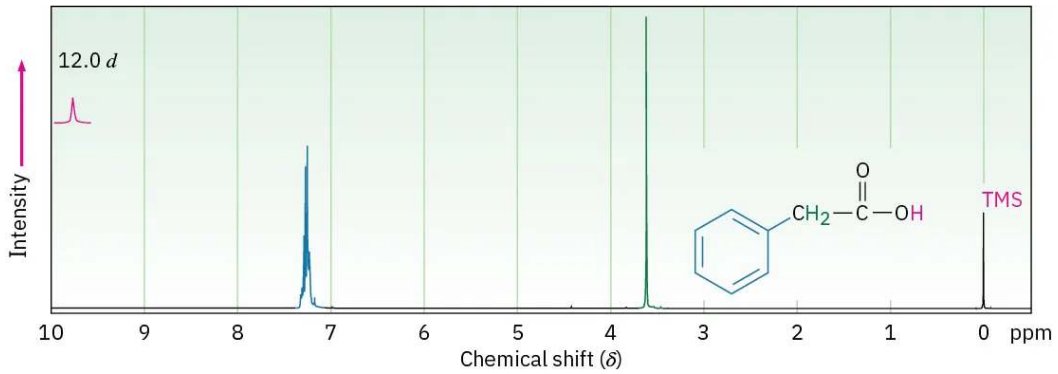


Figure 9.9.2: Proton NMR spectrum of phenylacetic acid, $C_6H_5CH_2CO_2H$.

? Exercise 9.9.2

How could you distinguish between the isomers cyclopentanecarboxylic acid and 4-hydroxycyclohexanone by ^{1}H and ^{13}C NMR spectroscopy? (See Problem 20-15.)

Answer

4-Hydroxycyclohexanone: H–C–O absorption near 4 δ in the ^{1}H spectrum and C═O absorption near 210 δ in the ^{13}C spectrum. Cyclopentanecarboxylic acid: –CO_2H absorption near 12 δ in the ^{1}H spectrum and –CO_2H absorption near 170 δ in the ^{13}C spectrum.

This page titled 9.9: Spectroscopy of Carboxylic Acids and Nitriles is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **20.8: Spectroscopy of Carboxylic Acids and Nitriles** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

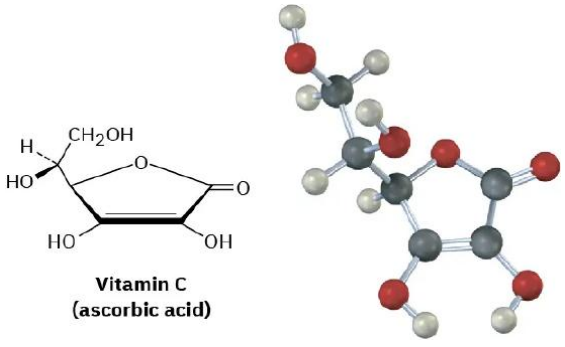
9.10: Chemistry Matters—Vitamin C

The word *vitamin*, despite its common usage, is actually an imprecise term. Generally speaking, a vitamin is an organic substance that a given organism requires in small amounts to live and grow but is unable to synthesize and must obtain in its diet. Thus, to be considered a vitamin, only a *small* amount of the substance is needed—anywhere from a few micrograms to 100 mg or so per day. Dietary substances needed in larger amounts, such as some amino acids and unsaturated fats, are not considered vitamins.

Figure 9.10.1: In addition to the hazards of weather, participants in early polar expeditions often suffered from scurvy, caused by a dietary vitamin C deficiency. (credit: "Shackleton's expedition to the Antarctic last moments of the Endurance" by Underwood & Underwood/Wikimedia Commons, Public Domain)

Furthermore, different organisms need different vitamins. More than 4000 species of mammals can synthesize ascorbic acid in their bodies, for instance, but humans are not among them. Ascorbic acid is therefore a human vitamin—what we all know as vitamin C—and must be provided by our diet. Small amounts of more than a dozen other substances are similarly required by humans: retinol (vitamin A), thiamine (vitamin B_1), and tocopherol (vitamin E), for instance.

Vitamin C is surely the best known of all human vitamins. It was the first to be discovered (1912), the first to be isolated (1928), the first to be structurally characterized (1933), and the first to be synthesized in the laboratory (1933). Over 121,000 tons of vitamin C is synthesized worldwide each year, more than the total amount of all other vitamins combined. In addition to its use as a supplement, vitamin C is used as a food preservative, a "flour improver" in bakeries, and an animal-food additive.



Vitamin C
(ascorbic acid)

Vitamin C is perhaps most well-known for its antiscorbutic properties, meaning that it prevents the onset of scurvy, a bleeding disease affecting those with a deficiency of fresh vegetables and citrus fruits in their diet. Sailors in the Age of Exploration were particularly susceptible to scurvy, and the death toll was high. The Portuguese explorer Vasco da Gama lost more than half his crew to scurvy during his two-year voyage around the Cape of Good Hope in 1497–1499.

More recently, large doses of vitamin C have been claimed to prevent the common cold, cure infertility, delay the onset of symptoms in acquired immunodeficiency syndrome (AIDS), and inhibit the development of gastric and cervical cancers. None of

these claims have been backed by medical evidence, however. In the largest study yet of the effect of vitamin C on the common cold, a meta-analysis of more than 100 separate trials covering 40,000 people found no difference in the incidence of colds between those who took supplemental vitamin C regularly and those who did not. When taken *during* a cold, however, vitamin C does appear to decrease the cold's duration by perhaps a day.

The industrial preparation of vitamin C involves an unusual blend of biological and laboratory organic chemistry, beginning with glucose and following the five-step route shown in Figure 9.10.2. Glucose, a pentahydroxy aldehyde, is first reduced to sorbitol, which is then oxidized by the microorganism *Acetobacter suboxydans*. No chemical reagent is known that is selective enough to oxidize only one of the six alcohol groups in sorbitol, so an enzymatic reaction is used. Treatment with acetone and an acid catalyst then converts four of the other hydroxyl groups into acetal linkages, and the remaining hydroxyl group is chemically oxidized to a carboxylic acid by reaction with aqueous NaOCl (household bleach). Hydrolysis with acid then removes the two acetal groups and causes an internal ester-forming reaction to give ascorbic acid. Each of the five steps has a yield better than 90%.

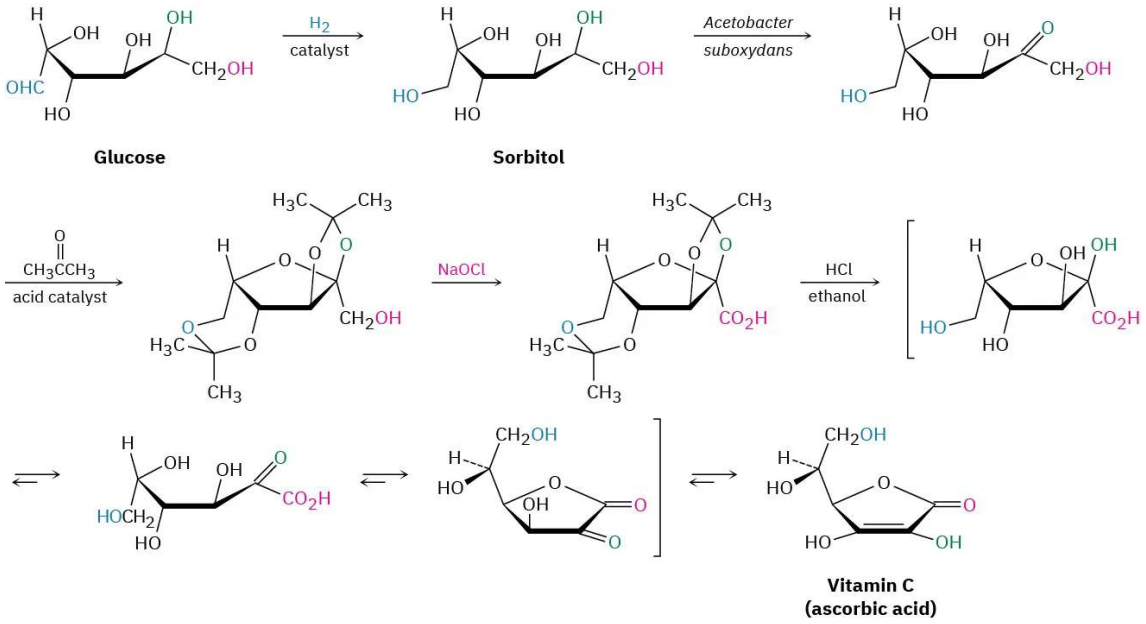


Figure 9.10.2: The industrial synthesis of ascorbic acid from glucose.

This page titled 9.10: Chemistry Matters—Vitamin C is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **20.9: Chemistry Matters—Vitamin C** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

9.11: Key Terms

- carboxyl group
- carboxylation
- carboxylic acid, RCO_2H
- Henderson–Hasselbalch equation
- nitrile

This page titled 9.11: Key Terms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **20.10: Key Terms** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

9.12: Summary

Carboxylic acids are among the most useful building blocks for synthesizing other molecules, both in nature and in the laboratory. Thus, an understanding of their properties and reactions is fundamental to understanding biological chemistry. In this chapter, we've looked both at acids and at their close relatives, **nitriles** (RC≡N).

Carboxylic acids are named systematically by replacing the terminal *-e* of the corresponding alkane name with *-oic acid*. Like aldehydes and ketones, the carbonyl carbon atom is sp^2-hybridized; like alcohols, carboxylic acids are associated through hydrogen-bonding and therefore have high boiling points.

The distinguishing characteristic of carboxylic acids is their acidity. Although weaker than mineral acids such as HCl, carboxylic acids dissociate much more readily than alcohols because the resultant carboxylate ions are stabilized by resonance between two equivalent forms.

Most carboxylic acids have pK_a values near 5, but the exact pK_a of a given acid depends on structure. Carboxylic acids substituted by electron-withdrawing groups are more acidic (have a lower pK_a) because their carboxylate ions are stabilized. Carboxylic acids substituted by electron-donating groups are less acidic (have a higher pK_a) because their carboxylate ions are destabilized. The extent of dissociation of a carboxylic acid in a buffered solution of a given pH can be calculated with the Henderson–Hasselbalch equation. Inside living cells, where the physiological pH = 7.3, carboxylic acids are entirely dissociated and exist as their carboxylate anions.

Methods of synthesis for carboxylic acids include:

1. oxidation of alkylbenzenes,
2. oxidation of primary alcohols or aldehydes,
3. reaction of Grignard reagents with CO_2 **(carboxylation)**, and
4. hydrolysis of nitriles.

General reactions of carboxylic acids include:

1. loss of the acidic proton,
2. nucleophilic acyl substitution at the carbonyl group,
3. substitution on the *α* carbon, and
4. reduction.

Nitriles are similar in some respects to carboxylic acids and are prepared either by S_N2 reaction of an alkyl halide with cyanide ion or by dehydration of an amide. Nitriles undergo nucleophilic addition to the polar C≡N bond in the same way that carbonyl compounds do. The most important reactions of nitriles are their hydrolysis to carboxylic acids, reduction to primary amines, and reaction with Grignard reagents to yield ketones.

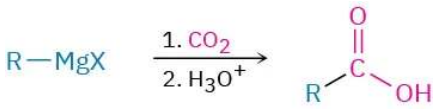
Carboxylic acids and nitriles are easily distinguished spectroscopically. Acids show a characteristic IR absorption at 2500 to 3300 cm^{-1} due to the O−H bond and another at 1710 to 1760 cm^{-1} due to the C=O bond; nitriles have an absorption at 2250 cm^{-1}. Acids also show ^{13}C NMR absorptions at 165 to 185 *δ* and ^{1}H NMR absorptions near 12 *δ*. Nitriles have a ^{13}C NMR absorption in the range 115 to 130 *δ*.

This page titled 9.12: Summary is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

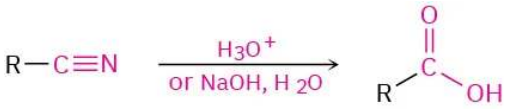
- **20.11: Summary** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

9.13: Summary of Reactions

1. Preparation of carboxylic acids (Section 20.5)
   a. Carboxylation of Grignard reagents

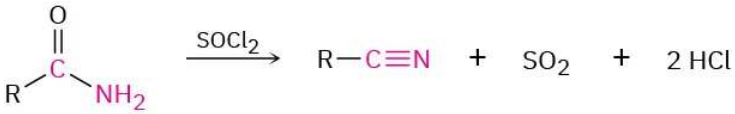


- Hydrolysis of nitriles

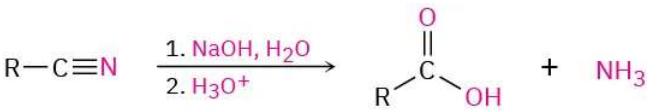


- Preparation of nitriles (Section 20.7)
  a. S_N2 reaction of alkyl halides

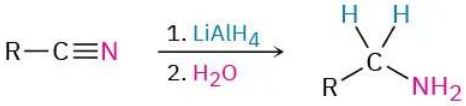
- Dehydration of amides



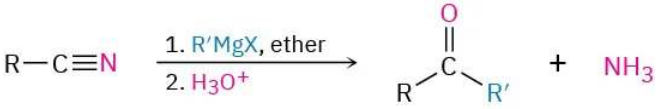
- Reactions of nitriles (Section 20.7)
  a. Hydrolysis to yield carboxylic acids



  b. Reduction to yield primary amines



  c. Reaction with Grignard reagents to yield ketones



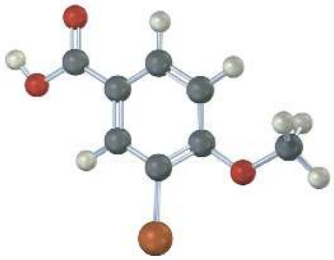
This page titled 9.13: Summary of Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

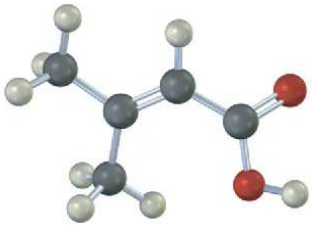
- **20.12: Summary of Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

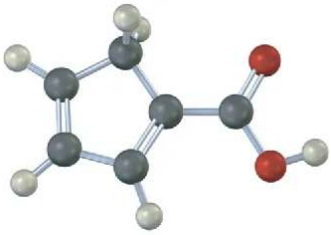
9.14: Additional Problems

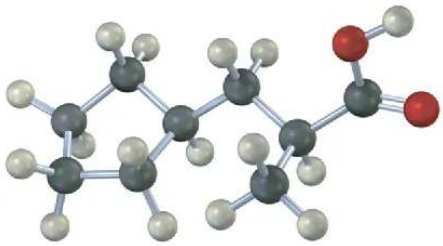
Visualizing Chemistry

PROBLEM 20-17 Give IUPAC names for the following carboxylic acids (reddish brown = Br):

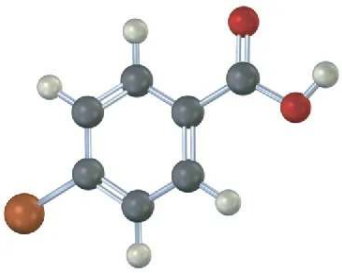
(a) 

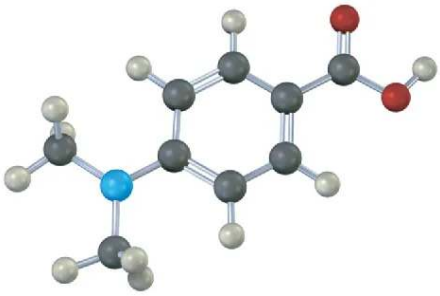
(b) 

(c) 

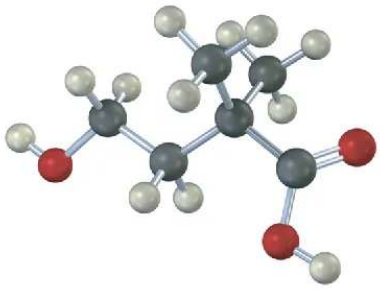
(d) 

PROBLEM 20-18 Would you expect the following carboxylic acids to be more acidic or less acidic than benzoic acid? Explain. (Reddish brown = Br.)

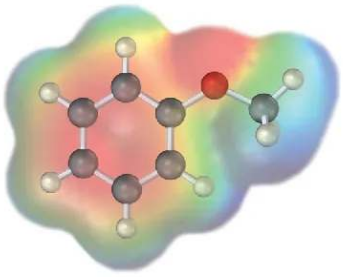
(a) 

(b) 

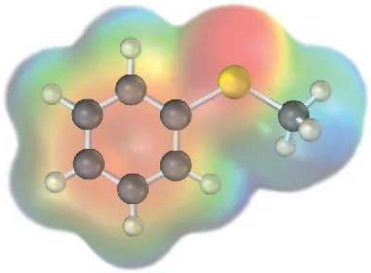
PROBLEM 20-19 The following carboxylic acid can't be prepared from an alkyl halide by either the nitrile hydrolysis route or the Grignard carboxylation route. Explain.



PROBLEM 20-20 Electrostatic potential maps of anisole and thioanisole are shown. Which do you think is the stronger acid, *p*-methoxybenzoic acid or *p*-(methylthio)benzoic acid? Explain.



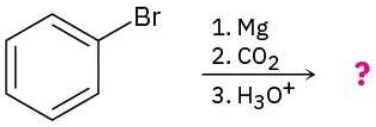
Anisole ($C_6H_5OCH_3$)

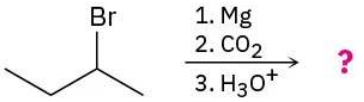


Thioanisole ($C_6H_5SCH_3$)

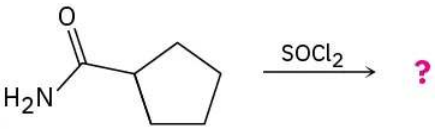
Mechanism Problems

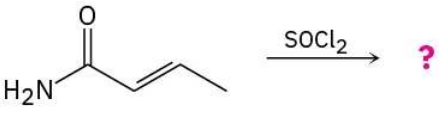
PROBLEM 20-21 Predict the product(s) and write the mechanism of each of the following reactions:

(a) 

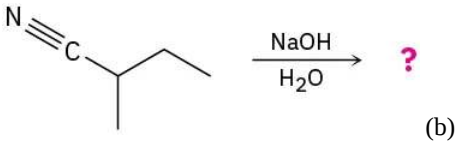
(b) 

Problem 20-22 Predict the product(s) and write the mechanism of each of the following reactions:

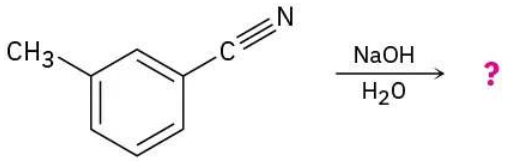
(a) 

(b) 

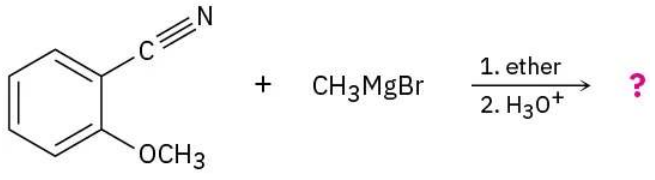
Problem 20-23 Predict the product(s) and write the mechanism of each of the following reactions:

(a) 

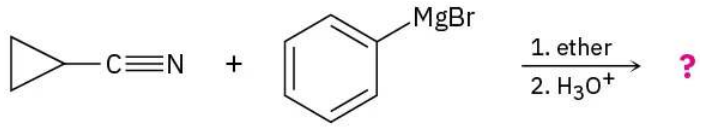
(b)

(b) 

Problem 20-24 Predict the product(s) and write the complete mechanism of each of the following reactions:

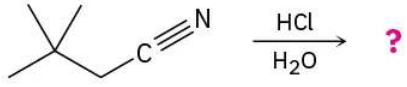
(a) 

(b)

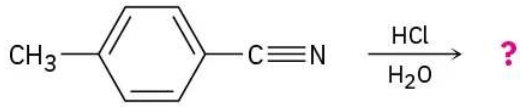


Problem 20-25 Acid-catalyzed hydrolysis of a nitrile to give a carboxylic acid occurs by initial protonation of the nitrogen atom, followed by nucleophilic addition of water. Review the mechanism of base-catalyzed nitrile hydrolysis in Section 20.7 and then predict the products for the following reactions. Write the steps involved in the acid-catalyzed reaction, using curved arrows.

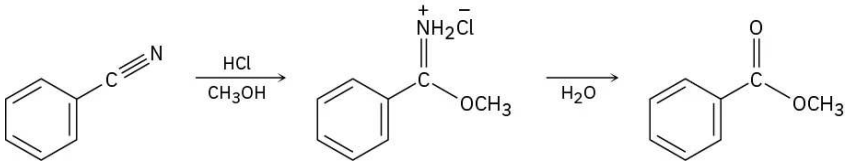
(a)



(b)



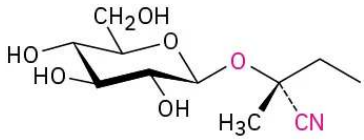
Problem 20-26 Nitriles can be converted directly to esters by the Pinner reaction, which first produces an iminoester salt that is isolated and then treated with water to give the final product. Propose a mechanism for the Pinner reaction using curved arrows to show the flow of electrons at each step.



Problem 20-27 Naturally occurring compounds called <i">cyanogenic glycosides, such as lotaustralin, release hydrogen cyanide, HCN, when treated with aqueous acid. The reaction occurs by hydrolysis of the acetal linkage to form a cyanohydrin, which then expels HCN and gives a carbonyl compound.

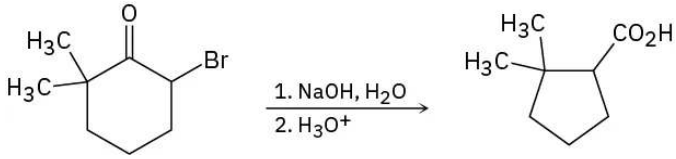
(a) Show the mechanism of the acetal hydrolysis and the structure of the cyanohydrin that results.

(b) Propose a mechanism for the loss of HCN, and show the structure of the carbonyl compound that forms.

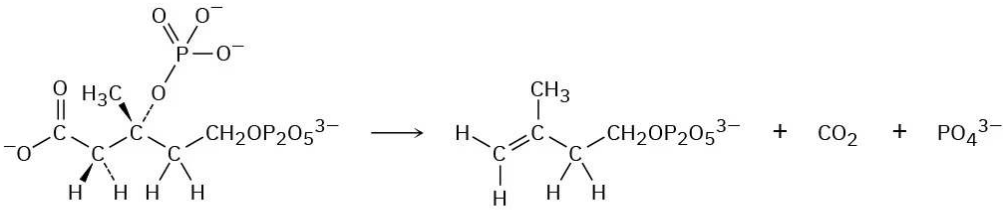


Lotaustralin

Problem 20-28 2-Bromo-6,6-dimethylcyclohexanone gives 2,2-dimethylcyclopentanecarboxylic acid on treatment with aqueous NaOH followed by acidification, a process called the Favorskii reaction. Propose a mechanism.

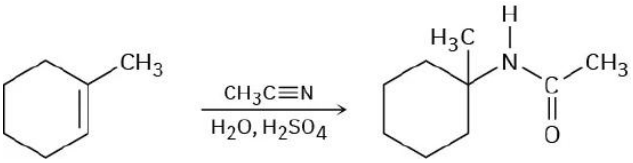


Problem 20-29 Naturally occurring compounds called *terpenoids*, which we'll discuss in **Section 27.5**, are biosynthesized by a pathway that involves loss of CO_2 from 3-phosphomevalonate 5-diphosphate to yield isopentenyl diphosphate. Use curved arrows to show the mechanism of this reaction.



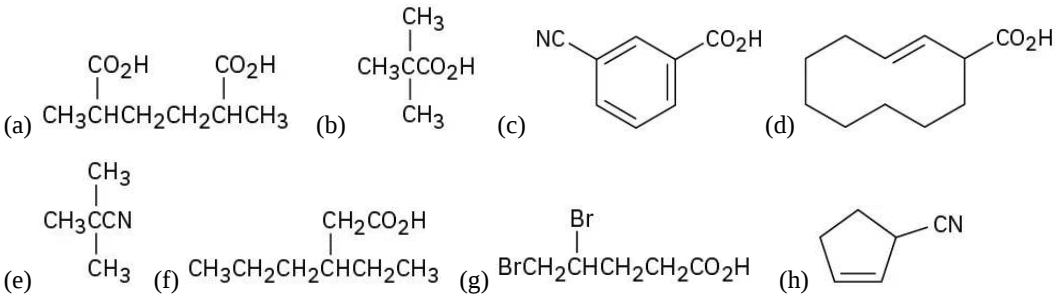
3-Phosphomevalonate 5-diphosphate **Isopentenyl diphosphate**

Problem 20-30 In the Ritter reaction, an alkene reacts with a nitrile in the presence of strong aqueous sulfuric acid to yield an amide. Propose a mechanism.



Naming Carboxylic Acids and Nitriles

Problem 20-31 Give the IUPAC names for the following compounds:



Problem 20-32 Draw structures corresponding to the following IUPAC names:

(a) *cis*-1,2-Cyclohexanedicarboxylic acid (b) Heptanedioic acid (c) 2-Hexen-4-ynoic acid (d) 4-Ethyl-2-propyloctanoic acid (e) 3-Chlorophthalic acid (f) Triphenylacetic acid (g) 2-Cyclobutenecarbonitrile (h) *m*-Benzoylbenzonitrile

Problem 20-33 Draw and name the following compounds:

(a) The eight carboxylic acids with the formula $C_6H_{12}O_2$

(b) Three nitriles with the formula C_5H_7N

Problem 20-34 Pregabalin, marketed as Lyrica, is an anticonvulsant drug that is also effective in treating chronic pain. The IUPAC name of pregabalin is (*S*)-3-(aminomethyl)-5-methylhexanoic acid. (An aminomethyl group is $–CH_2NH_2$.) Draw the structure of pregabalin.

Problem 20-35 Isocitric acid, an intermediate in the citric acid cycle of food metabolism, has the systematic name (2*R*,3*S*)-3-carboxy-2-hydroxypentanedioic acid. Draw the structure.

Acidity of Carboxylic Acids

Problem 20-36 Order the compounds in each of the following sets with respect to increasing acidity:

(a) Acetic acid, oxalic acid, formic acid

(b) *p*-Bromobenzoic acid, *p*-nitrobenzoic acid, 2,4-dinitrobenzoic acid

(c) Fluoroacetic acid, 3-fluoropropanoic acid, iodoacetic acid

Problem 20-37 Arrange the compounds in each of the following sets in order of increasing basicity:

(a) Magnesium acetate, magnesium hydroxide, methylmagnesium bromide

(b) Sodium benzoate, sodium *p*-nitrobenzoate, sodium acetylide

(c) Lithium hydroxide, lithium ethoxide, lithium formate

Problem 20-38 Calculate the pK_a's of the following acids:

(a) Lactic acid, $K_a = 8.4 \times 10^{-4}$

(b) Acrylic acid, $K_a = 5.6 \times 10^{-6}$

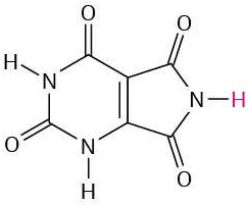
Problem 20-39 Calculate the K_a's of the following acids:

(a) Citric acid, $pK_a = 3.14$

(b) Tartaric acid, $pK_a = 2.98$

Problem 20-40 Thioglycolic acid, $HSCH_2CO_2H$, a substance used in depilatory agents (hair removers) has $pK_a = 3.42$. What is the percent dissociation of thioglycolic acid in a buffer solution at pH = 3.0?

Problem 20-41 In humans, the final product of purine degradation from DNA is uric acid, $pK_a = 5.61$, which is excreted in the urine. What is the percent dissociation of uric acid in urine at a typical pH = 6.0? Why do you think uric acid is acidic even though it does not have a CO_2H group?



Uric acid

Problem 20-42 Some pK_a data for simple dibasic acids are shown. How can you account for the fact that the difference between the first and second ionization constants decreases with increasing distance between the carboxyl groups?

Name/th>	Structure	pK_1	pK_2
Oxalic	HO_2CCO_2H	1.2	4.2
Succinic	$HO_2CCH_2CH_2CO_2H$	4.2	5.6
Adipic	$HO_2C(CH_2)_4CO_2H$	4.4	5.4

Reactions of Carboxylic Acids and Nitriles

Problem 20-43 How could you convert butanoic acid into the following compounds? Write each step showing the reagents needed.

(a) 1-Butanol (b) 1-Bromobutane (c) Pentanoic acid (d) 1-Butene (e) Octane

Problem 20-44 How could you convert each of the following compounds into butanoic acid? Write each step showing all reagents.

(a) 1-Butanol (b) 1-Bromobutane (c) 1-Butene (d) 1-Bromopropane (e) 4-Octene

Problem 20-45 How could you convert butanenitrile into the following compounds? Write each step showing the reagents needed.

(a) 1-Butanol (b) Butylamine (c) 2-Methyl-3-hexanone

Problem 20-46 How would you prepare the following compounds from benzene? More than one step is needed in each case.

(a) *m*-Chlorobenzoic acid (b) *p*-Bromobenzoic acid (c) Phenylacetic acid, $C_6H_5CH_2CO_2H$

Problem 20-47 Predict the product of the reaction of *p*-methylbenzoic acid with each of the following:

(a) $LiAlH_4$, then H_3O^+

(b) *N*-Bromosuccinimide in CCl_4

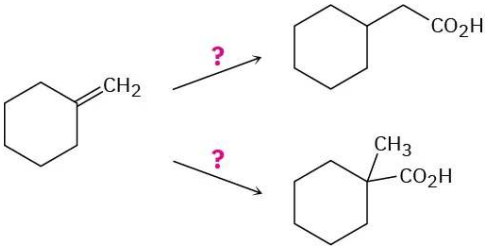
(c) CH_3MgBr in ether, then H_3O^+

(d) $KMnO_4$, H_3O^+

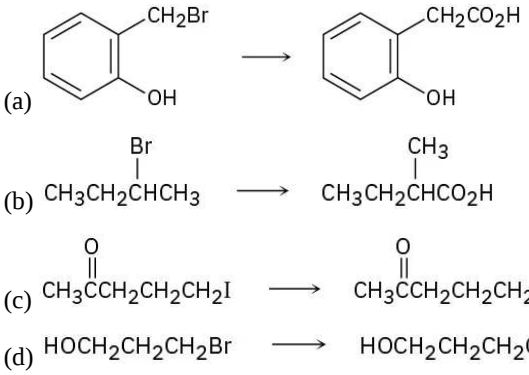
Problem 20-48 Using $^{13}CO_2$ as your only source of labeled carbon, along with any other compounds needed, how would you synthesize the following compounds?

(a) $CH_3CH_2{}^{13}CO_2H$ (b) PRODC$H_3{}^{13}CH_2CO_2H$

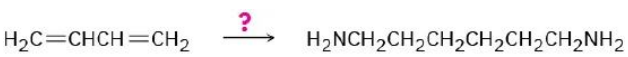
Problem 20-49 How would you carry out the following transformations?



Problem 20-50 Which method—Grignard carboxylation or nitrile hydrolysis—would you use for each of the following reactions? Explain.



Problem 20-51 1,6-Hexanediamine, a starting material needed for making nylon, can be made from 1,3-butadiene. How would you accomplish the synthesis?

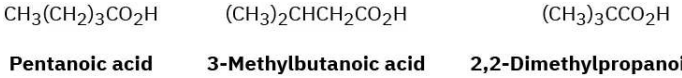


Problem 20-52 3-Methyl-2-hexenoic acid (mixture of *E* and *Z* isomers) has been identified as the substance responsible for the odor of human sweat. Synthesize the compound from starting materials having five or fewer carbons.

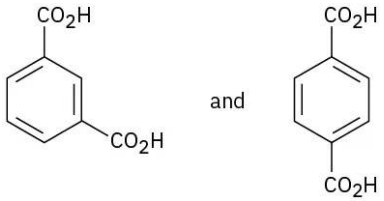
Spectroscopy

Problem 20-53 Propose a structure for a compound $C_6H_{12}O_2$ that dissolves in dilute NaOH and shows the following ^1H NMR spectrum: 1.08 δ (9 H, singlet), 2.2 δ (2 H, singlet), and 11.2 δ (1 H, singlet).

Problem 20-54 What spectroscopic method could you use to distinguish among the following three isomeric acids? Tell what characteristic features you would expect for each acid.

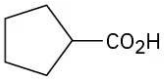


Problem 20-55 How would you use NMR (either ^{13}C or ^1H) to distinguish between the following pairs of isomers?

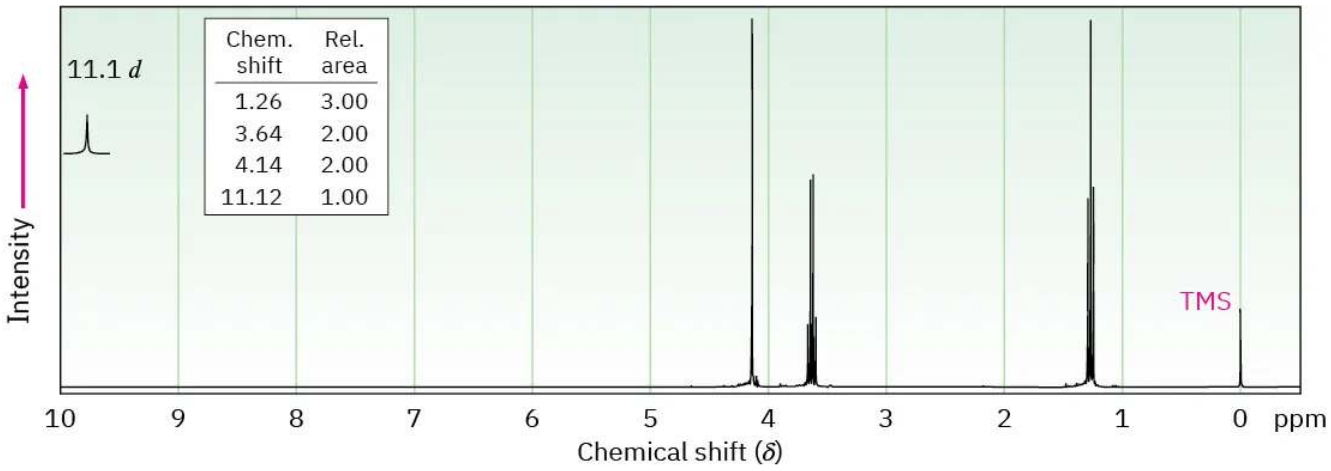
(a)  and

(b) $HO_2CCH_2CH_2CO_2H$ and $CH_3CH(CO_2H)_2$

(c) $CH_3CH_2CH_2CO_2H$ and $HOCH_2CH_2CH_2CHO$

(d) $(CH_3)_2C{=}CHCH_2CO_2H$ and 

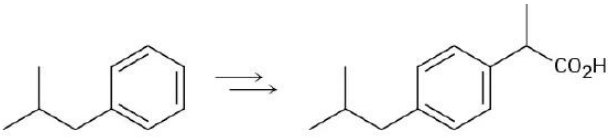
Problem 20-56 Compound **A**, $C_4H_8O_3$, has infrared absorptions at 1710 and 2500 to 3100 cm^{-1} and has the ^1H NMR spectrum shown. Propose a structure for **A**.



General Problems

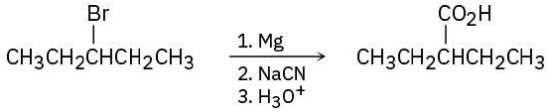
Problem 20-57 A chemist in need of 2,2-dimethylpentanoic acid decided to synthesize some by reaction of 2-chloro-2-methylpentane with NaCN, followed by hydrolysis of the product. After the reaction sequence was carried out, however, none of the desired product could be found. What do you suppose went wrong?

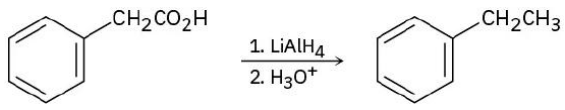
Problem 20-58 Show how you might prepare the anti-inflammatory agent ibuprofen starting from isobutylbenzene. More than one step is needed.

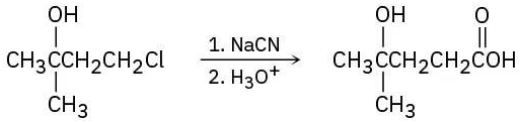


Isobutylbenzene **Ibuprofen**

Problem 20-59 The following synthetic schemes all have at least one flaw in them. What is wrong with each?

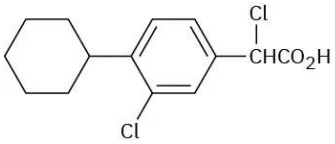
(a) 

(b) 

(c) 

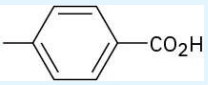
Problem 20-60 *p*-Aminobenzoic acid (PABA) was once widely used as a sunscreen agent. Propose a synthesis of PABA starting from toluene.

Problem 20-61 Propose a synthesis of the anti-inflammatory drug fenclorac from phenylcyclohexane.

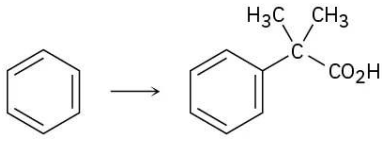


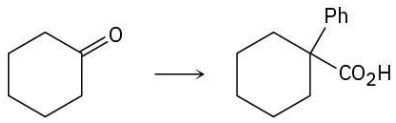
Fenclorac

Problem 20-62 The pK_a's of five *p*-substituted benzoic acids ($YC_6H_4CO_2H$) are listed below. Rank the corresponding substituted benzenes (YC_6H_5) in order of their increasing reactivity toward electrophilic aromatic substitution. If benzoic acid has pK_a = 4.19, which of the substituents are activators and which are deactivators?

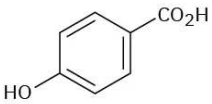
Substituent Y	**pK_a of** 
–Si(CH$_3$)$_3$	**4.27**
–CH=CHC≡N	**4.03**
–HgCH$_3$	**4.10**
–OSO$_2$CH$_3$	**3.84**
–PCl$_2$	**3.59**

Problem 20-63 How would you carry out the following transformations? More than one step is needed in each case.

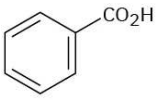
(a) 

(b) 

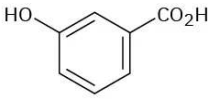
Problem 20-64 The following pK_a values have been measured. Explain why a hydroxyl group in the para position decreases the acidity while a hydroxyl group in the meta position increases the acidity.



pK_a = 4.48

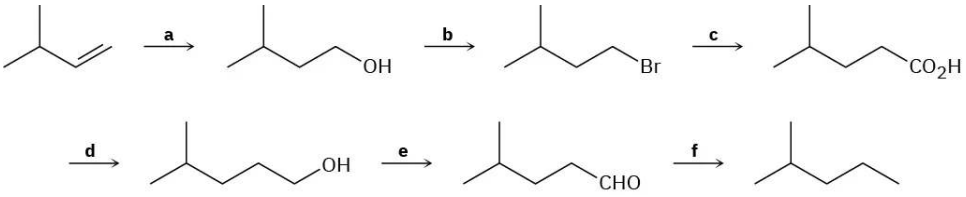


pK_a = 4.19

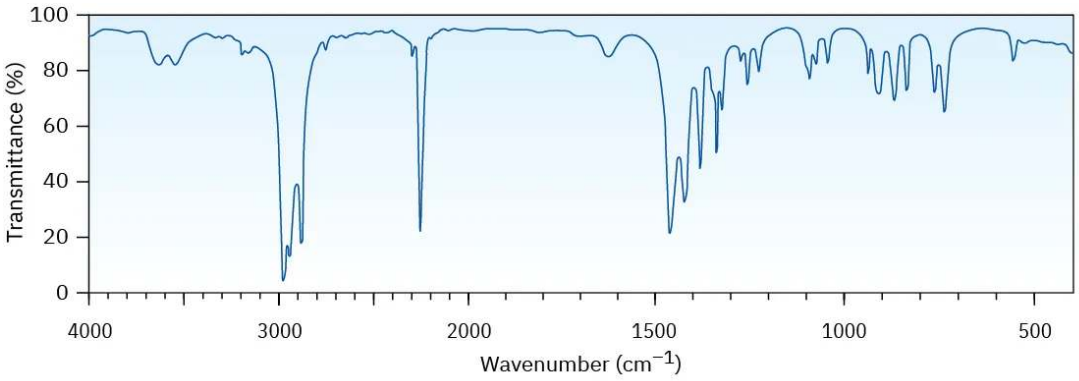


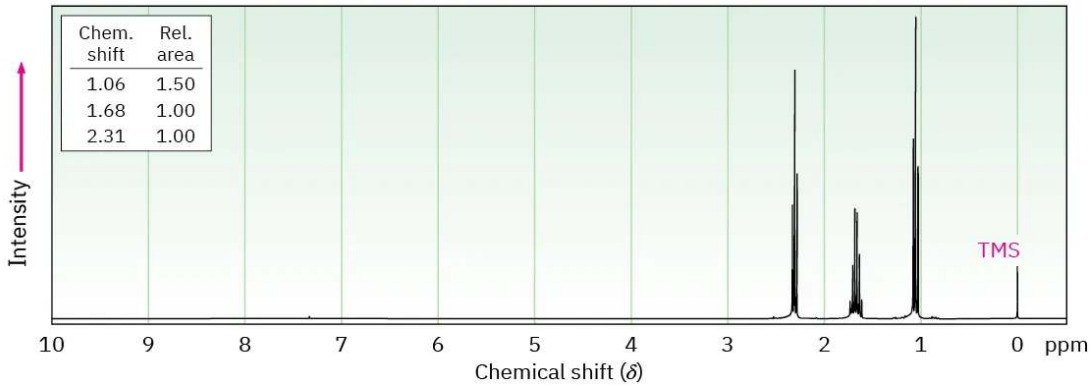
pK_a = 4.07

Problem 20-65 Identify the missing reagents **a**–**f** in the following scheme:

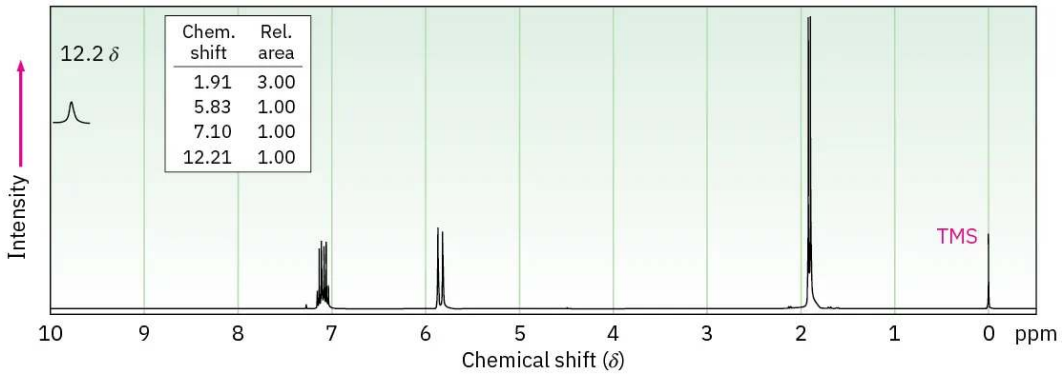


Problem 20-66 Propose a structure for a compound, C_4H_7N, that has the following IR and ^1H NMR spectra:

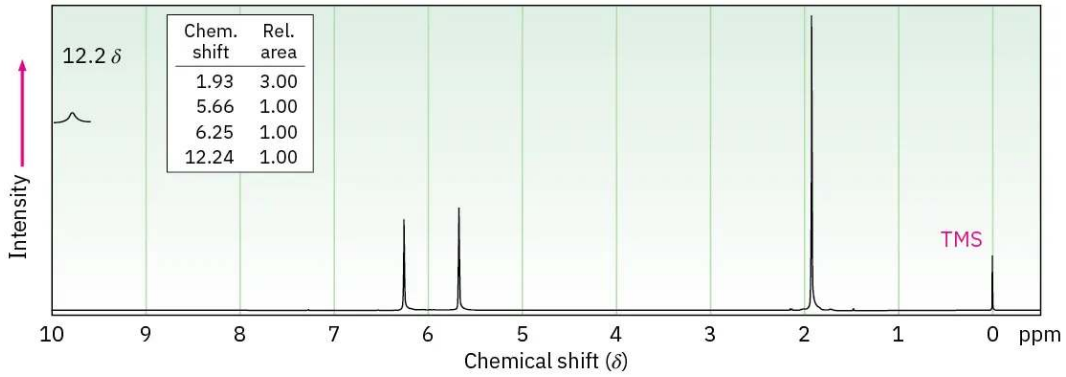




Problem 20-67 The two ^1H NMR spectra shown here belong to crotonic acid (*trans*-CH_3CH=Math input error$_2H$) and methacrylic acid [H_2C=$C(CH_3)CO_2H$]. Which spectrum corresponds to which acid? Explain.

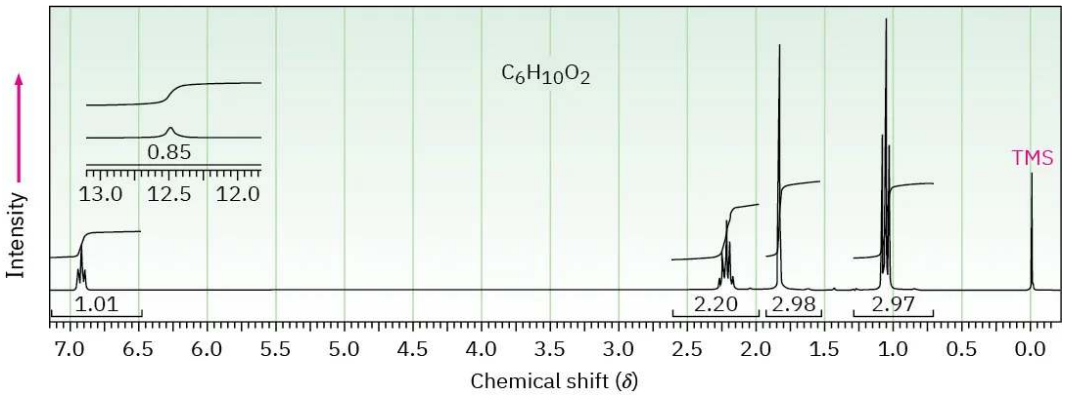


(a)

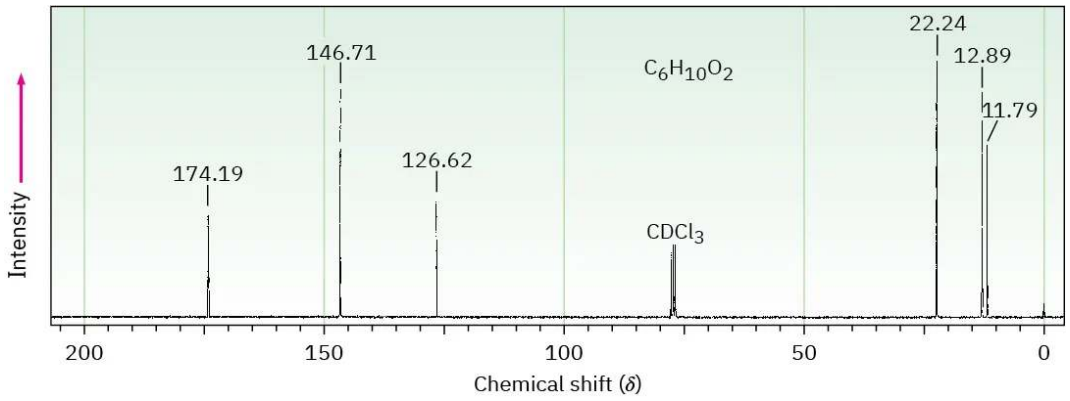


(b)

Problem 20-68 The ^{1}H and ^{13}C NMR spectra below belong to a compound with formula $C_6H_{10}O_2$. Propose a structure for this compound.



(a)



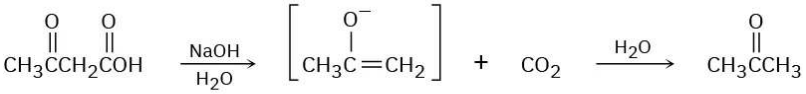
(b)

Problem 20-69 Propose structures for carboxylic acids that show the following peaks in their ^{13}C NMR spectra. Assume that the kinds of carbons (1°, 2°, 3°, or 4°) have been assigned by DEPT-NMR.

(a) $C_7H_{12}O_2$: 25.5 δ (2°), 25.9 δ (2°), 29.0 δ (2°), 43.1 δ (3°), 183.0 δ (4°)

(b) $C_8H_8O_2$: 21.4 δ (1°), 128.3 δ (4°), 129.0 δ (3°), 129.7 δ (3°), 143.1 δ (4°), 168.2 δ (4°)

Problem 20-70 Carboxylic acids having a second carbonyl group two atoms away lose CO_2 *(decarboxylate)* through an intermediate enolate ion when treated with base. Write the mechanism of this decarboxylation reaction using curved arrows to show the electron flow in each step.



An enolate ion

https://chem.libretexts.org/@go/page/564291

This page titled 9.14: Additional Problems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **20.13: Additional Problems** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

CHAPTER OVERVIEW

10: Carboxylic Acid Derivatives- Nucleophilic Acyl Substitution Reactions

The compounds discussed in this chapter are all considered to be derived from carboxylic acids, and include acid halides, acid anhydrides, esters and amides (thioesters and acyl phosphates are also briefly mentioned). As you proceed through the chapter, you should be looking for similarities in behaviour among the various classes of compounds. These similarities can be readily understood once you appreciate the fact that, in most of their reactions, carboxylic acid derivatives react via the nucleophilic acyl substitution mechanism.

In this chapter, we describe the nomenclature of the various types of carboxylic acid derivatives, and explain the relative reactivity of these compounds in terms of resonance contributions to the ground state of each type of compound.

We describe the reactions of carboxylic acids, acid halides, acid anhydrides, esters, amides, polyamides and polyesters in detail, and discuss the biological importance of thiol esters briefly. The chapter concludes with a look at how infrared spectroscopy and NMR spectroscopy can be used in the identification of unknown carboxylic acid derivatives.

10.1: Why This Chapter?
10.2: Naming Carboxylic Acid Derivatives
10.3: Nucleophilic Acyl Substitution Reactions
10.4: Reactions of Carboxylic Acids
10.5: Chemistry of Acid Halides
10.6: Chemistry of Acid Anhydrides
10.7: Chemistry of Esters
10.8: Chemistry of Amides
10.9: Chemistry of Thioesters and Acyl Phosphates - Biological Carboxylic Acid Derivatives
10.10: Polyamides and Polyesters - Step-Growth Polymers
10.11: Spectroscopy of Carboxylic Acid Derivatives
10.12: Chemistry Matters—β-Lactam Antibiotics
10.13: Key Terms
10.14: Summary
10.15: Summary of Reactions
10.16: Additional Problems
10.17: Carbonyl Condensation Reactions

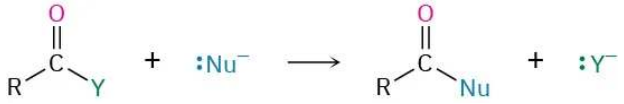
This page titled 10: Carboxylic Acid Derivatives- Nucleophilic Acyl Substitution Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

10.1: Why This Chapter?

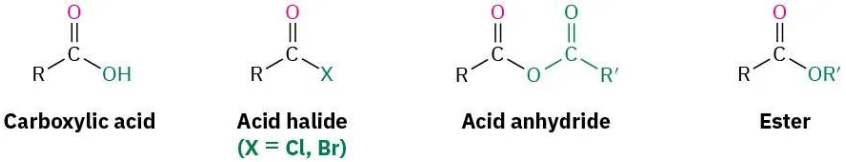
Carboxylic acid derivatives are among the most widely occurring of all molecules, both in laboratory chemistry and in biological pathways. Thus, a study of them and their primary reaction—nucleophilic acyl substitution—is fundamental to understanding organic chemistry. We'll begin this chapter by first learning about carboxylic acid derivatives, and we'll then explore the chemistry of acyl substitution reactions.

Figure 10.1.1: The lives of rock climbers depend on their ropes, typically made of a nylon polymer prepared by a nucleophilic acyl substitution reaction. (credit: "110823-A-NR754-001" by USASOC News Service/Flickr, CC BY 2.0)

Closely related to the carboxylic acids and nitriles discussed in the previous chapter are the carboxylic acid derivatives, compounds in which an acyl group is bonded to an electronegative atom or substituent that can act as a leaving group in the nucleophilic acyl substitution reaction that we saw briefly in the Preview of Carbonyl Chemistry:



Many kinds of acid derivatives are known, but we'll be concerned primarily with four of the most common ones: acid halides, acid anhydrides, esters, and amides. Acid halides and acid anhydrides are used only in the laboratory, while esters and amides are common in both laboratory and biological chemistry. In addition, carboxylic acid derivatives called thioesters and acyl phosphates are encountered primarily in biological chemistry. Note the structural similarity between acid anhydrides and acyl phosphates.



Carboxylic acid | **Acid halide (X = Cl, Br)** | **Acid anhydride** | **Ester**

Amide | **Thioester** | **Acyl phosphate**

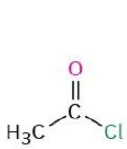
This page titled 10.1: Why This Chapter? is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **21.0: Why This Chapter?** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

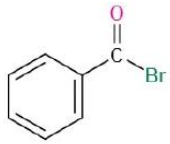
10.2: Naming Carboxylic Acid Derivatives

Acid Halides, RCOX

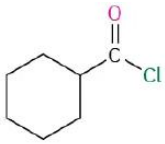
Acid halides are named by identifying first the acyl group and then the halide. As described in Section 20.1 and shown in Table 20.1, the acyl group name is derived from the carboxylic acid name by replacing the *-ic acid* or *-oic acid* ending with *-oyl*, or the *-carboxylic acid* ending with *-carbonyl*. To keep things interesting, however, IUPAC recognizes eight exceptions for which a *-yl* rather than an *-oyl* ending is used: formic (formyl), acetic (acetyl), propionic (propionyl), butyric (butyryl), oxalic (oxalyl), malonic (malonyl), succinic (succinyl), and glutaric (glutaryl).



Acetyl chloride



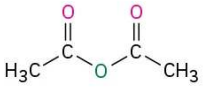
Benzoyl bromide



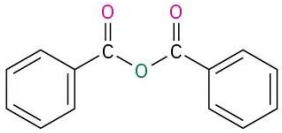
Cyclohexanecarbonyl chloride

Acid Anhydrides, RCO_2COR'

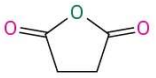
Symmetrical anhydrides of unsubstituted monocarboxylic acids and cyclic anhydrides of dicarboxylic acids are named by replacing the word *acid* with *anhydride*.



Acetic anhydride

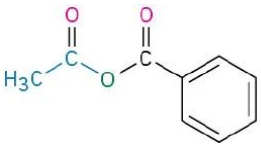


Benzoic anhydride



Succinic anhydride

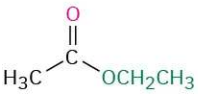
Unsymmetrical anhydrides—those prepared from two different carboxylic acids—are named by listing the two acids alphabetically and then adding *anhydride*.



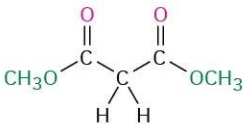
Acetic benzoic anhydride

Esters, RCO_2R'

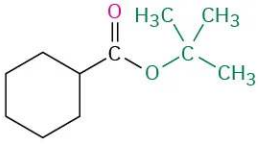
Esters are named by first identifying the alkyl group attached to oxygen and then the carboxylic acid, with the *-ic acid* ending replaced by *-ate*.



Ethyl acetate



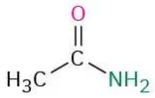
Dimethyl malonate



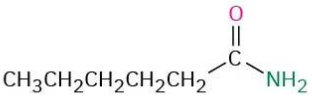
***tert*-Butyl cyclohexane-carboxylate**

Amides, $RCONH_2$

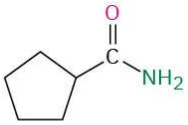
Amides with an unsubstituted $–NH_2$ group are named by replacing the *-oic acid* or *-ic acid* ending with *-amide*, or by replacing the *-carboxylic acid* ending with *-carboxamide*.



Acetamide

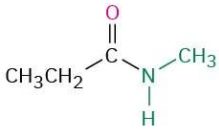


Hexanamide

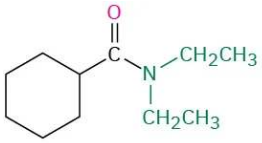


Cyclopentane-carboxamide

If the nitrogen atom is further substituted, the compound is named by first identifying the substituent groups and then the parent amide. The substituents are preceded by the letter *N* to identify them as being directly attached to nitrogen.



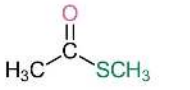
***N*-Methylpropanamide**



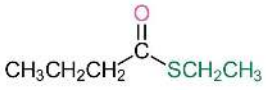
***N,N*-Diethylcyclohexanecarboxamide**

Thioesters, RCOSR′

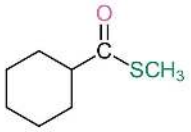
Thioesters are named like the corresponding esters. The name begins with the alkyl group attached to the sulfur preceded with the letter *S*. If the related ester has a common name, the prefix *thio-* is added to the name of the carboxylate: acetate becomes thioacetate, for instance. If the related ester has a systematic name, the *-oate* or *-carboxylate* ending is replaced by *-thioate* or *-carbothioate:* butanoate becomes butanethioate and cyclohexanecarboxylate becomes cyclohexanecarbothioate, for instance.



***S*-Methyl thioacetate**



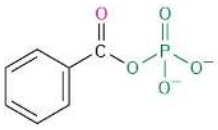
***S*-Ethyl butanethioate**



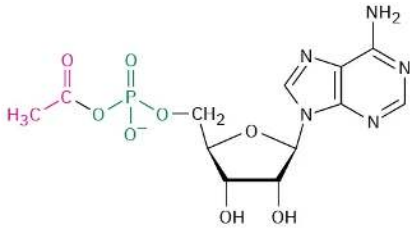
***S*-Methyl cyclohexane-carbothioate**

Acyl Phosphates, $RCO_2PO_3^{2-}$ and $RCO_2PO_3R^-$

Acyl phosphates are named by citing the acyl group and adding the word *phosphate.* If an alkyl group is attached to one of the phosphate oxygens, it is identified after the name of the acyl group. In biological chemistry, acyl adenosyl phosphates are particularly common.



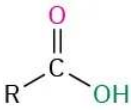
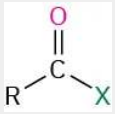
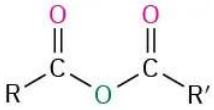
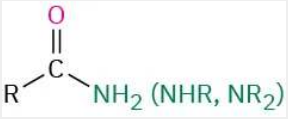
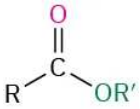
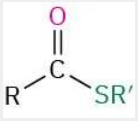
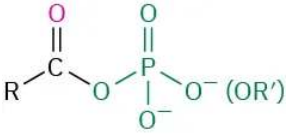
Benzoyl phosphate



Acetyl adenosyl phosphate

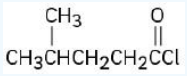
A summary of nomenclature rules for carboxylic acid derivatives is given in Table 10.2.1.

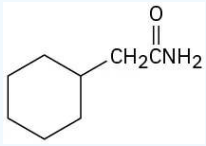
Table 10.2.1: Nomenclature of Carboxylic Acid Derivatives

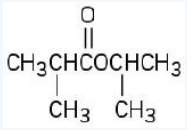
Functional group	Structure	Name ending
Carboxylic acid		*-ic acid* *(-carboxylic acid)*
Acid halide		*-oyl halide* *(-carbonyl halide)*
Acid anhydride		*anhydride*
Amide		*-amide* *(-carboxamide)*
Ester		*-oate* *(-carboxylate)*
Thioester		*-thioate* *(-carbothioate)*
Acyl phosphate		*-oyl phosphate*

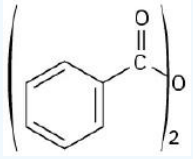
Exercise 10.2.1

Give IUPAC names for the following substances:

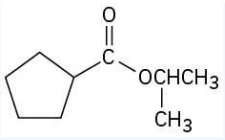
a. 

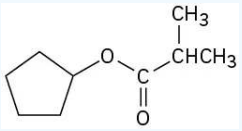
b. 

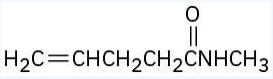
c. 

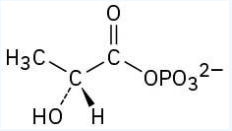
d. 

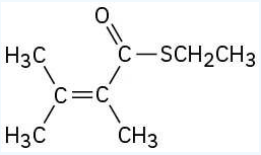
https://chem.libretexts.org/@go/page/564294

e. 

f. 

g. 

h. 

i. 

Answer

a. 4-Methylpentanoyl chloride
b. Cyclohexylacetamide
c. Isopropyl 2-methylpropanoate
d. Benzoic anhydride
e. Isopropyl cyclopentanecarboxylate
f. Cyclopentyl 2-methylpropanoate
g. N-Methyl-4-pentenamide
h. (R)-2-Hydroxypropanoyl phosphate
i. Ethyl 2,3-dimethyl-2-butenethioate

? Exercise 10.2.2

Draw structures corresponding to the following names:

a. Phenyl benzoate
b. N-Ethyl-N-methylbutanamide
c. 2,4-Dimethylpentanoyl chloride
d. Methyl 1-methylcyclohexanecarboxylate
e. Ethyl 3-oxopentanoate
f. Methyl p-bromobenzenethioate
g. Formic propanoic anhydride
h. cis-2-Methylcyclopentanecarbonyl bromide

Answer

This page titled 10.2: Naming Carboxylic Acid Derivatives is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **21.1: Naming Carboxylic Acid Derivatives** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

10.3: Nucleophilic Acyl Substitution Reactions

The addition of a nucleophile to a polar C=O bond is the key step in three of the four major carbonyl-group reactions. We saw in the chapter on Aldehydes and Ketones: Nucleophilic Addition Reactions that when a nucleophile adds to an aldehyde or ketone, the initially formed tetrahedral intermediate can be protonated to yield an alcohol. When a nucleophile adds to a carboxylic acid derivative, however, a different reaction path is taken. The initially formed tetrahedral intermediate eliminates one of the two substituents originally bonded to the carbonyl carbon, leading to a net nucleophilic acyl substitution reaction (Figure 10.3.1).

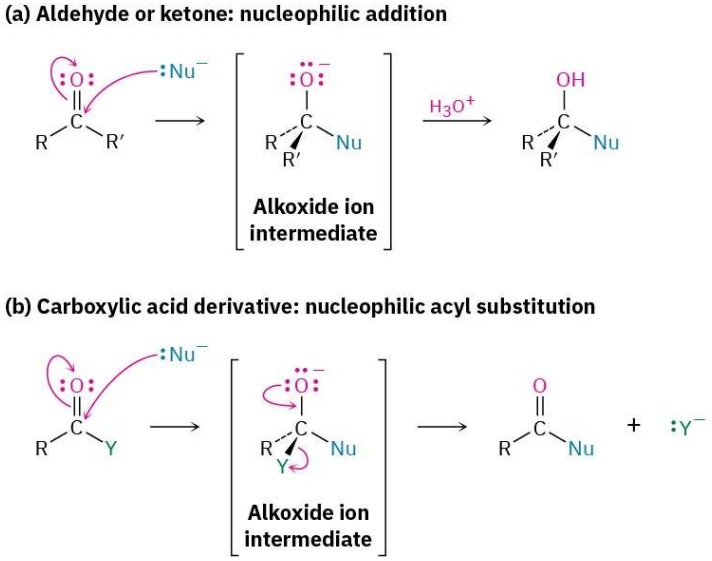
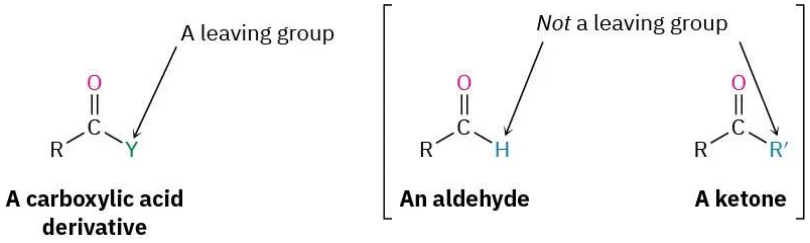


Figure 10.3.1: The general mechanisms of nucleophilic addition and nucleophilic acyl substitution reactions. Both reactions begin with addition of a nucleophile to a polar C=O bond to give a tetrahedral, alkoxide ion intermediate. **(a)** The intermediate formed from an aldehyde or ketone is protonated to give an alcohol, but **(b)** the intermediate formed from a carboxylic acid derivative expels a leaving group to give a new carbonyl compound.

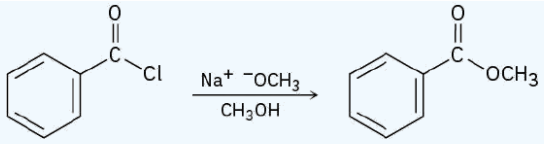
The difference in behavior between aldehydes/ketones and carboxylic acid derivatives is a consequence of structure. Carboxylic acid derivatives have an acyl carbon bonded to a group –Y that can act as a leaving group, often as a stable anion. As soon as the tetrahedral intermediate is formed, the leaving group is expelled to generate a new carbonyl compound. Aldehydes and ketones, however, have no such leaving group, however, and therefore don't undergo substitution.



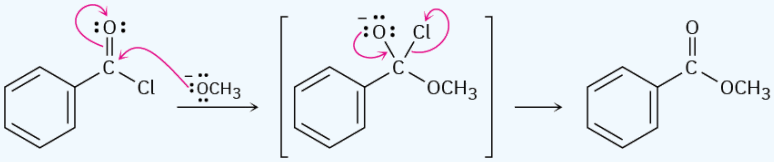
The net effect of the addition/elimination sequence is a substitution of the nucleophile for the –Y group that was originally bonded to the acyl carbon. Thus, the overall reaction is superficially similar to the kind of nucleophilic substitution that occurs during an S_N2 reaction (Section 11.3), but the mechanisms of the two reactions are completely different. An S_N2 reaction occurs in a single step by backside displacement of the leaving group, while a nucleophilic acyl substitution takes place in two steps and involves a tetrahedral intermediate.

? Exercise 10.3.1

Show the mechanism of the following nucleophilic acyl substitution reaction, using curved arrows to indicate the electron flow in each step:



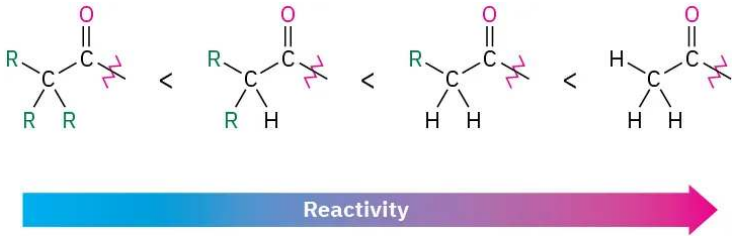
Answer



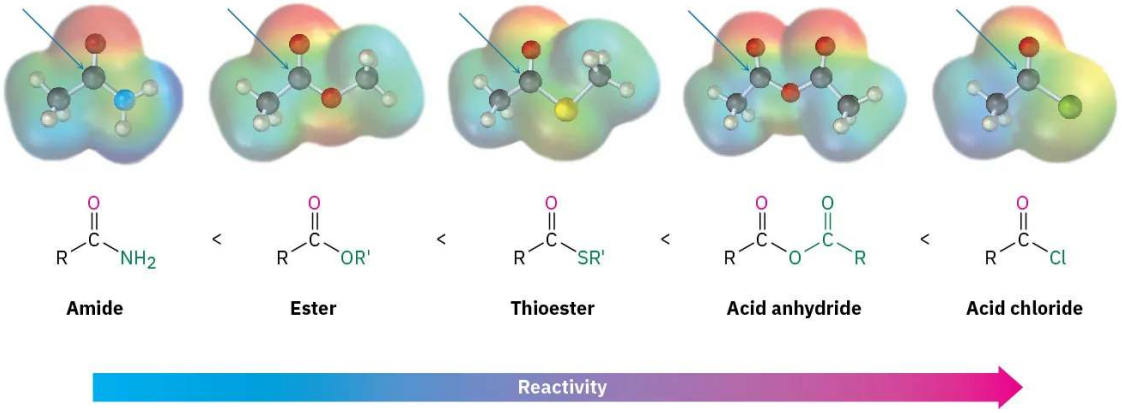
Relative Reactivity of Carboxylic Acid Derivatives

Both the initial addition step and the subsequent elimination step can affect the overall rate of a nucleophilic acyl substitution reaction, but the addition is usually the rate-limiting step. Thus, any factor that makes the carbonyl group more reactive toward nucleophiles favors the substitution process.

Steric and electronic factors are both important in determining reactivity. Sterically, we find within a series of similar acid derivatives that unhindered, accessible carbonyl groups react with nucleophiles more readily than do sterically hindered carbonyl groups. The reactivity order is



Electronically, we find that strongly polarized acyl compounds react more readily than less polar ones. Thus, acid chlorides are the most reactive because the electronegative chlorine atom withdraws electrons from the carbonyl carbon, whereas amides are the least reactive. Although subtle, electrostatic potential maps of various carboxylic acid derivatives indicate these differences by the relative blueness on the C═O carbons. Acyl phosphates are hard to place on this scale because they are not often used in the laboratory, but in biological systems they appear to be somewhat more reactive than thioesters.



The way in which various substituents affect the polarization of a carbonyl group is similar to the way they affect the reactivity of an aromatic ring toward electrophilic substitution (Section 16.4). A chlorine substituent, for example, inductively withdraws electrons from an acyl group in the same way that it withdraws electrons from and thus deactivates an aromatic ring. Similarly, amino, methoxyl, and methylthio substituents donate electrons to acyl groups by resonance in the same way that they donate electrons to, and thus activate, aromatic rings.

As a consequence of these reactivity differences, it's usually possible to convert a more reactive acid derivative into a less reactive one. Acid chlorides, for instance, can be directly converted into anhydrides, thioesters, esters, and amides, but amides can't be directly converted into esters, thioesters, anhydrides, or acid chlorides. Remembering the reactivity order is therefore a way to keep track of a large number of reactions (Figure 10.3.2). Another consequence, as noted previously, is that only acyl phosphates, thioesters, esters, and amides are commonly found in nature. Acid halides and acid anhydrides react so rapidly with water that they can't exist for long in living organisms.

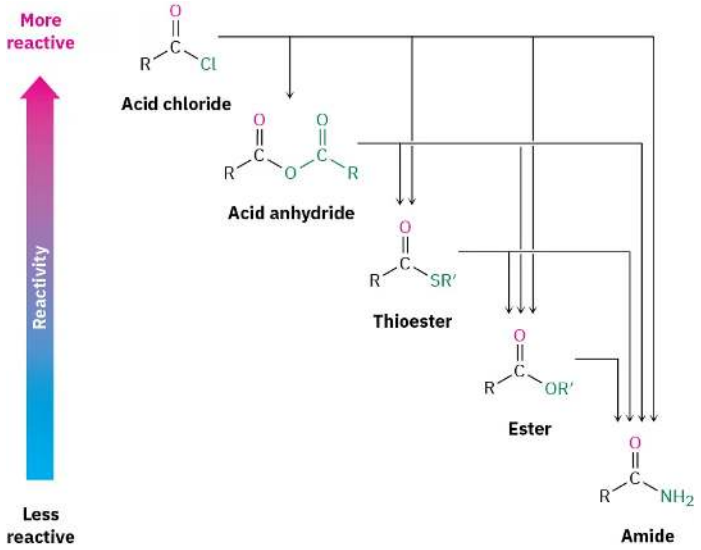


Figure 10.3.2: Interconversions of carboxylic acid derivatives. A more reactive acid derivative can be converted into a less reactive one, but not vice versa.

In studying the chemistry of carboxylic acid derivatives in the next few sections, we'll be concerned largely with the reactions of just a few nucleophiles and will see that the same kinds of reactions tend to reoccur (Figure 10.3.3).

- **Hydrolysis**: Reaction with water to yield a carboxylic acid
- **Alcoholysis**: Reaction with an alcohol to yield an ester
- **Aminolysis**: Reaction with ammonia or an amine to yield an amide
- **Reduction**: Reaction with a hydride reducing agent to yield an aldehyde or an alcohol
- **Grignard reaction**: Reaction with an organometallic reagent to yield a ketone or an alcohol

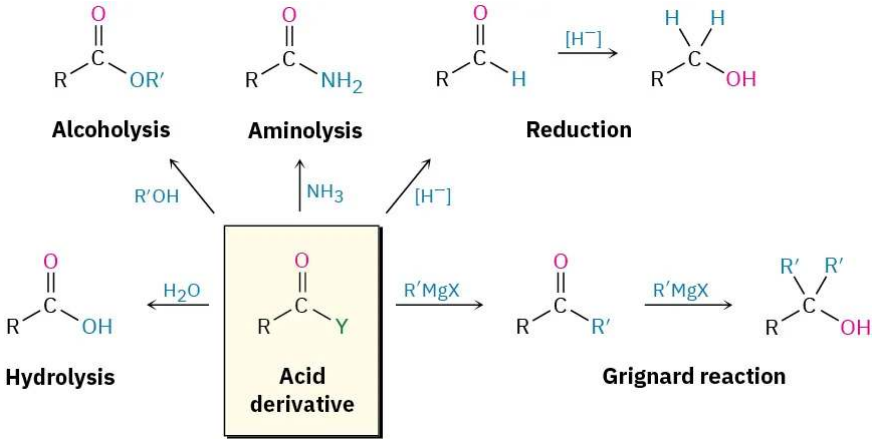
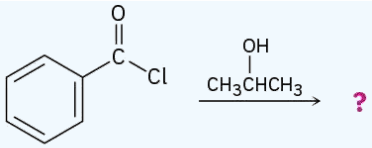


Figure 10.3.3: Some general reactions of carboxylic acid derivatives.

Worked Example 10.3.1: Predicting the Product of a Nucleophilic Acyl Substitution Reaction

Predict the product of the following nucleophilic acyl substitution reaction of benzoyl chloride with 2-propanol:

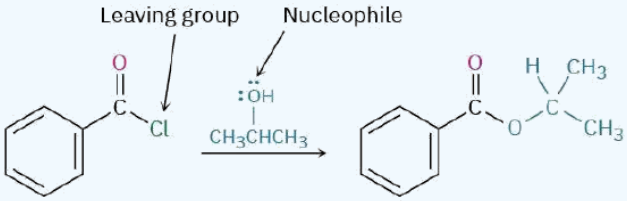


Benzoyl chloride

Strategy

A nucleophilic acyl substitution reaction involves the substitution of a nucleophile for a leaving group in a carboxylic acid derivative. Identify the leaving group (Cl^- in the case of an acid chloride) and the nucleophile (an alcohol in this case), and replace one by the other. The product is isopropyl benzoate.

Solution



Benzoyl chloride **Isopropyl benzoate**

Exercise 10.3.2

Rank the compounds in each of the following sets in order of their expected reactivity toward nucleophilic acyl substitution:

a. CH_3CCl, CH_3COCH_3, CH_3CNH_2

b. $CH_3COCH_2CH_3$, $CH_3COCH_2CCl_3$, $CH_3COCH(CF_3)_2$

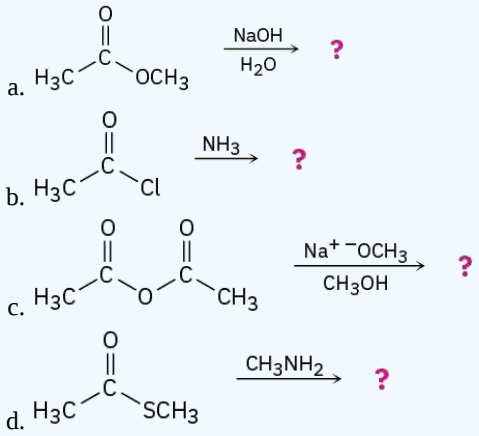
Answer

a. Acetyl chloride > Methyl acetate > Acetamide

b. Hexafluoroisopropyl acetate > 2,2,2-Trichloroethyl acetate > Ethyl acetate

Exercise 10.3.3

Predict the products of the following nucleophilic acyl substitution reactions:



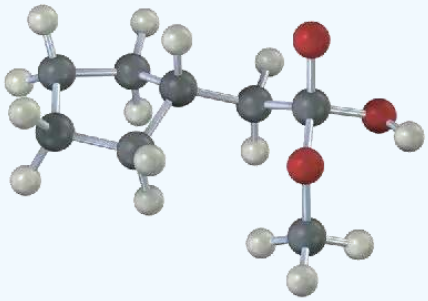
Answer

a. $CH_3CO_2^-\ Na^+$

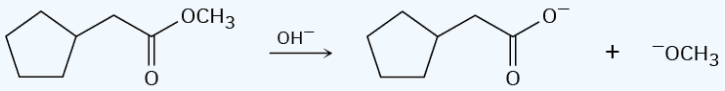
b. CH_3CONH_2
c. $CH_3CO_2CH_3 + CH_3CO_2^- Na^+$
d. $CH_3CONHCH_3$

? Exercise 10.3.4

The following structure represents a tetrahedral alkoxide ion intermediate formed by addition of a nucleophile to a carboxylic acid derivative. Identify the nucleophile, the leaving group, the starting acid derivative, and the ultimate product.



Answer



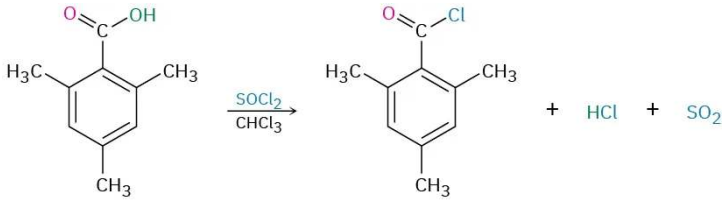
This page titled 10.3: Nucleophilic Acyl Substitution Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

10.4: Reactions of Carboxylic Acids

The direct nucleophilic acyl substitution of a carboxylic acid is difficult because –OH is a poor leaving group (Section 11.3). Thus, it's usually necessary to enhance the reactivity of the acid, either by using a strong acid catalyst to protonate the carboxyl and make it a better acceptor or by converting the –OH into a better leaving group. Under the right circumstances, however, acid chlorides, anhydrides, esters, and amides can all be prepared from carboxylic acids by nucleophilic acyl substitution reactions.

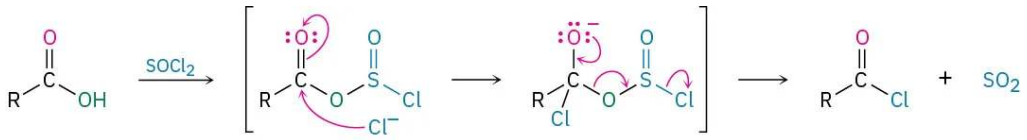
Conversion of Carboxylic Acids into Acid Chlorides

In the laboratory, carboxylic acids are converted into acid chlorides by treatment with thionyl chloride, $SOCl_2$.



2,4,6-Trimethylbenzoic acid **2,4,6-Trimethylbenzoyl chloride (90%)**

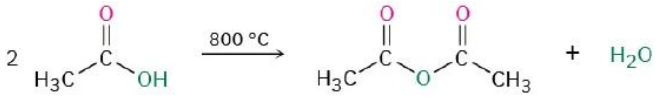
This reaction occurs by a nucleophilic acyl substitution pathway in which the carboxylic acid is first converted into an acyl chlorosulfite intermediate, thereby replacing the –OH of the acid with a much better leaving group. The chlorosulfite then reacts with a nucleophilic chloride ion. You might recall from Section 17.6 that an analogous chlorosulfite is involved in the reaction of an alcohol with $SOCl_2$ to yield an alkyl chloride.



Carboxylic acid **A chlorosulfite** **Acid chloride**

Conversion of Carboxylic Acids into Acid Anhydrides

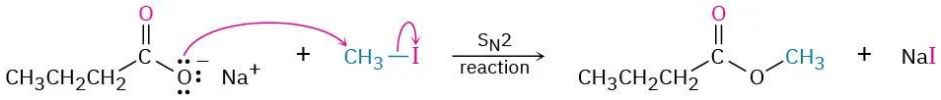
Acid anhydrides can be derived from two molecules of carboxylic acid by heating to remove 1 equivalent of water. Because of the high temperatures needed, however, only acetic anhydride is commonly prepared this way.



Acetic acid **Acetic anhydride**

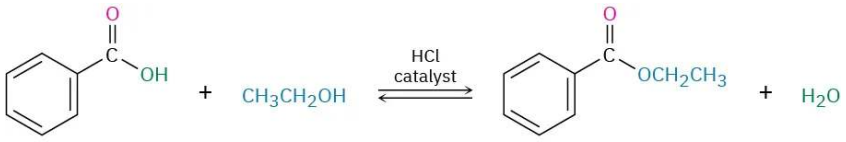
Conversion of Carboxylic Acids into Esters

Perhaps the most useful reaction of carboxylic acids is their conversion into esters. There are many methods for accomplishing this, including the S_N2 reaction of a carboxylate anion with a primary alkyl halide that we saw in Section 11.3.



Sodium butanoate **Methyl butanoate (97%)**

Esters can also be synthesized by an acid-catalyzed nucleophilic acyl substitution reaction of a carboxylic acid with an alcohol, a process called the Fischer esterification reaction. Unfortunately, the need for an excess of a liquid alcohol as solvent effectively limits the method to the synthesis of methyl, ethyl, propyl, and butyl esters.



Benzoic acid **Ethyl benzoate (91%)**

The mechanism of the Fischer esterification reaction is shown in Figure 10.4.1. Carboxylic acids are not reactive enough to undergo nucleophilic addition directly, but their reactivity is greatly enhanced in the presence of a strong acid such as HCl or H_2SO_4. The mineral acid protonates the carbonyl-group oxygen atom, thereby giving the carboxylic acid a positive charge and rendering it much more reactive toward nucleophiles. Subsequent loss of water from the tetrahedral intermediate yields the ester product.

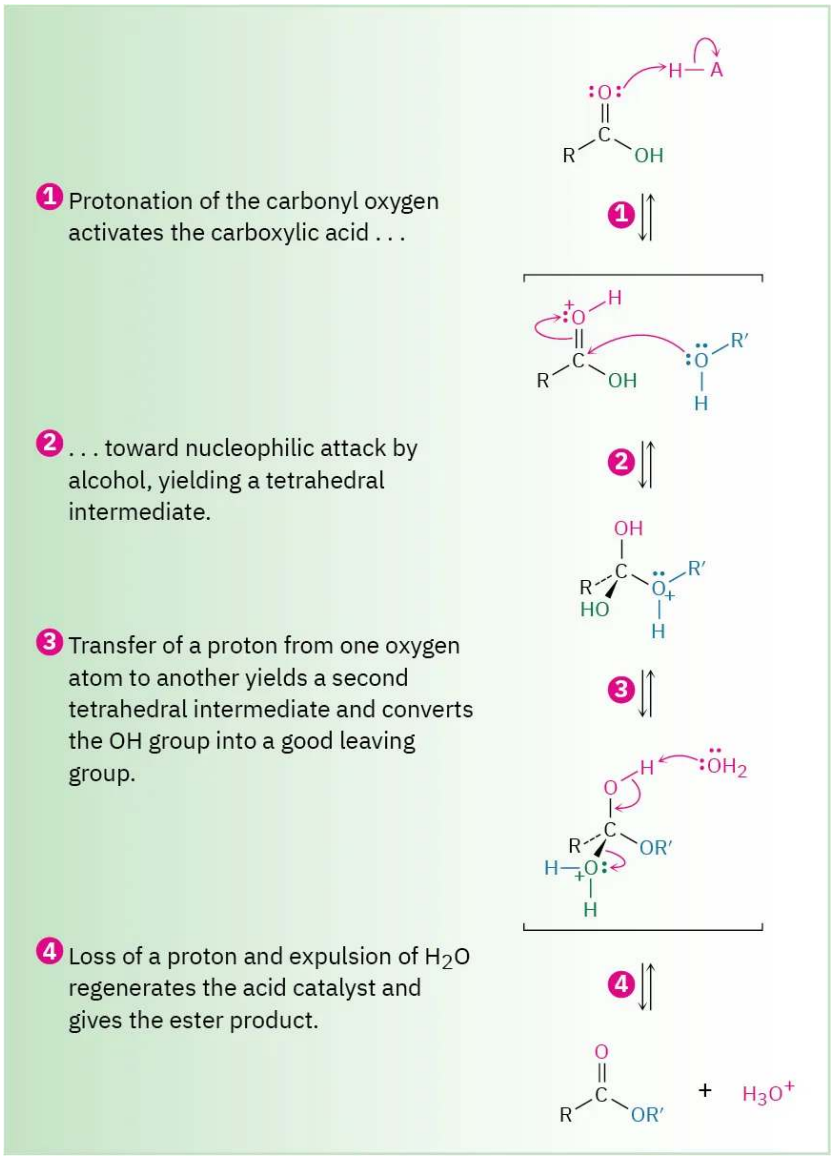
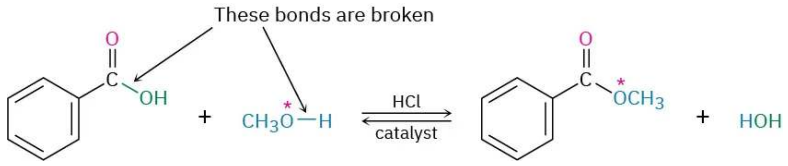


Figure 10.4.1: Mechanism of Fischer esterification. The reaction is an acid-catalyzed, nucleophilic acyl substitution of a carboxylic acid.

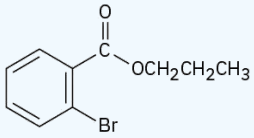
The net effect of Fischer esterification is substitution of an –OH group by –OR′. All steps are reversible, and the reaction typically has an equilibrium constant close to 1. Thus, the reaction can be driven in either direction by the choice of reaction conditions. Ester formation is favored when a large excess of alcohol is used as solvent, but carboxylic acid formation is favored when a large excess of water is present.

Evidence in support of the mechanism shown in Figure 10.4.1 comes from isotope-labeling experiments. When ^{18}O-labeled methanol reacts with benzoic acid, the methyl benzoate produced is found to be ^{18}O-labeled whereas the water produced is unlabeled. Thus, it is the C–OH bond of the carboxylic acid that is broken during the reaction rather than the CO–H bond and the RO–H bond of the alcohol that is broken rather than the R–OH bond.



Worked Example 10.4.1: Synthesizing an Ester from an Acid

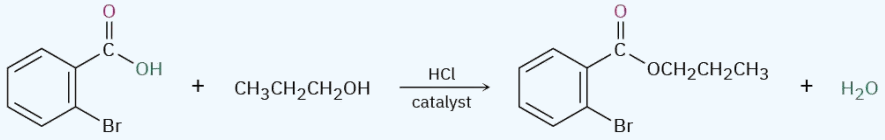
How might you prepare the following ester using a Fischer esterification reaction?



Strategy

Begin by identifying the two parts of the ester. The acyl part comes from the carboxylic acid and the –OR part comes from the alcohol. In this case, the target molecule is propyl *o*-bromobenzoate, so it can be prepared by treating *o*-bromobenzoic acid with 1-propanol.

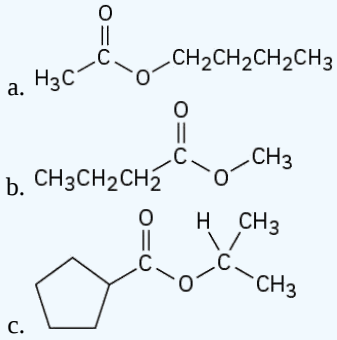
Solution



***o*-Bromobenzoic acid** **1-Propanol** **Propyl *o*-bromobenzoate**

Exercise 10.4.1

How might you prepare the following esters from the corresponding acids?

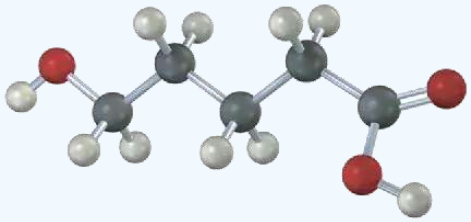


Answer

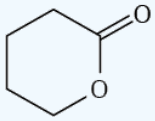
a. Acetic acid + 1-butanol
b. Butanoic acid + methanol
c. Cyclopentanecarboxylic acid + isopropyl alcohol

Exercise 10.4.2

If the following molecule is treated with acid catalyst, an intramolecular esterification reaction occurs. What is the structure of the product? (*Intramolecular* means within the same molecule.)

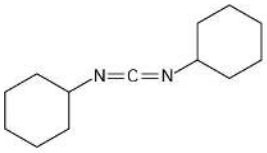


Answer

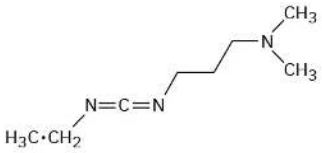


Conversion of Carboxylic Acids into Amides

Amides are difficult to prepare by direct reaction of carboxylic acids with amines because amines are bases that convert acidic carboxyl groups into their unreactive carboxylate anions. Thus, the –OH must be replaced by a better, nonacidic leaving group to carry out a nucleophilic acyl substitution. In practice, amides are often prepared by activating the carboxylic acid with a carbodiimide (R–N=C=N–R), followed by addition of the amine. Dicyclohexylcarbodiimide (DCC) and 1-ethyl-3-(3-dimethylaminopropylcarbodiimide (EDEC) are commonly used.



Dicyclohexylcarbodiimide



1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide

As shown in Figure 10.4.2, the acid first adds to a C=N double bond of DCC, and nucleophilic acyl substitution by amine then ensues. Alternatively, and depending on the reaction solvent, the reactive acyl intermediate might also react with a second equivalent of carboxylate ion to generate an acid anhydride that then reacts with the amine. The product from either pathway is the same.

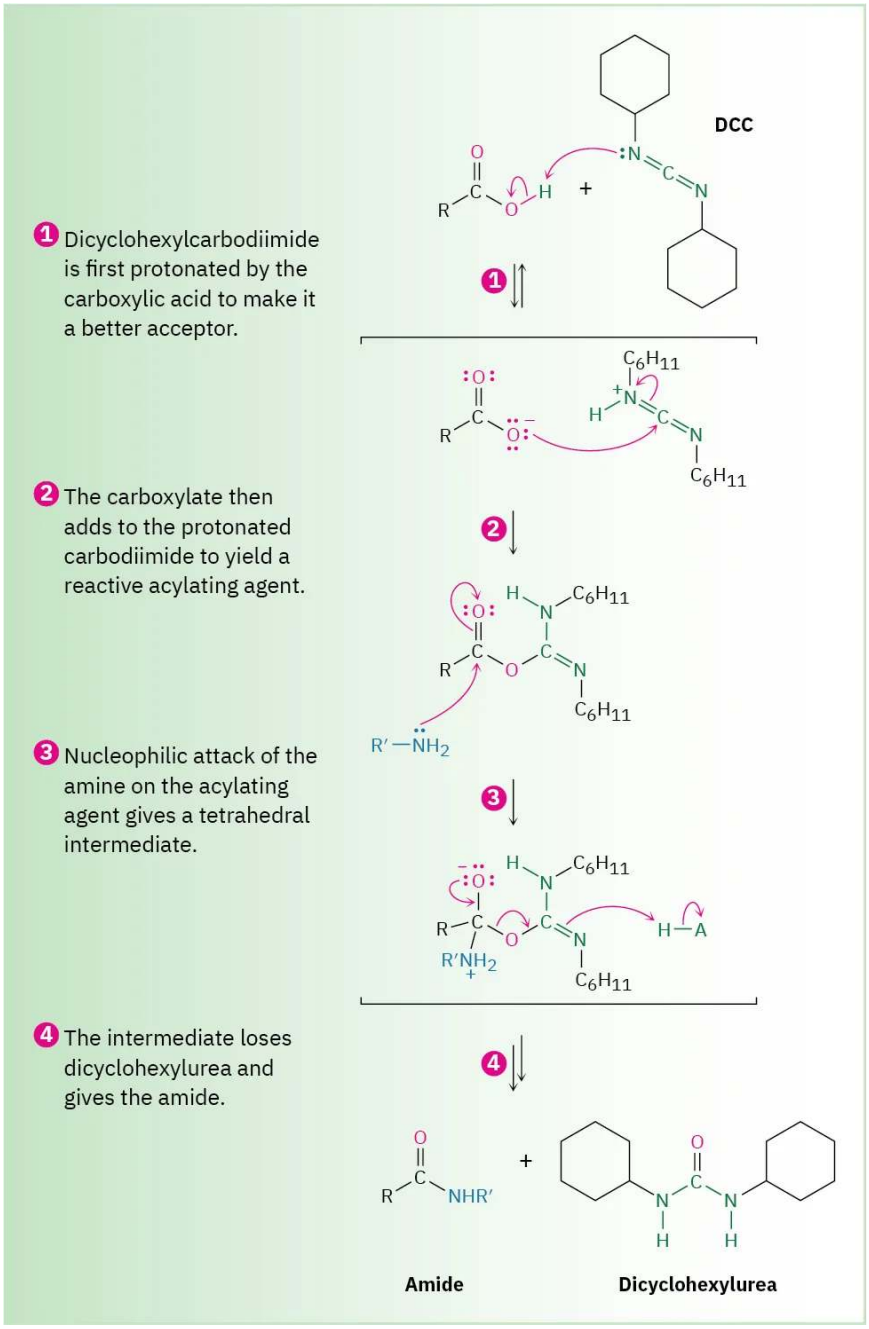
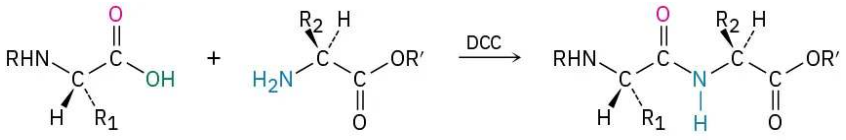


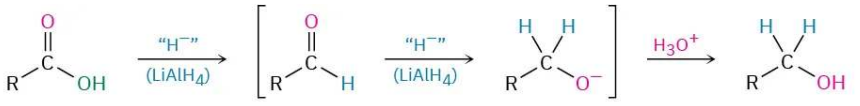
Figure 10.4.2: Mechanism of amide formation by reaction of a carboxylic acid and an amine with dicyclohexylcarbodiimide (DCC).

We'll see in **Section 26.7** that this carbodiimide method of amide formation is the key step in the laboratory synthesis of small proteins, or *peptides*. For instance, when one amino acid with its NH_2 rendered unreactive and a second amino acid with its $–CO_2H$ rendered unreactive are treated with carbodiimide, a dipeptide is formed.



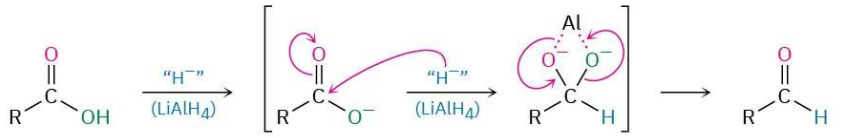
Conversion of Carboxylic Acids into Alcohols

We said in Section 17.4 that carboxylic acids are reduced by $LiAlH_4$ to give primary alcohols, but we deferred a discussion of the reaction mechanism at that time. In fact, the reduction is a nucleophilic acyl substitution reaction in which –H replaces –OH to give an aldehyde that is further reduced by nucleophilic addition to produce a primary alcohol. The aldehyde intermediate is much more reactive than the starting acid, so it reacts instantly and is not isolated.



A carboxylic acid | **An aldehyde (not isolated)** | **An alkoxide ion** | **A 1° alcohol**

Because hydride ion is a base as well as a nucleophile, the actual nucleophilic acyl substitution step takes place on the carboxylate ion rather than on the free carboxylic acid and gives a high-energy **dianion** intermediate. In this intermediate, the two oxygens are complexed to a Lewis acidic aluminum species. Thus, the reaction is relatively difficult, and acid reductions require higher temperatures and extended reaction times.



A carboxylic acid | **A carboxylate** | **A dianion** | **An aldehyde**

Alternatively, borane in tetrahydrofuran (BH_3/THF) is a useful reagent for reducing carboxylic acids to primary alcohols. Reaction of an acid with BH_3/THF occurs rapidly at room temperature, and the procedure is often preferred to reduction with $LiAlH_4$ because of its relative ease and safety. Borane reacts with carboxylic acids faster than with any other functional group, thereby allowing selective transformations such as that on *p*-nitrophenylacetic acid. If the reduction of *p*-nitrophenylacetic acid were done with $LiAlH_4$, both the nitro and carboxyl groups would be reduced.

***p*-Nitrophenylacetic acid** | **2-(*p*-Nitrophenyl)ethanol (94%)**

Biological Conversions of Carboxylic Acids

The direct conversion of a carboxylic acid to an acyl derivative by nucleophilic acyl substitution does not occur in biological chemistry. As in the laboratory, the acid must first be activated by converting the –OH into a better leaving group. This activation is often accomplished in living organisms by reaction of the acid with adenosine triphosphate (ATP) to give an acyl adenosyl phosphate, or *acyl adenylate*, a mixed anhydride combining a carboxylic acid and adenosine monophosphate (AMP, also known as adenylic acid). In the biosynthesis of fats, for example, a long-chain carboxylic acid reacts with ATP to give an acyl adenylate, followed by subsequent nucleophilic acyl substitution of a thiol group in coenzyme A to give the corresponding acyl CoA (Figure 10.4.3).

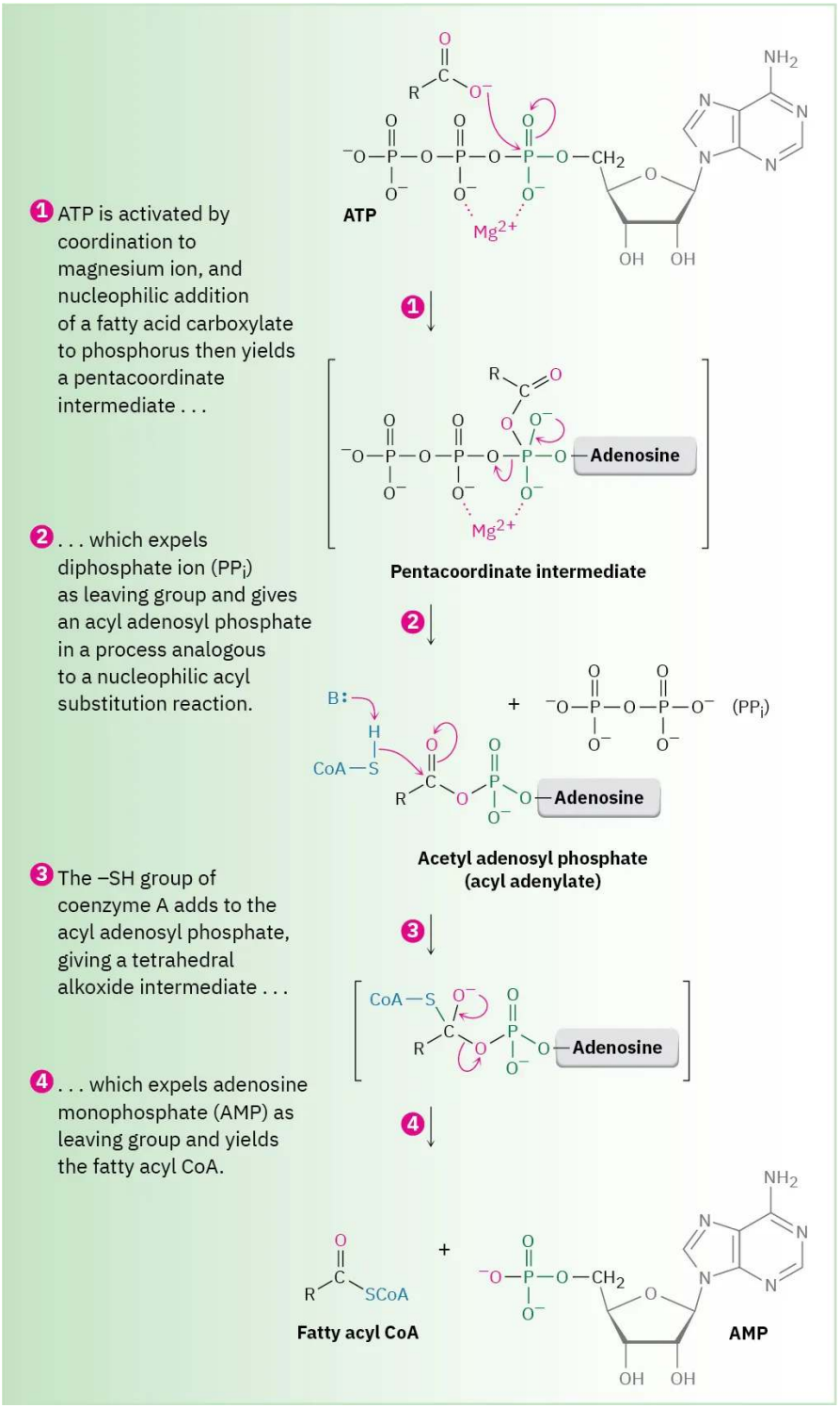


Figure 10.4.3: In fatty-acid biosynthesis, a carboxylic acid is activated by reaction with ATP to give an acyl adenylate, which undergoes nucleophilic acyl substitution with the –SH group on coenzyme A. (ATP = adenosine triphosphate; AMP = adenosine monophosphate.)

Note that the first step in Figure 10.4.3—reaction of the carboxylate with ATP to give an acyl adenylate—is itself a nucleophilic acyl substitution *on phosphorus*. The carboxylate first adds to a P=O double bond, giving a five-coordinate phosphorus intermediate that expels diphosphate ion as a leaving group.

This page titled 10.4: Reactions of Carboxylic Acids is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **21.3: Reactions of Carboxylic Acids** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

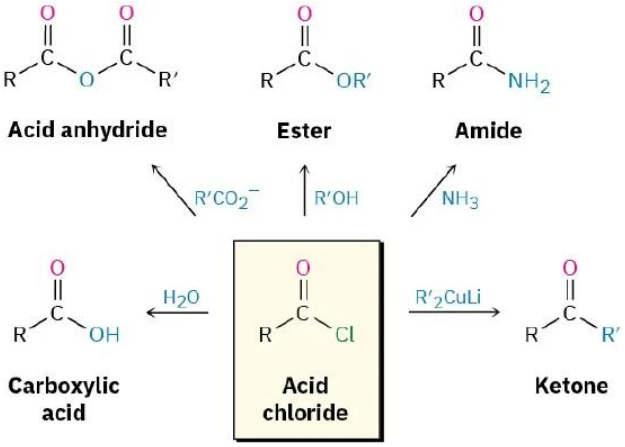
10.5: Chemistry of Acid Halides

Preparation of Acid Halides

Acid chlorides are prepared from carboxylic acids by reaction with thionyl chloride ($SOCl_2$), as we saw in the previous section. Similar reaction of a carboxylic acid with phosphorus tribromide (PBr_3) yields the acid bromide.

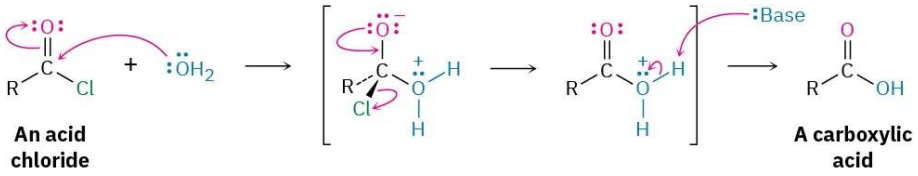
Reactions of Acid Halides

Acid halides are among the most reactive of carboxylic acid derivatives and can be converted into many other kinds of compounds by nucleophilic acyl substitution mechanisms. The halogen can be replaced by –OH to yield an acid, by –OCOR to yield an anhydride, by –OR to yield an ester, by $–NH_2$ to yield an amide, or by R′ to yield a ketone. In addition, the reduction of an acid halide yields a primary alcohol, and reaction with a Grignard reagent yields a tertiary alcohol. Although the reactions we'll be discussing in this section are illustrated only for acid chlorides, similar processes take place with other acid halides.



Conversion of Acid Halides into Carboxylic Acids: Hydrolysis

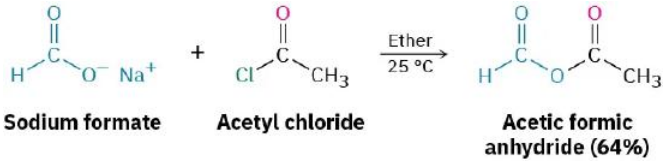
Acid chlorides react with water to yield carboxylic acids. This hydrolysis reaction is a typical nucleophilic acyl substitution process and is initiated by attack of water on the acid chloride carbonyl group. The tetrahedral intermediate undergoes elimination of Cl^- and loss of H^+ to give the product carboxylic acid plus HCl.



Because HCl is formed during hydrolysis, the reaction is often carried out in the presence of a base such as pyridine or NaOH to remove the HCl and prevent it from causing side reactions.

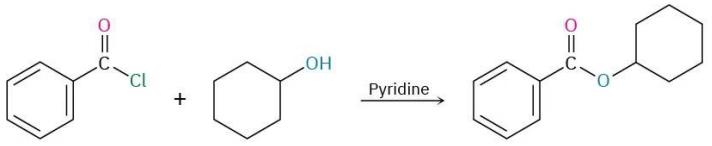
Conversion of Acid Halides into Anhydrides

Nucleophilic acyl substitution reaction of an acid chloride with a carboxylate anion gives an acid anhydride. Both symmetrical and unsymmetrical acid anhydrides can be prepared.



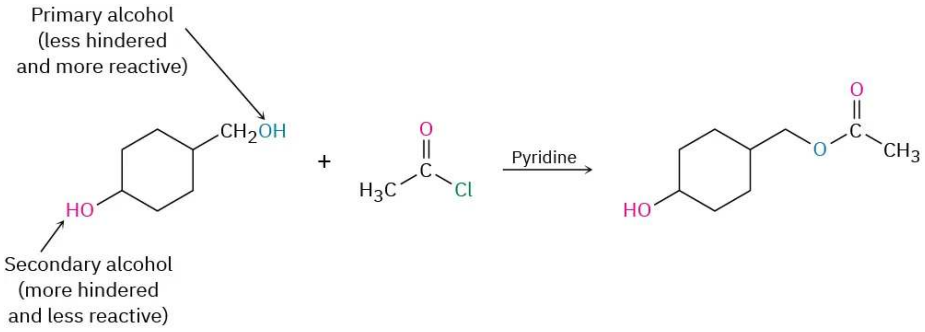
Conversion of Acid Halides into Esters: Alcoholysis

Acid chlorides react with alcohols to yield esters in a process analogous to their reaction with water to yield acids. In fact, this reaction is probably the most common method for preparing esters in the laboratory. As with hydrolysis, alcoholysis reactions are usually carried out in the presence of pyridine or NaOH to react with the HCl formed.



Benzoyl chloride **Cyclohexanol** **Cyclohexyl benzoate (97%)**

The reaction of an alcohol with an acid chloride is strongly affected by steric hindrance. Bulky groups on either partner slow down the reaction considerably, resulting in a reactivity order among alcohols of primary > secondary > tertiary. As a result, it's often possible to selectively esterify an unhindered alcohol in the presence of a more hindered one. This can be important in complex syntheses in which it's sometimes necessary to distinguish between similar functional groups. For example,



Exercise 10.5.1

Add exercises text here.

a. $CH_3CH_2CO_2CH_3$
b. $CH_3CO_2CH_2CH_3$
c. Ethyl benzoate

Answer

a. Propanoyl chloride + methanol
b. Acetyl chloride + ethanol
c. Benzoyl chloride + ethanol

Exercise 10.5.2

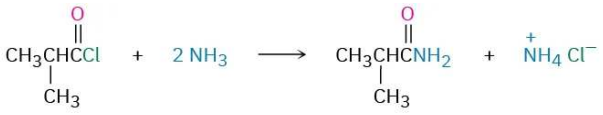
Which method would you choose if you wanted to prepare cyclohexyl benzoate—Fischer esterification or reaction of an acid chloride with an alcohol? Explain.

Answer

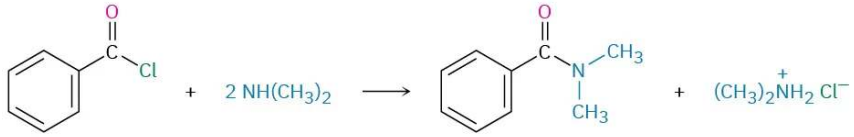
Benzoyl chloride + cyclohexanol

Conversion of Acid Halides into Amides: Aminolysis

Acid chlorides react rapidly with ammonia and amines to give amides. As with the acid chloride-plus-alcohol method for preparing esters, this reaction of acid chlorides with amines is the most commonly used laboratory method for preparing amides. Both monosubstituted and disubstituted amines can be used, but not trisubstituted amines (R_3N).

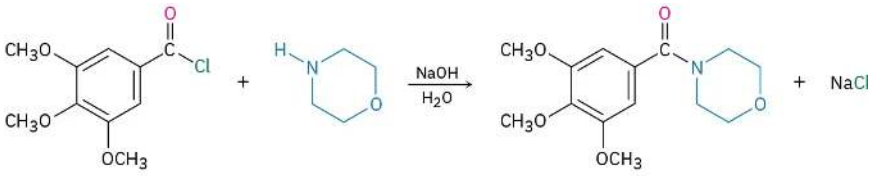


2-Methylpropanoyl chloride | **2-Methylpropanamide (83%)**



Benzoyl chloride | ***N,N*-Dimethylbenzamide (92%)**

Because HCl is formed during the reaction, two equivalents of the amine must be used. One equivalent reacts with the acid chloride, and one equivalent reacts with the HCl by-product to form an ammonium chloride salt. If, however, the amine component is valuable, amide synthesis is often carried out using one equivalent of the amine plus one equivalent of an inexpensive base such as NaOH. For example, the sedative trimetozine is prepared commercially by reaction of 3,4,5-trimethoxybenzoyl chloride with the amine morpholine in the presence of one equivalent of NaOH.



3,4,5-Trimethoxy-benzoyl chloride | **Morpholine** | **Trimetozine (an amide)**

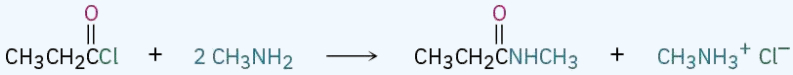
✔ Worked Example 10.5.1: Synthesizing an Amide from an Acid Chloride

How might you prepare *N*-methylpropanamide by reaction of an acid chloride with an amine?

Strategy

As its name implies, *N*-methylpropanamide can be made by reaction of *methylamine* with the acid chloride of *propanoic* acid.

Solution



Propanoyl chloride | **Methylamine** | ***N*-Methylpropanamide**

? Exercise 10.5.3

Write the mechanism of the reaction just shown between 3,4,5-trimethoxybenzoyl chloride and morpholine to form trimetozine. Use curved arrows to show the electron flow in each step.

Answer

This is a typical nucleophilic acyl substitution reaction, with morpholine as the nucleophile and chloride as the leaving group.

? Exercise 10.5.4

Write the mechanism of the reaction just shown between 3,4,5-trimethoxybenzoyl chloride and morpholine to form trimetozine. Use curved arrows to show the electron flow in each step.

a. $CH_3CH_2CONHCH_3$

b. N,N-Diethylbenzamide
c. Propanamide

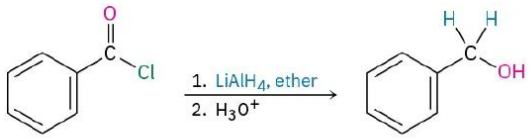
Answer

a. Propanoyl chloride + methylamine
b. Benzoyl chloride + diethylamine
c. Propanoyl chloride + ammonia

Conversion of Acid Chlorides into Alcohols: Reduction and Grignard Reaction

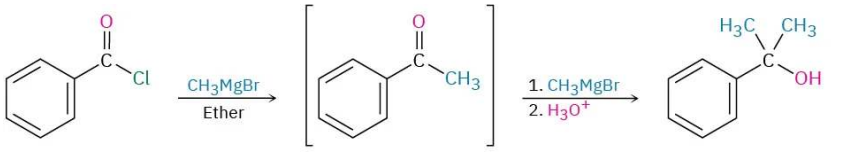
Acid chlorides are reduced by $LiAlH_4$ to yield primary alcohols. The reaction is of little practical value, however, because the parent carboxylic acids are generally more readily available and can themselves be reduced by $LiAlH_4$ to yield alcohols.

Reduction occurs via a typical nucleophilic acyl substitution mechanism in which a hydride ion ($H:^-$) adds to the carbonyl group, yielding a tetrahedral intermediate that expels Cl^-. The net effect is a substitution of –Cl by –H to yield an aldehyde, which is then further reduced by $LiAlH_4$ in a second step to yield the primary alcohol.



Benzoyl chloride **Benzyl alcohol (96%)**

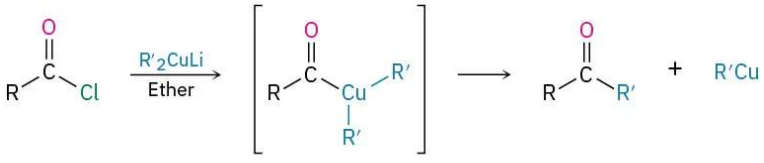
Grignard reagents react with acid chlorides to yield tertiary alcohols with two identical substituents. The mechanism of the reaction is similar to that of $LiAlH_4$ reduction. The first equivalent of Grignard reagent adds to the acid chloride, loss of Cl^- from the tetrahedral intermediate yields a ketone, and a second equivalent of Grignard reagent immediately adds to the ketone to produce an alcohol.



Benzoyl chloride **Acetophenone** ***(Not isolated)*** **2-Phenyl-2-propanol (92%)**

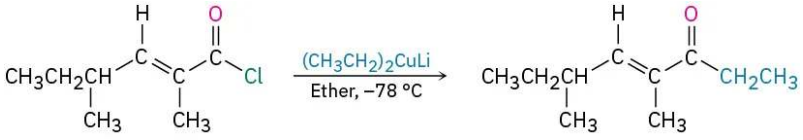
Conversion of Acid Chlorides into Ketones: Diorganocopper Reaction

The ketone intermediate formed in the reaction of an acid chloride with a Grignard reagent can't usually be isolated because addition of the second equivalent of organomagnesium reagent occurs too rapidly. A ketone *can*, however, be isolated from the reaction of an acid chloride with a lithium diorganocopper (Gilman) reagent, $Li^+ R'_2Cu^-$. The reaction occurs by initial nucleophilic acyl substitution on the acid chloride by the diorganocopper anion to yield an acyl diorganocopper intermediate, followed by loss of R′Cu and formation of the ketone.



An acid chloride **An acyl diorganocopper** **A ketone**

The reaction is generally carried out at –78 °C in ether solution, and yields are often excellent. For example, manicone, a substance secreted by male ants to coordinate ant pairing and mating, has been synthesized by reaction of lithium diethylcopper with (*E*)-2,4-dimethyl-2-hexenoyl chloride.



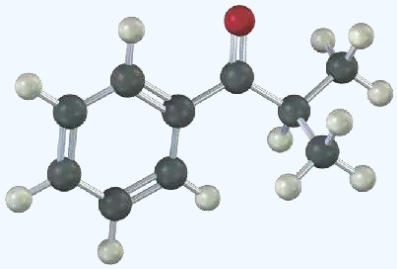
2,4-Dimethyl-2-hexenoyl chloride **4,6-Dimethyl-4-octen-3-one (manicone, 92%)**

Note that the diorganocopper reaction occurs only with acid chlorides. Carboxylic acids, esters, acid anhydrides, and amides do not react with lithium diorganocopper reagents.

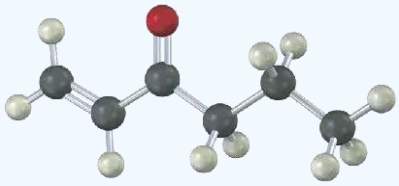
? Exercise 10.5.5

How could you prepare the following ketones by reaction of an acid chloride with a lithium diorganocopper reagent?

a.



b.



Answer

a. Benzoyl chloride + $[(CH_3)_2CH]_2CuLi$, or 2-methylpropanoyl chloride + Ph_2CuLi

b. 2-Propenoyl chloride + $(CH_3CH_2CH_2)_2CuLi$, or butanoyl chloride + $(H_2C{=}CH)_2CuLi$

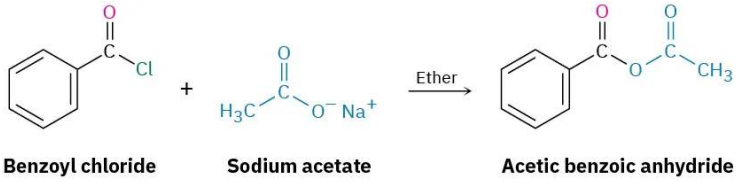
This page titled 10.5: Chemistry of Acid Halides is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **21.4: Chemistry of Acid Halides** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

10.6: Chemistry of Acid Anhydrides

Preparation of Acid Anhydrides

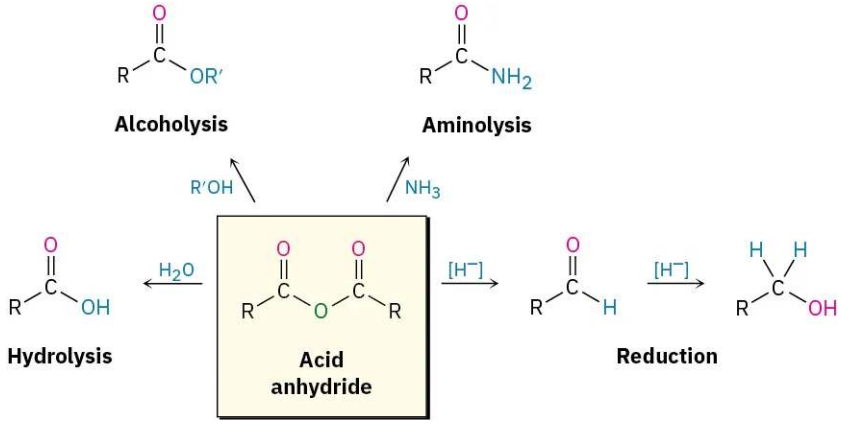
Acid anhydrides are typically prepared by nucleophilic acyl substitution reaction of an acid chloride with a carboxylate anion, as we saw in the previous section. Both symmetrical and unsymmetrical acid anhydrides can be prepared in this way.



Benzoyl chloride **Sodium acetate** **Acetic benzoic anhydride**

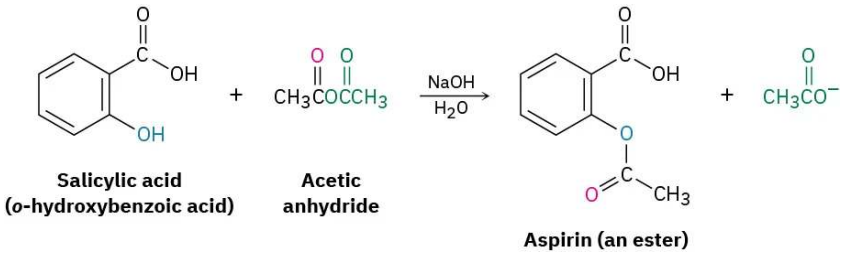
Reactions of Acid Anhydrides

The chemistry of acid anhydrides is similar to that of acid chlorides, although anhydrides react more slowly. Thus, acid anhydrides react with water to form acids, with alcohols to form esters, with amines to form amides, and with $LiAlH_4$ to form primary alcohols. Only the ester- and amide-forming reactions are commonly used, however.



Conversion of Acid Anhydrides into Esters

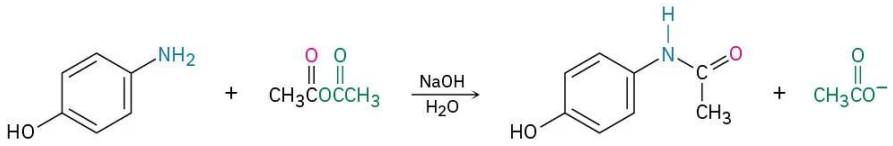
Acetic anhydride is often used to prepare acetate esters from alcohols. For example, aspirin (acetylsalicylic acid) is prepared commercially by the acetylation of *o*-hydroxybenzoic acid (salicylic acid) with acetic anhydride.



Salicylic acid (*o*-hydroxybenzoic acid) **Acetic anhydride** **Aspirin (an ester)**

Conversion of Acid Anhydrides into Amides

Acetic anhydride is also commonly used to prepare *N*-substituted acetamides from amines. For example, acetaminophen, a drug used in over-the-counter analgesics such as Tylenol, is prepared by reaction of *p*-hydroxyaniline with acetic anhydride. Only the more nucleophilic $–NH_2$ group reacts rather than the less nucleophilic –OH group.



p-Hydroxyaniline | **Acetic anhydride** | **Acetaminophen**

Notice in both of the previous reactions that only “half” of the anhydride molecule is used, while the other half acts as the leaving group during the nucleophilic acyl substitution step and produces acetate ion as a by-product. Thus, anhydrides are inefficient, and acid chlorides are normally preferred for introducing acyl substituents other than acetyl groups.

? Exercise 10.6.1

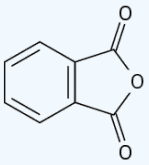
Write the mechanism of the reaction between p-hydroxyaniline and acetic anhydride to prepare acetaminophen.

Answer

This is a typical nucleophilic acyl substitution reaction, with *p*-hydroxyaniline as the nucleophile and acetate ion as the leaving group.

? Exercise 10.6.2

What product would you expect from reaction of one equivalent of methanol with a cyclic anhydride, such as phthalic anhydride (1,2-benzenedicarboxylic anhydride)? What is the fate of the second “half” of the anhydride?



Phthalic anhydride

Answer

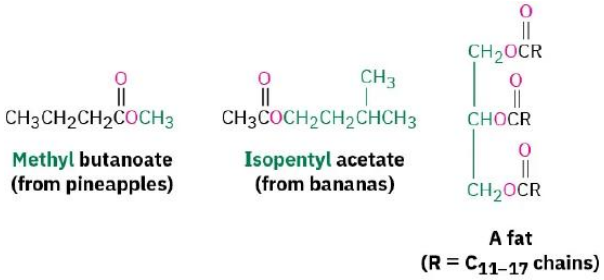
Monomethyl ester of benzene-1,2-dicarboxylic acid

This page titled 10.6: Chemistry of Acid Anhydrides is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

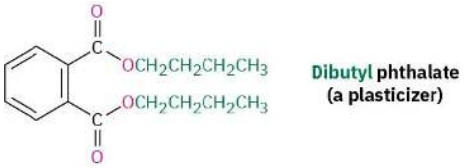
- **21.5: Chemistry of Acid Anhydrides** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

10.7: Chemistry of Esters

Esters are among the most widespread of all naturally occurring compounds. Many simple esters are pleasant-smelling liquids that are responsible for the fragrant odors of fruits and flowers. For example, methyl butanoate is found in pineapple oil, and isopentyl acetate is a constituent of banana oil. The ester linkage is also present in animal fats and in many biologically important molecules.

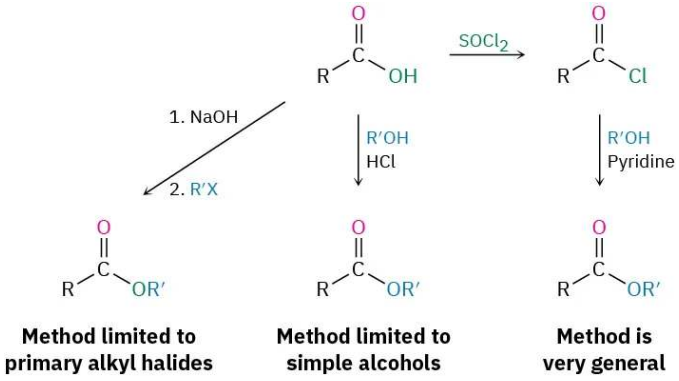


The chemical industry uses esters for a variety of purposes. Ethyl acetate, for instance, is a commonly used solvent, and dialkyl phthalates are used as plasticizers to keep polymers from becoming brittle. You may be aware that there is current concern about the possible toxicity of phthalates at high concentrations, although a recent assessment by the U.S. Food and Drug Administration found the risk to be minimal for most people, with the possible exception of male infants.



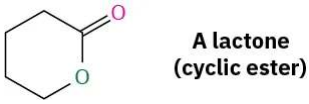
Preparation of Esters

Esters are usually prepared from carboxylic acids by the methods already discussed. Thus, carboxylic acids are converted directly into esters by S_N2 reaction of a carboxylate ion with a primary alkyl halide or by Fischer esterification of a carboxylic acid with an alcohol in the presence of a mineral acid catalyst. In addition, acid chlorides are converted into esters by treatment with an alcohol in the presence of base (Section 21.4).



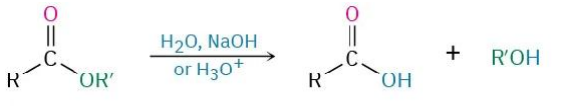
Reactions of Esters

Esters undergo the same kinds of reactions that we've seen for other carboxylic acid derivatives, but they are less reactive toward nucleophiles than either acid chlorides or anhydrides. All their reactions are applicable to both acyclic and cyclic esters, called lactones.



Conversion of Esters into Carboxylic Acids: Hydrolysis

An ester is hydrolyzed, either by aqueous base or aqueous acid, to yield a carboxylic acid plus an alcohol.



Ester **Acid** **Alcohol**

Ester hydrolysis in basic solution is called saponification, after the Latin word *sapo*, meaning "soap." We'll see in **Section 27.2** that soap is in fact made by boiling animal fat with aqueous base to hydrolyze the ester linkages.

As shown in Figure 10.7.1, ester hydrolysis occurs through a typical nucleophilic acyl substitution pathway in which hydroxide ion is the nucleophile that adds to the ester carbonyl group to give a tetrahedral intermediate. Loss of alkoxide ion then gives a carboxylic acid, which is deprotonated to give the carboxylate ion. Addition of aqueous HCl, in a separate step after the saponification is complete, protonates the carboxylate ion and gives the carboxylic acid.

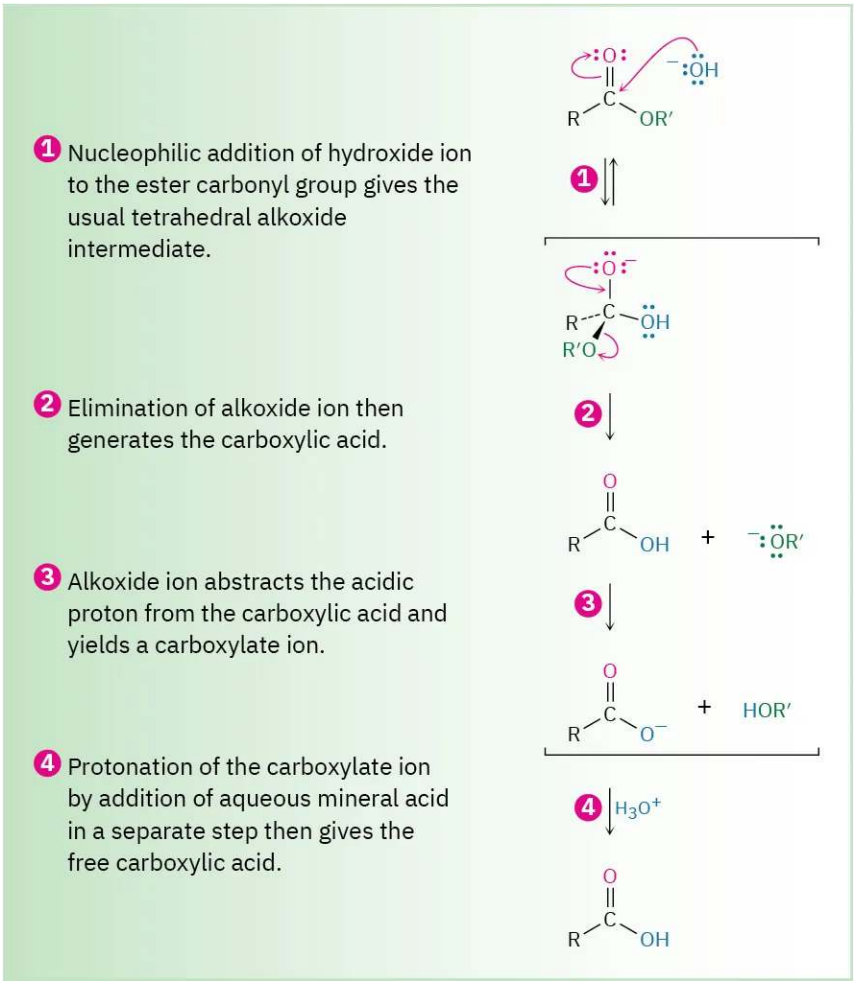
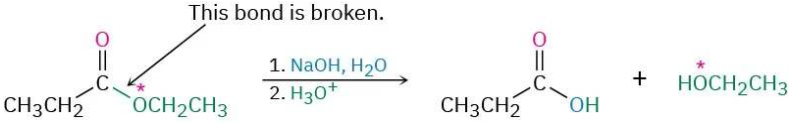


Figure 10.7.1: Mechanism of base-induced ester hydrolysis (saponification).

The mechanism shown in Figure 10.7.1 is supported by isotope-labeling studies. When ethyl propanoate labeled with ^{18}O in the ether-like oxygen is hydrolyzed in aqueous NaOH, the ^{18}O label shows up exclusively in the ethanol product. None of the label remains with the propanoic acid, indicating that saponification occurs by cleavage of the C–OR′ bond rather than the CO–R′ bond.



Acid-catalyzed ester hydrolysis can occur by more than one mechanism, depending on the structure of the ester. The usual pathway, however, is just the reverse of a Fischer esterification reaction (Section 21.3). As shown in Figure 10.7.2, the ester is first activated toward nucleophilic attack by protonation of the carboxyl oxygen atom, and nucleophilic addition of water then occurs. Transfer of a proton and elimination of alcohol yields the carboxylic acid. Because this hydrolysis reaction is the reverse of a Fischer esterification reaction, Figure 10.7.2 is the reverse of Figure 10.7.1.

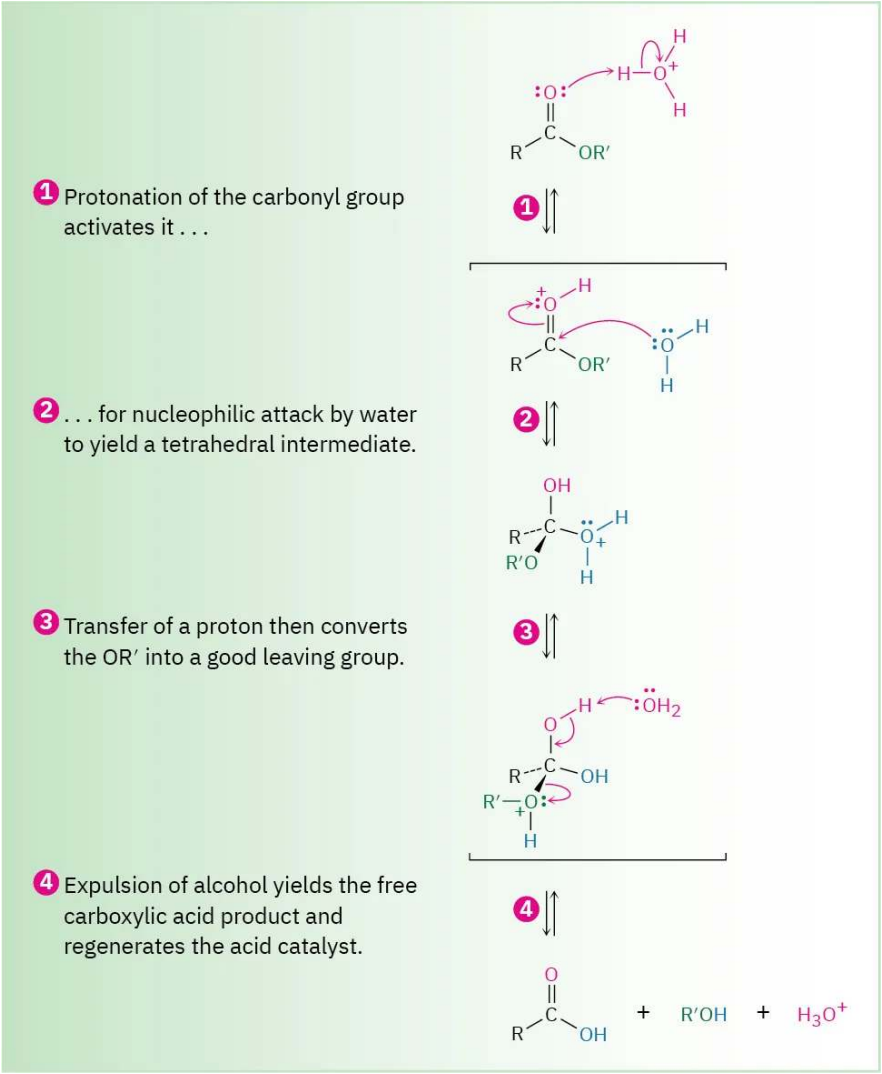
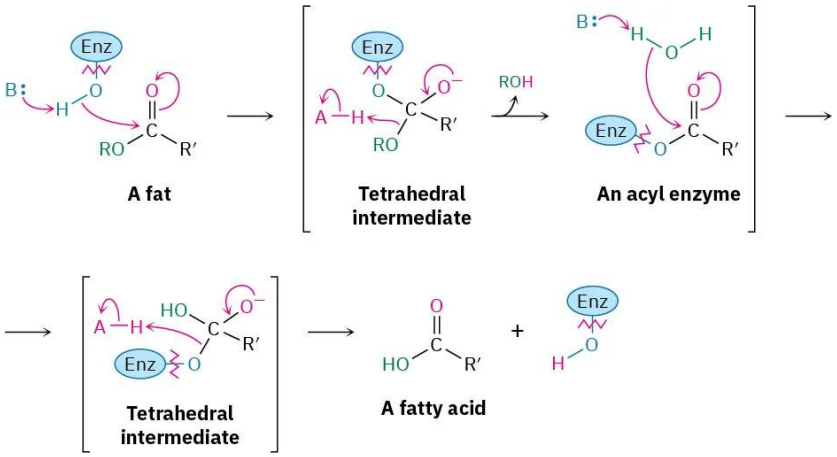


Figure 10.7.2: Mechanism of acid-catalyzed ester hydrolysis. The forward reaction is a hydrolysis; the back-reaction is a Fischer esterification and is thus the reverse of Figure 10.7.1.

Ester hydrolysis is common in biological chemistry, particularly in the digestion of dietary fats and oils. We'll save a complete discussion of the mechanistic details of fat hydrolysis until **Section 29.2** but will note for now that the reaction is catalyzed by various lipase enzymes and involves two sequential nucleophilic acyl substitution reactions. The first is a *transesterification* reaction in which an alcohol group on the lipase adds to an ester linkage in the fat molecule to give a tetrahedral intermediate that expels alcohol and forms an acyl enzyme intermediate. The second is an addition of water to the acyl enzyme, followed by expulsion of the enzyme to give a hydrolyzed acid and a regenerated enzyme.



? Exercise 10.7.1

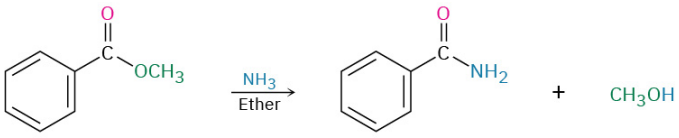
Why is the saponification of an ester irreversible? In other words, why doesn't treatment of a carboxylic acid with an alkoxide ion yield an ester?

Answer

Reaction of a carboxylic acid with an alkoxide ion gives the carboxylate ion.

Conversion of Esters into Amides: Aminolysis

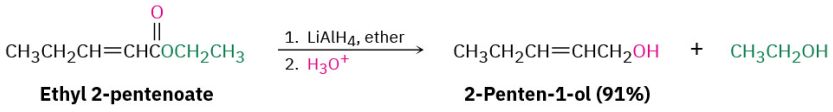
Esters react with ammonia and amines to yield amides. The reaction is not often used, however, because it's usually easier to prepare an amide by starting with an acid chloride (Section 21.4).



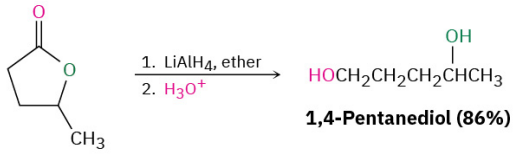
Methyl benzoate **Benzamide**

Conversion of Esters into Alcohols: Reduction

Esters are easily reduced by treatment with $LiAlH_4$ to yield primary alcohols (Section 17.4).

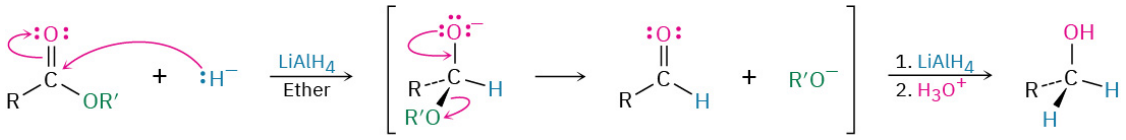


Ethyl 2-pentenoate **2-Penten-1-ol (91%)**



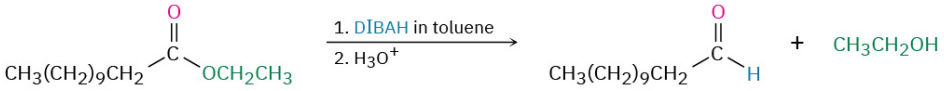
A lactone **1,4-Pentanediol (86%)**

The mechanism of ester reduction is similar to that of acid chloride reduction in that a hydride ion first adds to the carbonyl group, followed by elimination of alkoxide ion to yield an aldehyde. Further reduction of the aldehyde gives the primary alcohol.

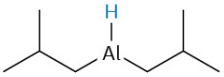


Aldehyde **A primary alcohol**

The aldehyde intermediate can be isolated if 1 equivalent of diisobutylaluminum hydride (DIBAH, or DIBAL-H) is used as the reducing agent instead of $LiAlH_4$. The reaction has to be carried out at –78 °C to avoid further reduction to the alcohol. Such partial reductions of carboxylic acid derivatives to aldehydes also occur in numerous biological pathways, although the substrate is either a thioester or acyl phosphate rather than an ester.

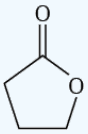


Ethyl dodecanoate **Dodecanal (88%)**

where DIBAH = 

? Exercise 10.7.1

a. What product would you expect from the reaction of butyrolactone with $LiAlH_4$?
b. What product would you expect from the reaction of butyrolactone with DIBAH?



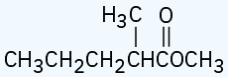
Butyrolactone

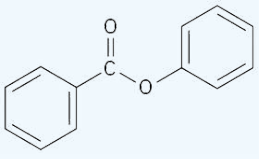
Answer

a. LiAlH4 gives $HOCH_2CH_2CH_2CH_2OH$
b. DIBAH gives $HOCH_2CH_2CH_2CHO$.

? Exercise 10.7.1

Show the products you would obtain by reduction of the following esters with $LiAlH_4$:

a. 

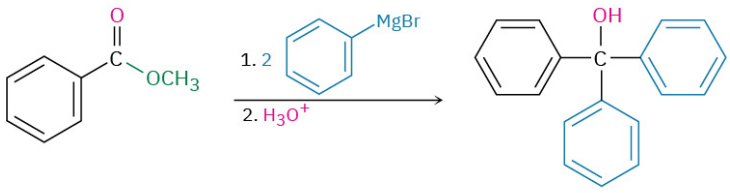
b. 

Answer

a. $CH_3CH_2CH_2CH(CH_3)CH_2OH + CH_3OH$
b. $PhOH + PhCH_2OH$

Conversion of Esters into Alcohols: Grignard Reaction

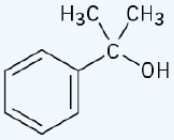
Esters react with 2 equivalents of a Grignard reagent to yield a tertiary alcohol in which two of the substituents are identical (Section 17.5). The reaction occurs by the usual nucleophilic substitution mechanism to give an intermediate ketone, which reacts further with the Grignard reagent to yield a tertiary alcohol.

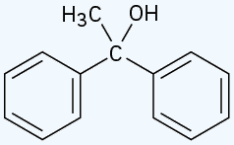


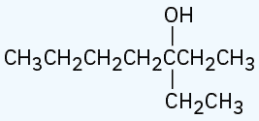
Methyl benzoate **Triphenylmethanol (96%)**

? Exercise 10.7.1

What ester and what Grignard reagent might you start with to prepare the following alcohols?

1. 

2. 

3. 

Answer

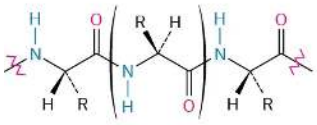
a. Ethyl benzoate + 2 CH_3MgBr
b. Ethyl acetate + 2 $PhMgBr$
c. Ethyl pentanoate + 2 CH_3CH_2MgBr

This page titled 10.7: Chemistry of Esters is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

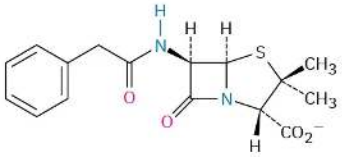
- **21.6: Chemistry of Esters** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

10.8: Chemistry of Amides

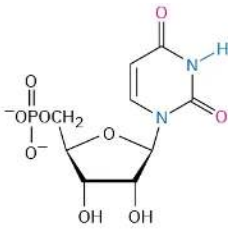
Amides, like esters, are abundant in all living organisms. Proteins, nucleic acids, and many pharmaceutical agents have amide functional groups. The reason for this abundance of amides is that they are stable in the aqueous conditions found in living organisms. Amides are the least reactive of the common acid derivatives and undergo relatively few nucleophilic acyl substitution reactions.



A protein segment



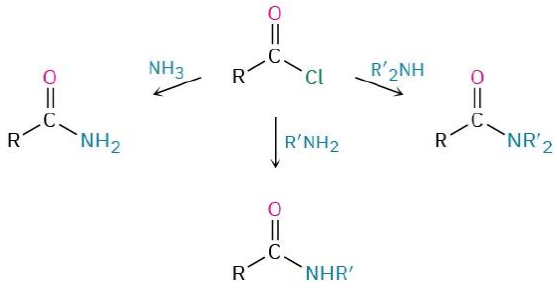
Benzylpenicillin (penicillin G)



Uridine 5′-phosphate (a ribonucleotide)

Preparation of Amides

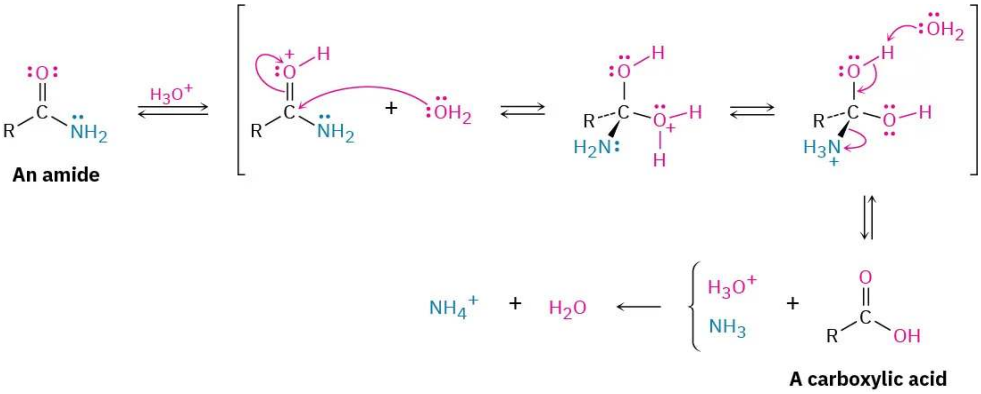
Amides are usually prepared by reaction of an amine with an acid chloride (Section 21.4). Ammonia, monosubstituted amines, and disubstituted amines all undergo the reaction.



Reactions of Amides

Conversion of Amides into Carboxylic Acids: Hydrolysis

Amides undergo hydrolysis to yield carboxylic acids plus ammonia or an amine upon heating in either aqueous acid or aqueous base. The conditions required for amide hydrolysis are more extreme than those required for the hydrolysis of acid chlorides or esters, but the mechanisms are similar. Acidic hydrolysis reaction occurs by nucleophilic addition of water to the protonated amide, followed by transfer of a proton from oxygen to nitrogen to make the nitrogen a better leaving group, and subsequent elimination. The steps are reversible, with the equilibrium shifted toward product by protonation of NH_3 in the final step.

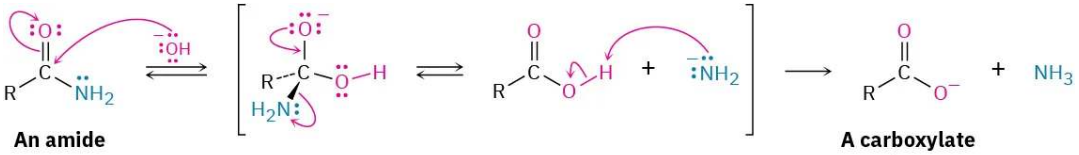


An amide

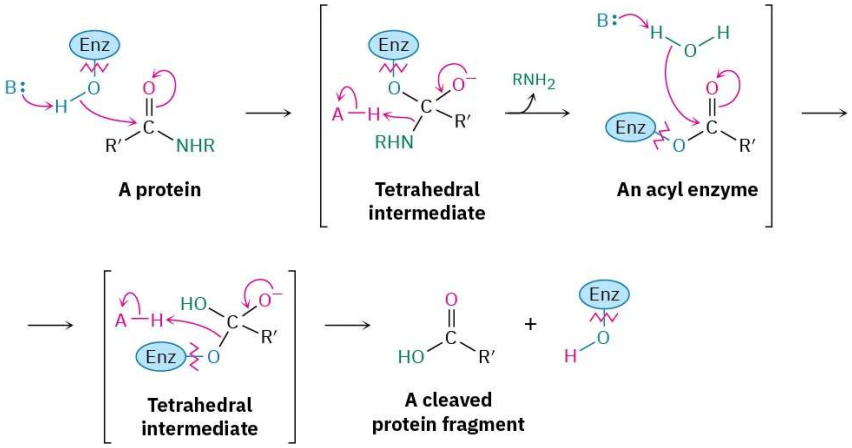
A carboxylic acid

Basic hydrolysis occurs by nucleophilic addition of OH^- to the amide carbonyl group, followed by elimination of amide ion ($^-NH_2$) and subsequent deprotonation of the initially formed carboxylic acid by ammonia. The steps are reversible, with the equilibrium

shifted toward product by the final deprotonation of the carboxylic acid. Basic hydrolysis is substantially more difficult than the analogous acid-catalyzed reaction because amide ion is a very poor leaving group, making the elimination step difficult.

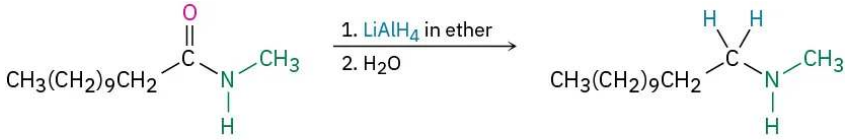


Amide hydrolysis is common in biological chemistry. Just as the hydrolysis of esters is the initial step in the digestion of dietary fats, the hydrolysis of amides is the initial step in the digestion of dietary proteins. The reaction is catalyzed by protease enzymes and occurs by a mechanism almost identical to what we just saw for fat hydrolysis. That is, an initial nucleophilic acyl substitution of an alcohol group in the enzyme on an amide linkage in the protein gives an acyl enzyme intermediate, which then undergoes hydrolysis.

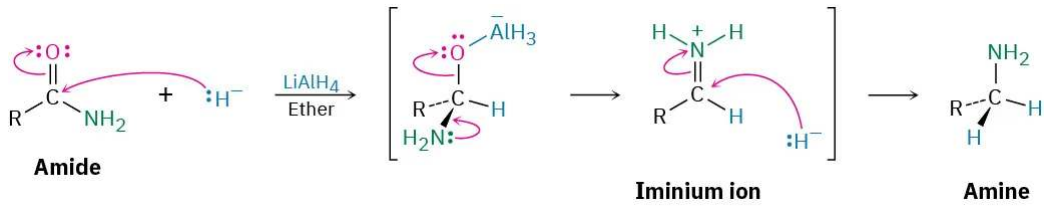


Conversion of Amides into Amines: Reduction

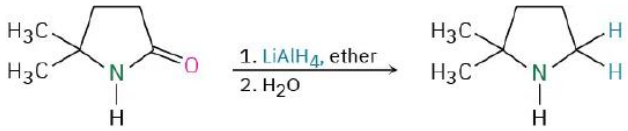
Like other carboxylic acid derivatives, amides can be reduced by $LiAlH_4$. The product of the reduction, however, is an amine rather than an alcohol. The net effect of an amide reduction is thus the conversion of the amide carbonyl group into a methylene group ($C{=}O \longrightarrow CH_2$). This kind of reaction is specific to amides and does not occur with other carboxylic acid derivatives.



Amide reduction occurs by nucleophilic addition of hydride ion to the amide carbonyl group, followed by expulsion of the *oxygen* atom as an aluminate anion leaving group to give an iminium ion intermediate. The intermediate iminium ion is further reduced by $LiAlH_4$ to yield the amine.



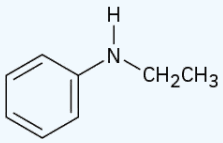
The reaction is effective with both acyclic and cyclic amides, or lactams, and is a good method for preparing cyclic amines.



A lactam **A cyclic amine (80%)**

Worked Example 10.8.1: Synthesizing an Amine from an Amide

How could you prepare *N*-ethylaniline by reduction of an amide with $LiAlH_4$?

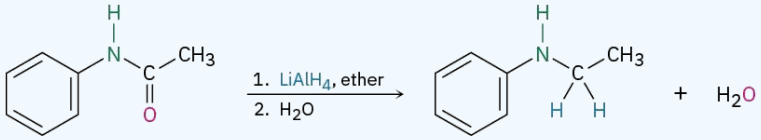


***N*-Ethylaniline**

Strategy

Reduction of an amide with $LiAlH_4$ yields an amine. To find the starting material for synthesis of *N*-ethylaniline, look for a CH_2 position next to the nitrogen atom and replace that CH_2 by C═O. In this case, the amide is *N*-phenylacetamide.

Solution



***N*-Phenylacetamide** ***N*-Ethylaniline**

Exercise 10.8.1

N-ethylbenzamide to each of the following products?

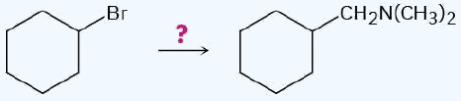
a. Benzoic acid
b. Benzyl alcohol
c. $C_6H_5CH_2NHCH_2CH_3$

Answer

a. H_2O, NaOH
b. Benzoic acid + $LiAlH_4$
c. $LiAlH_4$

Exercise 10.8.2

How would you use the reaction of an amide with $LiAlH_4$ as the key step in going from bromocyclohexane to (*N*,*N*-dimethylaminomethyl)cyclohexane? Write all the steps in the reaction sequence.



(*N*,*N*-Dimethylaminomethyl)cyclohexane

Answer

1. Mg; 2. CO_2, then H_3O^+; 3. $SOCl_2$; 4. $(CH_3)_2NH$; 5. $LiAlH_4$

This page titled 10.8: Chemistry of Amides is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **21.7: Chemistry of Amides** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

10.9: Chemistry of Thioesters and Acyl Phosphates - Biological Carboxylic Acid Derivatives

As mentioned in the chapter introduction, the substrate for a nucleophilic acyl substitution reaction in living organisms is generally either a thioester (RCOSR′) or an acyl phosphate ($RCO_2PO_3^{2-}$ or $RCO_2PO_3R'^-$). Neither is as reactive as an acid chloride or acid anhydride, yet both are stable enough to exist in living organisms while still reactive enough to undergo acyl substitution.

Acyl CoA's, such as acetyl CoA, are the most common thioesters in nature. Coenzyme A, abbreviated CoA, is a thiol formed by a phosphoric anhydride linkage (O═P−O−P═O) between phosphopantetheine and adenosine 3′,5′-bisphosphate. (The prefix bis- means "two" and indicates that adenosine 3′,5′-bisphosphate has two phosphate groups, one on C3′ and one on C5′.) Reaction of coenzyme A with an acyl phosphate or acyl adenylate gives acyl CoA (Figure 10.9.1). As we saw in Section 21.3, formation of the acyl adenylate occurs by reaction of a carboxylic acid with ATP and is itself a nucleophilic acyl substitution reaction that takes place on phosphorus.

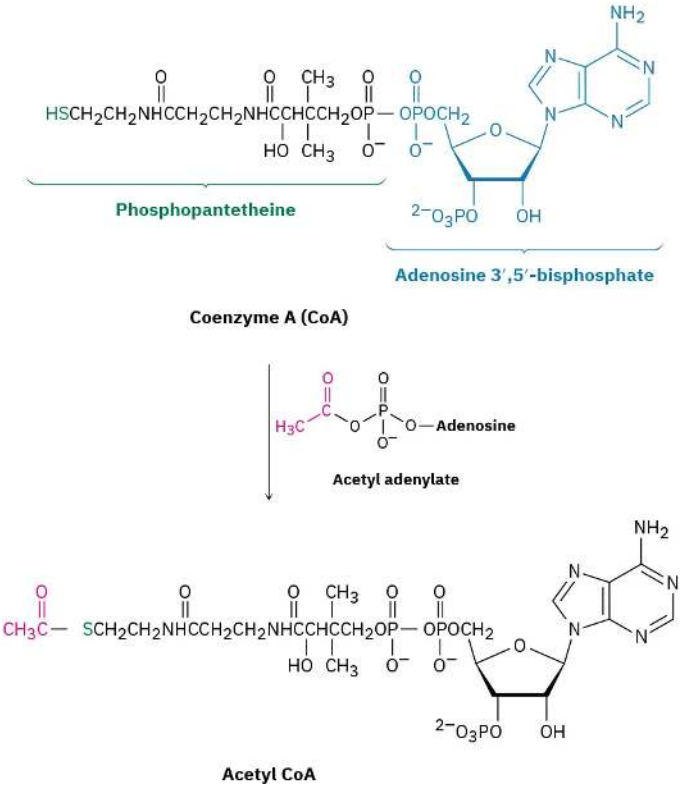
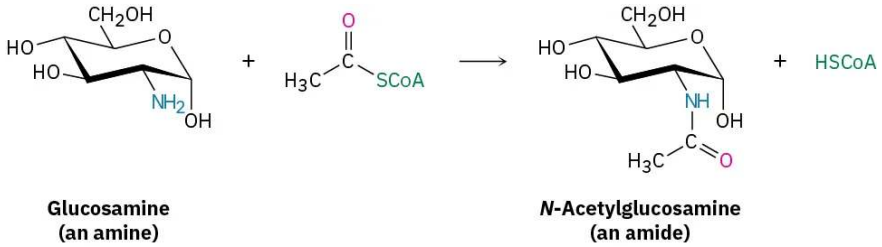


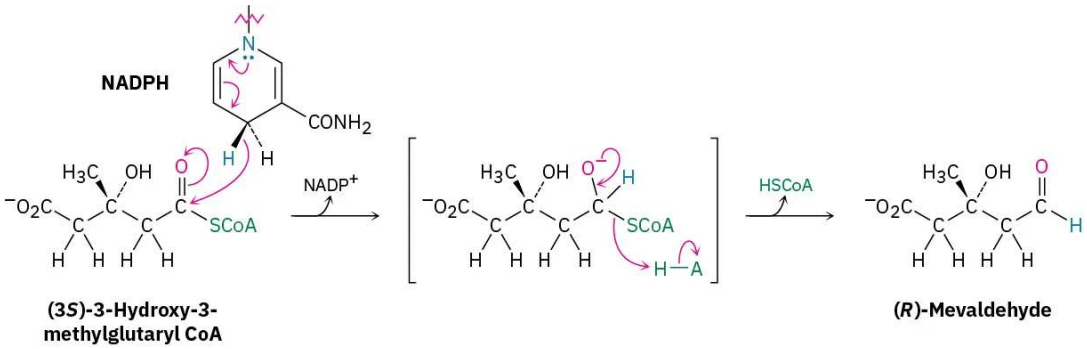
Figure 10.9.1: Formation of the thioester acetyl CoA by nucleophilic acyl substitution reaction of coenzyme A (CoA) with acetyl adenylate.

Once formed, an acyl CoA is a substrate for further nucleophilic acyl substitution reactions. For example, *N*-acetylglucosamine, a component of cartilage and other connective tissues, is synthesized by an aminolysis reaction between glucosamine and acetyl CoA.



Another example of a nucleophilic acyl substitution reaction on a thioester—this one a substitution by hydride ion to effect the partial reduction of a thioester to an aldehyde—occurs in the biosynthesis of mevaldehyde, an intermediate in terpenoid synthesis,

which we'll discuss in some detail in **Section 27.5**. In this reaction, (3*S*)-3-hydroxy-3-methylglutaryl CoA is reduced by hydride donation from NADPH.

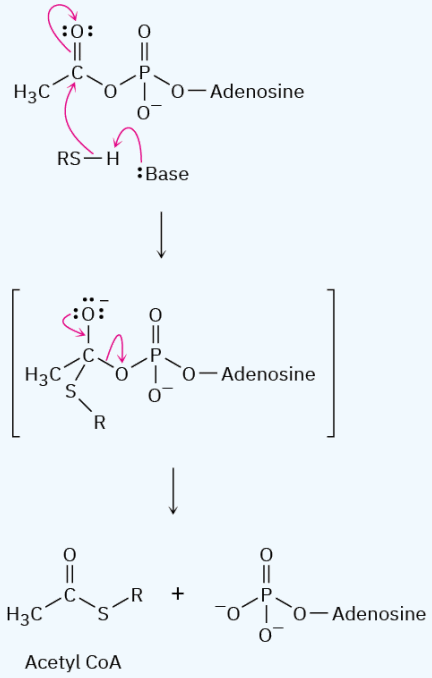


(3*S*)-3-Hydroxy-3-methylglutaryl CoA **(*R*)-Mevaldehyde**

Exercise 10.9.1

Write the mechanism of the reaction shown in Figure 10.9.1 between coenzyme A and acetyl adenylate to give acetyl CoA.

Answer

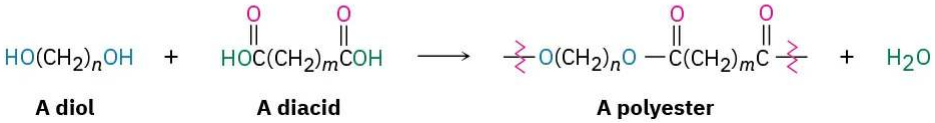


This page titled 10.9: Chemistry of Thioesters and Acyl Phosphates - Biological Carboxylic Acid Derivatives is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **21.8: Chemistry of Thioesters and Acyl Phosphates - Biological Carboxylic Acid Derivatives** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

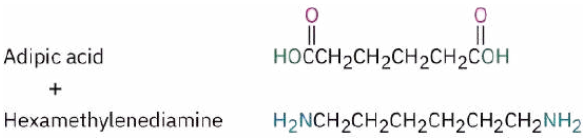
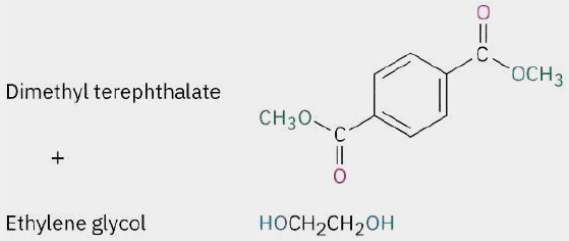
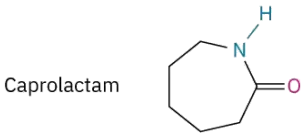
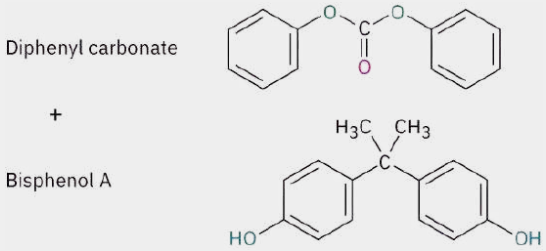
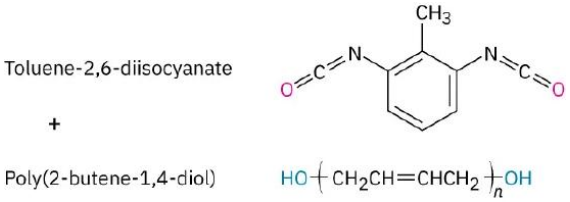
10.10: Polyamides and Polyesters - Step-Growth Polymers

When an amine reacts with an acid chloride, an amide is formed. What would happen, though, if a *diamine* and a *diacid chloride* were allowed to react? Each partner would form two amide bonds, linking more and more molecules together until a giant polyamide resulted. In the same way, reaction of a diol with a diacid would lead to a polyester.



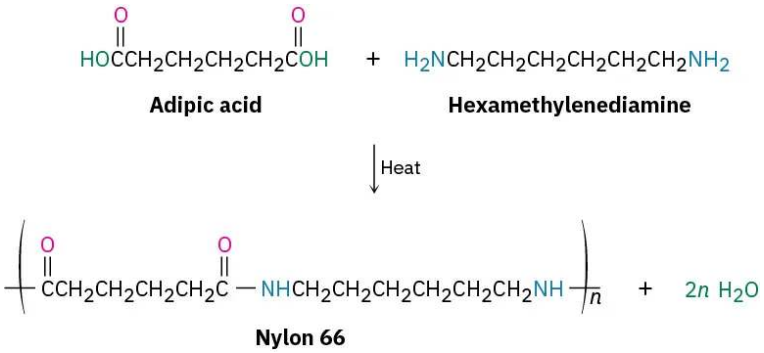
There are two main classes of synthetic polymers: *chain-growth polymers* and *step-growth polymers*. The polyethylene and other alkene and diene polymers that we saw in Section 8.10 and Section 14.6 are called **chain-growth polymers** because they are produced in chain-reaction processes. An initiator adds to a C=C bond to give a reactive intermediate, which adds to a second alkene molecule to produce a new intermediate, which adds to a third molecule, and so on. By contrast, polyamides and polyesters are **step-growth polymers** because each bond in the polymer is formed independently in a discrete step, often the nucleophilic acyl substitution reaction of a carboxylic acid derivative. Some commercially important step-growth polymers are shown in Table 10.10.1.

Table 10.10.1: Some Common Step-Growth Polymers and Their Uses

Monomers	Structure	Polymer	Uses
Adipic acid + Hexamethylenediamine		Nylon 66	Fibers, clothing, tire cord
Dimethyl terephthalate + Ethylene glycol		Dacron, Mylar, Terylene	Fibers, clothing, films, tire cord
Caprolactam		Nylon 6, Perlon	Fibers, castings
Diphenyl carbonate + Bisphenol A		Lexan, polycarbonate	Equipment housing, molded articles
Toluene-2,6-diisocyanate + Poly(2-butene-1,4-diol)		Polyurethane, Spandex	Fibers, coatings, foams

Polyamides (Nylons)

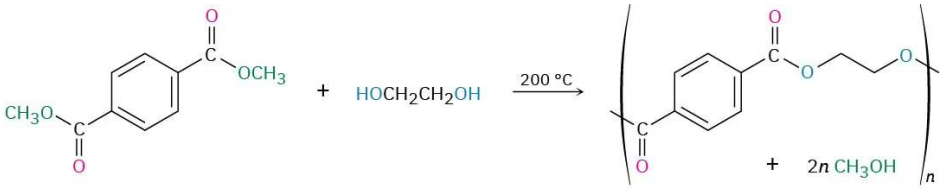
The best known step-growth polymers are the polyamides, or *nylons*, first prepared in 1930 by Wallace Carothers at the DuPont Company by heating a diamine with a diacid. For instance, nylon 66 is prepared by reaction of adipic acid (hexanedioic acid) with hexamethylenediamine (1,6-hexanediamine) at 280 °C. The designation “66” indicates the number of carbon atoms in the diamine (the first 6) and the diacid (the second 6).



Nylons are used both in engineering applications and in making fibers. A combination of high impact strength and abrasion resistance makes nylon an excellent metal substitute for bearings and gears. As fiber, nylon is used in a variety of applications, from clothing to tire cord to ropes.

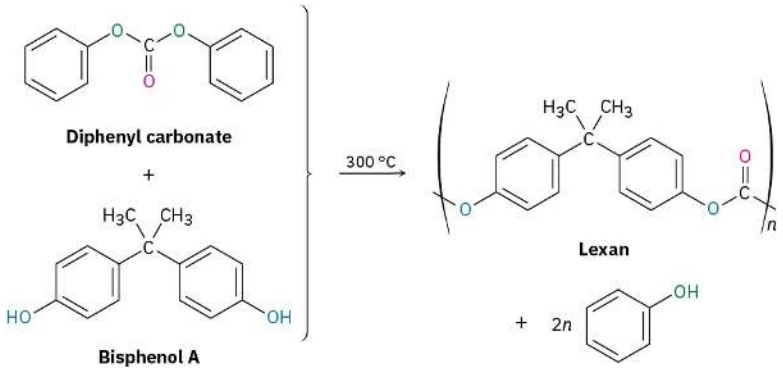
Polyesters

The most generally useful polyester is made by reaction between dimethyl terephthalate (dimethyl 1,4-benzenedicarboxylate) and ethylene glycol (1,2-ethanediol). The product is used under the trade name Dacron to make clothing fiber or tire cord and under the name Mylar to make recording tape. The tensile strength of poly(ethylene terephthalate) film is nearly equal to that of steel.



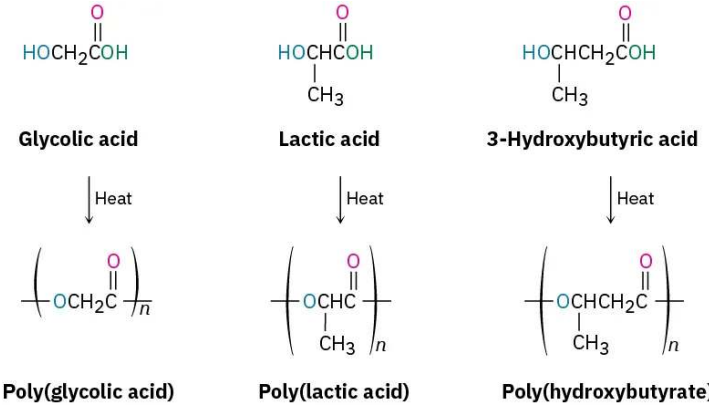
Dimethyl terephthalate **Ethylene glycol** **A polyester (Dacron, Mylar)**

Lexan, a polycarbonate prepared from diphenyl carbonate and bisphenol A, is another commercially valuable polyester. Lexan has an unusually high impact strength, making it valuable for use in bicycle helmets and laptop cases.



Sutures and Biodegradable Polymers

Because plastics are too often thrown away rather than recycled, much work has been carried out on developing biodegradable polymers, which can be broken down rapidly in landfills by soil microorganisms. Among the most common biodegradable polymers are poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and poly(hydroxybutyrate) (PHB). All are polyesters and are therefore susceptible to hydrolysis of their ester links. Copolymers of PGA with PLA have found a particularly wide range of uses. A 90/10 copolymer of poly(glycolic acid) with poly(lactic acid) is used to make absorbable sutures, for instance. The sutures are entirely hydrolyzed and absorbed by the body within 90 days after surgery.



Glycolic acid **Lactic acid** **3-Hydroxybutyric acid**

Poly(glycolic acid) **Poly(lactic acid)** **Poly(hydroxybutyrate)**

In Europe, interest has centered particularly on poly(hydroxybutyrate), which can be made into films for packaging as well as into molded items. The polymer degrades within four weeks in landfills, both by ester hydrolysis and by an E1cB elimination reaction

of the oxygen atom β to the carbonyl group. The use of poly(hydroxybutyrate) is limited at present by its cost—about four times that of polypropylene.

Exercise 10.10.1

Draw structures of the step-growth polymers you would expect to obtain from the following reactions:

a. $BrCH_2CH_2CH_2Br + HOCH_2CH_2CH_2OH \xrightarrow{\text{Base}} ?$

b. $HOCH_2CH_2OH + HO_2C(CH_2)_6CO_2H \xrightarrow{H_2SO_4\ \text{catalyst}} ?$

c. $H_2N(CH_2)_6NH_2 + ClC(=O)(CH_2)_4C(=O)Cl \longrightarrow ?$

Answer

a. $-\left(OCH_2CH_2CH_2OCH_2CH_2CH_2\right)_n-$

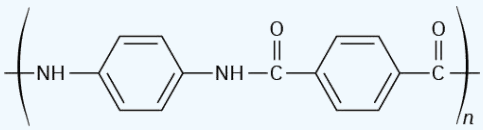
b. $-\left(OCH_2CH_2OC(=O)(CH_2)_6C(=O)\right)_n-$

c. $-\left(NH(CH_2)_6NHC(=O)(CH_2)_4C(=O)\right)_n-$

Exercise 10.10.2

Kevlar, a nylon polymer prepared by reaction of 1,4-benzenedicarboxylic acid (terephthalic acid) with 1,4-benzenediamine (*p*-phenylenediamine), is so strong that it's used to make bulletproof vests. Draw the structure of a segment of Kevlar.

Answer



This page titled 10.10: Polyamides and Polyesters - Step-Growth Polymers is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **21.9: Polyamides and Polyesters - Step-Growth Polymers** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

10.11: Spectroscopy of Carboxylic Acid Derivatives

Infrared Spectroscopy

All carbonyl-containing compounds have intense IR absorptions in the range 1650 to 1850 cm^{-1}. As shown in Table 10.11.1 the exact position of the absorption provides information about the specific kind of carbonyl group. For comparison, the IR absorptions of aldehydes, ketones, and carboxylic acids are included in the table, along with values for carboxylic acid derivatives.

Table 10.11.1: Infrared Absorptions of Some Carbonyl Compounds

Carbonyl type	Example	Absorption (cm^{-1})
Saturated acid chloride	Acetyl chloride	1810
Aromatic acid chloride	Benzoyl chloride	1770
Saturated acid anhydride	Acetic anhydride	1820, 1760
Saturated ester	Ethyl acetate	1735
Aromatic ester	Ethyl benzoate	1720
Saturated amide	Acetamide	1690
Aromatic amide	Benzamide	1675
N-Substituted amide	*N*-Methylacetamide	1680
N,*N*-Disubstituted amide	*N*,*N*-Dimethylacetamide	1650
Saturated aldehyde	Acetaldehyde	1730
Saturated ketone	Acetone	1715
Saturated carboxylic acid	Acetic acid	1710

Acid chlorides are easily detected by their characteristic absorption near 1810 cm^{-1}. Acid anhydrides can be identified by a pair of absorptions in the carbonyl region, one at 1820 cm^{-1} and another at 1760 cm^{-1}. Note that each of these functional groups has a strong electron-withdrawing group attached to the carbonyl. The inductive withdrawal of electron density shortens the C=O bond, thereby raising its stretching frequency. Esters are detected by their absorption at 1735 cm^{-1}, a position somewhat higher than that for either aldehydes or ketones. Amides, by contrast, absorb near the low-wavenumber end of the carbonyl region, with the degree of substitution on nitrogen affecting the exact position of the IR band. That is, for amides, the delocalization of electron density (resonance) from nitrogen into the carbonyl lengthens the C=O bond and lowers its stretching frequency.

? Exercise 10.11.1

What kinds of functional groups might compounds have if they show the following IR absorptions?

a. Absorption at 1735 cm^{-1}
b. Absorption at 1810 cm^{-1}
c. Absorptions at 2500 to 3300 cm^{-1} and 1710 cm^{-1}
d. Absorption at 1715 cm^{-1}

Answer

a. Ester
b. Acid chloride
c. Carboxylic acid
d. Aliphatic ketone or cyclohexanone

Exercise 10.11.2

Propose structures for compounds that have the following formulas and IR absorptions:

a. $C_6H_{12}O_2$, 1735 cm^{-1}
b. C_4H_9NO, 1650 cm^{-1}
c. C_4H_5ClO, 1780 cm^{-1}

Answer

a. $CH_3CH_2CH_2CO_2CH_2CH_3$ and other possibilities
b. $CH_3CON(CH_3)_2$
c. $CH_3CH=CHCOCl$ or $H_2C=C(CH_3)COCl$

Nuclear Magnetic Resonance Spectroscopy

Hydrogens on the carbon next to a carbonyl group are slightly deshielded and absorb near 2 δ in the ^1H NMR spectrum, although the exact identity of the carbonyl group can't be determined. Figure 10.11.1 shows the ^1H NMR spectrum of ethyl acetate.

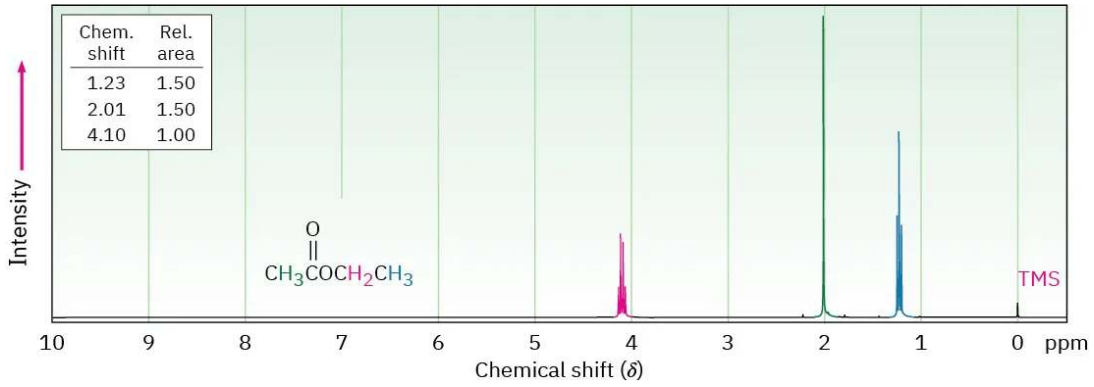


Figure 10.11.1: ^1H NMR spectrum of ethyl acetate.

Although ^{13}C NMR is useful for determining the presence or absence of a carbonyl group in a molecule, the identity of the carbonyl group is difficult to determine. Aldehydes and ketones absorb near 200 δ, while the carbonyl carbon atoms of various acid derivatives absorb in the range 160 to 180 δ (Table 10.11.2).

Table 10.11.2: ^{13}C NMR Absorptions of Some Carbonyl Compounds

Compound	Absorption (δ)
Acetic acid	177.3
Ethyl acetate	170.7
Acetyl chloride	170.3
Acetamide	172.6
Acetic anhydride	166.9
Acetone	205.6
Acetaldehyde	201.0

This page titled 10.11: Spectroscopy of Carboxylic Acid Derivatives is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **21.10: Spectroscopy of Carboxylic Acid Derivatives** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

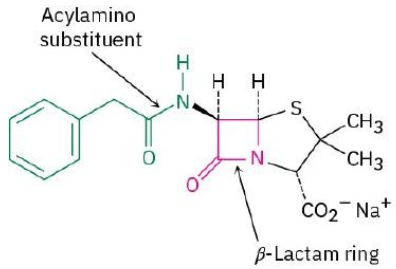
10.12: Chemistry Matters—β-Lactam Antibiotics

You should never underestimate the value of hard work and logical thinking, but it's also true that blind luck often plays a role in most real scientific breakthroughs. What has been called "the supreme example of luck in all scientific history" occurred in the late summer of 1928, when the Scottish bacteriologist Alexander Fleming went on vacation, leaving in his lab a culture plate recently inoculated with the bacterium *Staphylococcus aureus*.

While Fleming was away, an extraordinary chain of events occurred. First, a nine-day cold spell lowered the laboratory temperature to a point where the *Staphylococcus* in the culture plate could not grow. During this time, spores from a colony of the mold *Penicillium notatum*, being grown in a lab on the floor below, wafted up into Fleming's lab and landed in the culture plate. The temperature then rose, and both *Staphylococcus* and *Penicillium* began to grow. On returning from vacation, Fleming discarded the plate into a tray of antiseptic, intending to sterilize it. Evidently, though, the plate did not sink deeply enough into the antiseptic, because when Fleming happened to glance at it a few days later, what he saw changed the course of history. He noticed that the growing *Penicillium* mold appeared to dissolve the colonies of staphylococci.

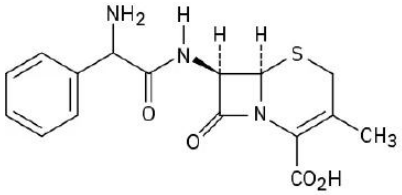
Fleming realized that the *Penicillium* mold must be producing a chemical that killed the *Staphylococcus* bacteria, and he spent several years trying to isolate the substance. Finally, in 1939, the Australian pathologist Howard Florey and the German refugee Ernst Chain managed to isolate the active substance, called *penicillin*. The dramatic ability of penicillin to cure infections in mice was soon demonstrated, and successful tests in humans followed shortly thereafter. By 1943, penicillin was being produced on a large scale for military use in World War II, and by 1944 it was being used on civilians. Fleming, Florey, and Chain shared the 1945 Nobel Prize in Physiology or Medicine.

Now called benzylpenicillin, or penicillin G, the substance first discovered by Fleming is but one member of a large class of so-called ***β*-lactam antibiotics**, compounds with a four-membered lactam (cyclic amide) ring. The four-membered lactam ring is fused to a five-membered, sulfur-containing ring, and the carbon atom next to the lactam carbonyl group is bonded to an acylamino substituent, RCONH–. This acylamino side chain can be varied in the laboratory to provide many hundreds of penicillin analogs with different biological activity profiles. Ampicillin, for instance, has an *α*-aminophenylacetamido substituent [$PhCH(NH_2)CONH–$].



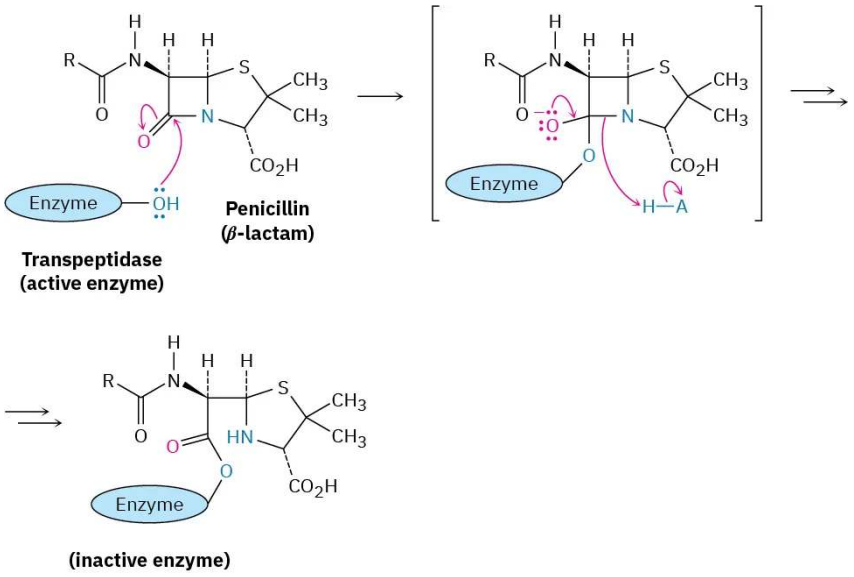
Benzylpenicillin (penicillin G)

Closely related to the penicillins are the *cephalosporins*, a group of *β*-lactam antibiotics that contain an unsaturated, six-membered, sulfur-containing ring. Cephalexin, marketed under the trade name Keflex, is an example. Cephalosporins generally have much greater antibacterial activity than penicillins, particularly against resistant strains of bacteria.



Cephalexin (a cephalosporin)

The biological activity of penicillins and cephalosporins is due to the presence of the strained *β*-lactam ring, which reacts with and deactivates the transpeptidase enzyme needed to synthesize and repair bacterial cell walls. With the wall either incomplete or weakened, the bacterial cell ruptures and dies.



This page titled 10.12: Chemistry Matters—β-Lactam Antibiotics is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **21.11: Chemistry Matters—β-Lactam Antibiotics** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

10.13: Key Terms

- acid anhydride
- acid halide
- acyl phosphate
- amide
- carboxylic acid derivative
- chain-growth polymer
- ester
- Fischer esterification reaction
- lactam
- lactone
- nucleophilic acyl substitution reaction
- saponification
- step-growth polymer
- thioester

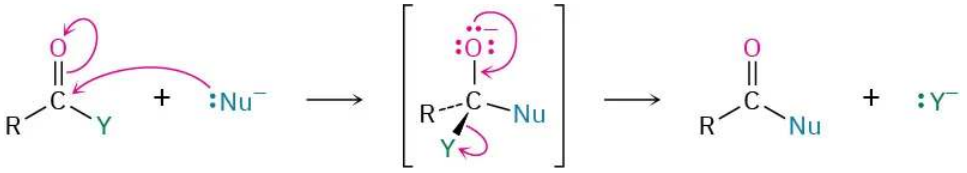
This page titled 10.13: Key Terms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **21.12: Key Terms** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

10.14: Summary

Carboxylic acid derivatives—compounds in which the –OH group of a carboxylic acid has been replaced by another substituent—are among the most widely occurring of all molecules and are involved in almost all biological pathways. In this chapter, we covered the chemistry necessary for understanding them and thus also necessary for understanding living organisms. **Acid halides, acid anhydrides, esters,** and **amides** are the most common such derivatives in the laboratory; **thioesters** and **acyl phosphates** are common in biological molecules.

The chemistry of carboxylic acid derivatives is dominated by the **nucleophilic acyl substitution reaction**. Mechanistically, these substitutions take place by addition of a nucleophile to the polar carbonyl group of the acid derivative to give a tetrahedral intermediate, followed by expulsion of a leaving group.



The reactivity of an acid derivative toward substitution depends both on the steric environment near the carbonyl group and on the electronic nature of the substituent, Y. The reactivity order is acid halide > acid anhydride > thioester > ester > amide.

The most common reactions of carboxylic acid derivatives are substitution by water to yield an acid (hydrolysis), by an alcohol to yield an ester (alcoholysis), by an amine to yield an amide (aminolysis), by hydride ion to yield an alcohol (reduction), and by an organomagnesium halide to yield an alcohol (Grignard reaction).

Step-growth polymers, such as polyamides and polyesters, are prepared by reactions between difunctional molecules. Polyamides (nylons) are formed by reaction between a diacid and a diamine; polyesters are formed from a diacid and a diol.

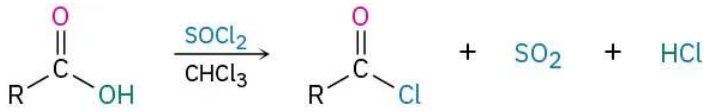
IR spectroscopy is a valuable tool for the structural analysis of acid derivatives. Acid chlorides, anhydrides, esters, and amides all show characteristic IR absorptions that can be used to identify these functional groups.

This page titled 10.14: Summary is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

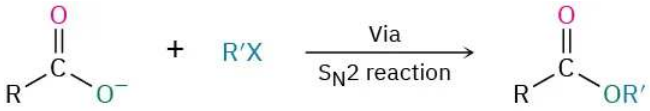
- **21.13: Summary** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

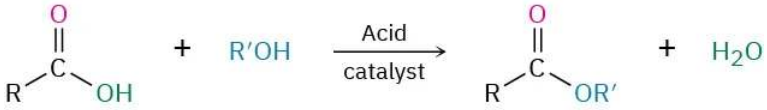
10.15: Summary of Reactions

1. Reactions of carboxylic acids (Section 21.3)
   a. Conversion into acid chlorides

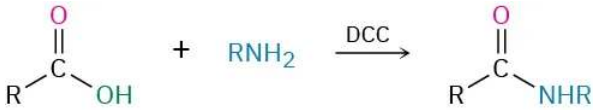


- Conversion into esters



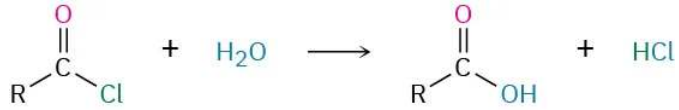


- Conversion into amides

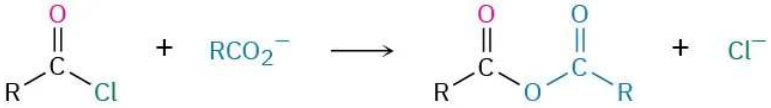


- Reduction to yield primary alcohols

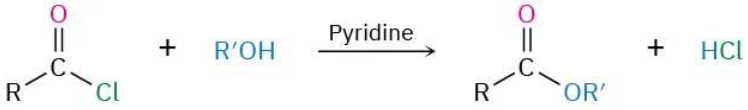
- Reactions of acid chlorides (Section 21.4)
   a. Hydrolysis to yield acids



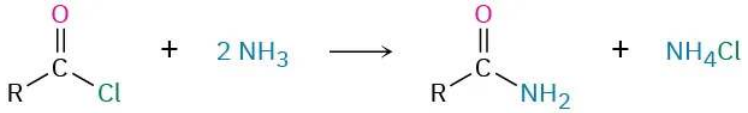
   b. Reaction with carboxylates to yield anhydrides



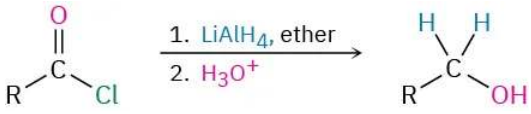
   c. Alcoholysis to yield esters



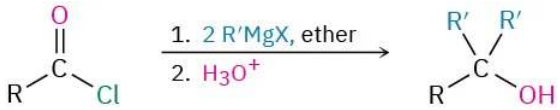
   d. Aminolysis to yield amides



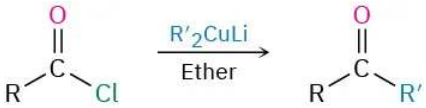
   e. Reduction to yield primary alcohols



   f. Grignard reaction to yield tertiary alcohols



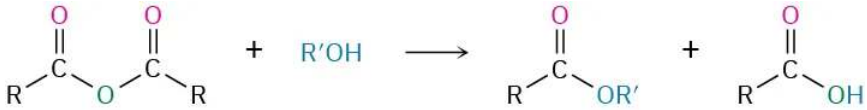
g. Diorganocopper reaction to yield ketones



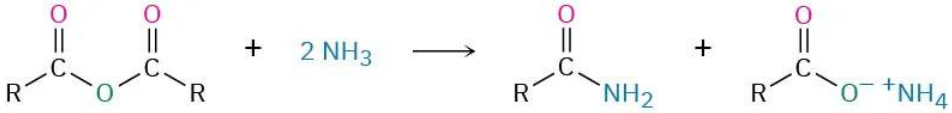
- Reactions of acid anhydrides (Section 21.5)

a. Hydrolysis to yield acids

b. Alcoholysis to yield esters

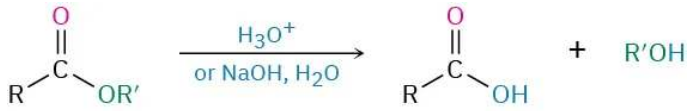


c. Aminolysis to yield amides

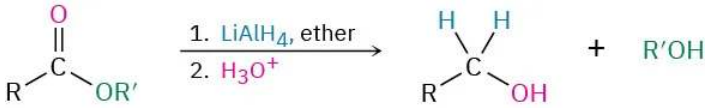


- Reactions of esters (Section 21.6)

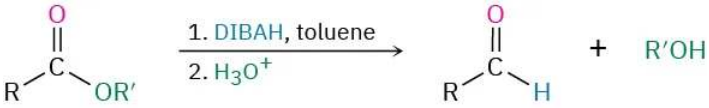
a. Hydrolysis to yield acids



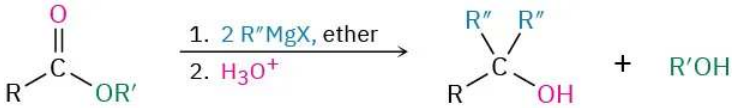
b. Reduction to yield primary alcohols



c. Partial reduction to yield aldehydes

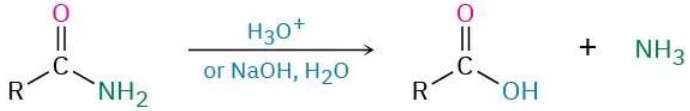


d. Grignard reaction to yield tertiary alcohols

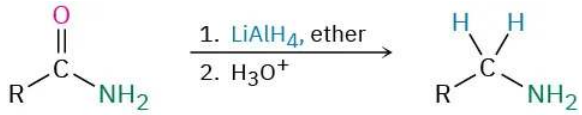


- Reactions of amides (Section 21.7)

a. Hydrolysis to yield acids



b. Reduction to yield amines



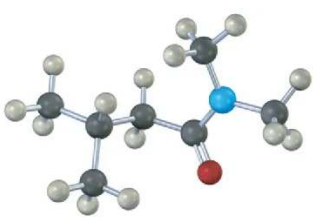
This page titled 10.15: Summary of Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **21.14: Summary of Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

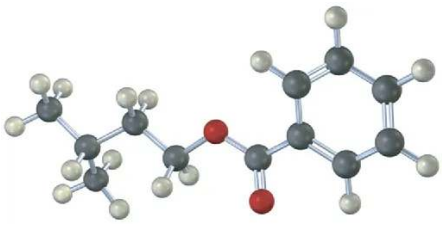
10.16: Additional Problems

Visualizing Chemistry

PROBLEM 21-27 Name the following compounds:

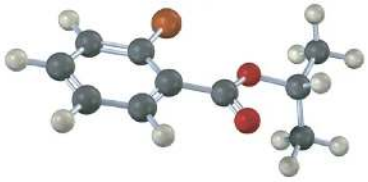


(a)



(b)

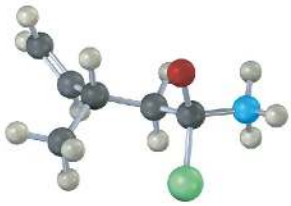
PROBLEM 21-28 How would you prepare the following compounds starting with an appropriate carboxylic acid and any other reagents needed? (reddish brown = Br.)



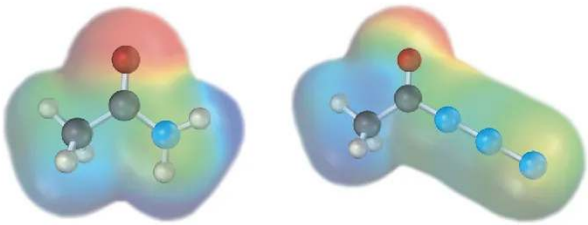
(a)

(b)

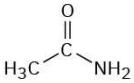
PROBLEM 21-29 The following structure represents a tetrahedral alkoxide-ion intermediate formed by addition of a nucleophile to a carboxylic acid derivative. Identify the nucleophile, the leaving group, the starting acid derivative, and the ultimate product (green = Cl).

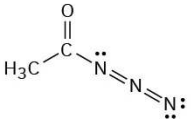


PROBLEM 21-30 Electrostatic potential maps of a typical amide (acetamide) and an acyl azide (acetyl azide) are shown. Which of the two do you think is more reactive in nucleophilic acyl substitution reactions? Explain.



Acetamide

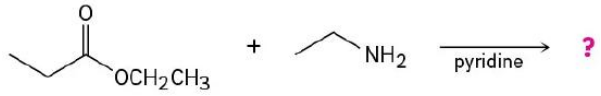


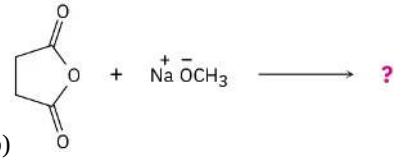


Acetyl azide

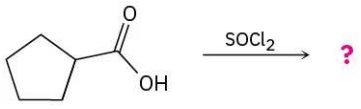
Mechanism Problems

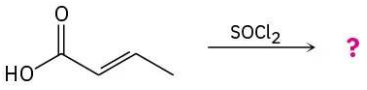
PROBLEM 21-31 Predict the product(s) and write the mechanism for the following reactions:

(a) 

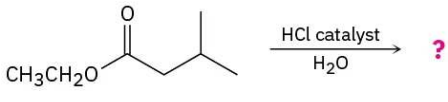
(b) 

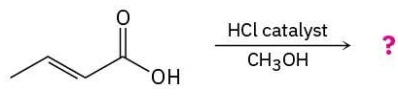
PROBLEM 21-32 Predict the product(s) and write the mechanism for the following reactions:

(a) 

(b) 

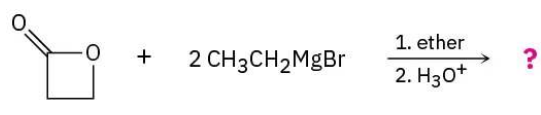
PROBLEM 21-33 Predict the product(s) and write the mechanism for the following reactions: (a) <p"> Predict the product(s) and write the mechanism for each of the following reactions:

(a) 

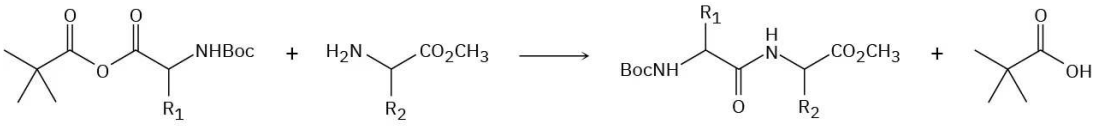
(b) 

PROBLEM 21-34 Predict the product(s) and write the mechanism for the following reactions: (a) <p"> Predict the product(s) and write the mechanism for the following reactions:

(a)

(b) 

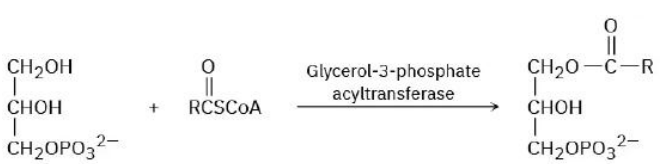
PROBLEM 21-35 Pivalic mixed anhydrides are often used to form amide bonds between amino acids. Unlike with a symmetrical anhydride, this reaction is highly regioselective, with the nucleophile adding only to the amino-acid carbonyl. Provide the complete mechanism for the following reaction and explain the regioselectivity.



Pivaloyl/amino-acid mixed anhydride

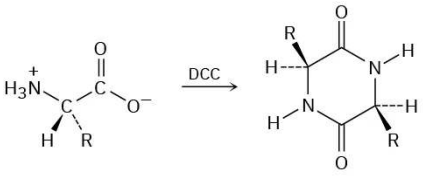
PROBLEM 21-36 When 4-dimethylaminopyridine (DMAP) is added in catalytic amounts to acetic anhydride and an alcohol, it significantly increases the rate of ester formation. The process begins with a reaction between acetic anhydride and DMAP to form a highly reactive acetylpyridinium intermediate that is more reactive than acetic anhydride itself. Propose a mechanism for this process that includes the formation and reaction of the acetylpyridinium intermediate.

PROBLEM 21-37 Fats are biosynthesized from glycerol 3-phosphate and fatty-acyl CoA's by a reaction sequence that begins with the following step. Show the mechanism of the reaction.



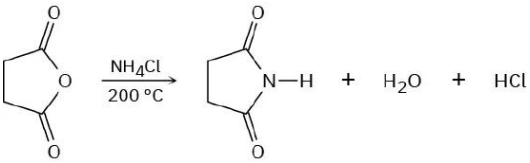
Glycerol 3-phosphate **Fatty-acyl CoA** **1-Acylglycerol 3-phosphate**

PROBLEM 21-38 Treatment of an α-amino acid with DCC yields a 2,5-diketopiperazine. Propose a mechanism.

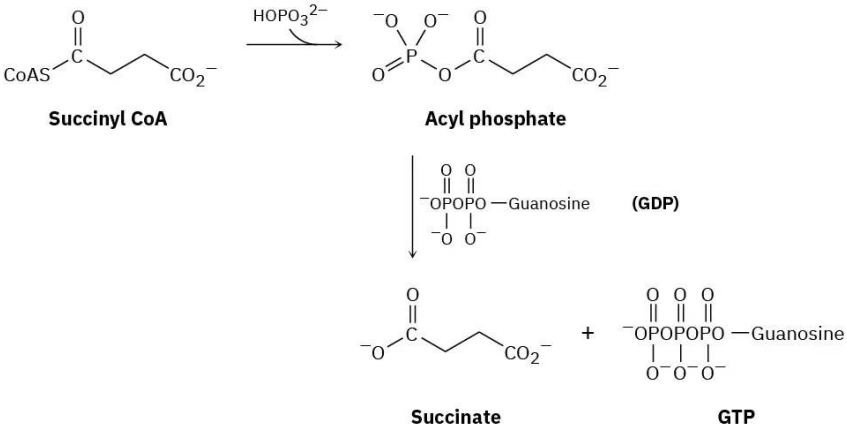


An α-amino acid **A 2,5-diketopiperazine**

PROBLEM 21-39 Succinic anhydride yields the cyclic imide succinimide when heated with ammonium chloride at 200 °C. Propose a mechanism for this reaction. Why do you suppose such a high reaction temperature is required?

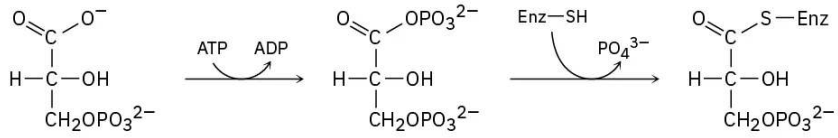


PROBLEM 21-40 The hydrolysis of a biological thioester to the corresponding carboxylate is often more complex than the overall result might suggest. The conversion of succinyl CoA to succinate in the citric acid cycle, for instance, occurs by initial formation of an acyl phosphate, followed by reaction with guanosine diphosphate (GDP, a relative of adenosine diphosphate [ADP]) to give succinate and guanosine triphosphate (GTP, a relative of ATP). Suggest mechanisms for both steps.

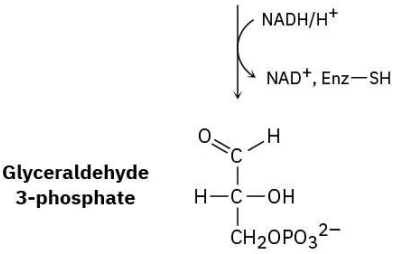


Succinyl CoA **Acyl phosphate** **Succinate** **GTP**

PROBLEM 21-41 One step in the *gluconeogenesis* pathway for the biosynthesis of glucose is the partial reduction of 3-phosphoglycerate to give glyceraldehyde 3-phosphate. The process occurs by phosphorylation with ATP to give 1,3-bisphosphoglycerate, reaction with a thiol group on the enzyme to give an enzyme-bound thioester, and reduction with NADH. Suggest mechanisms for all three reactions.

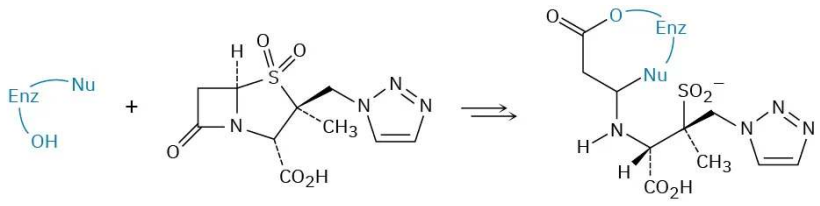


3-Phosphoglycerate **1,3-Bisphosphoglycerate** **(Enzyme-bound thioester)**



Glyceraldehyde 3-phosphate

PROBLEM 21-42 Bacteria typically develop a resistance to penicillins and other β-lactam antibiotics (see *Chemistry Matters* at the end of this chapter) due to bacterial synthesis of β-lactamase enzymes. Tazobactam, however, is able to inhibit the activity of the β-lactamase by trapping it, thereby preventing a resistance from developing.



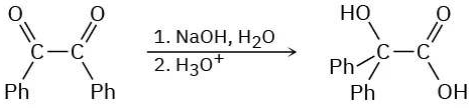
β-Lactamase **Tazobactam** **Trapped β-lactamase**

(a) The first step in trapping is reaction of a hydroxyl group on the β-lactamase to open the β-lactam ring of tazobactam. Show the mechanism.

(b) The second step is opening the sulfur-containing ring in tazobactam to give an acyclic imine intermediate. Show the mechanism.

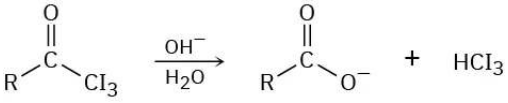
(c) Cyclization of the imine intermediate gives the trapped β-lactamase product. Show the mechanism.

PROBLEM 21-43 The following reaction, called the *benzilic acid rearrangement*, takes place by typical carbonyl-group reactions. Propose a mechanism (Ph = phenyl).



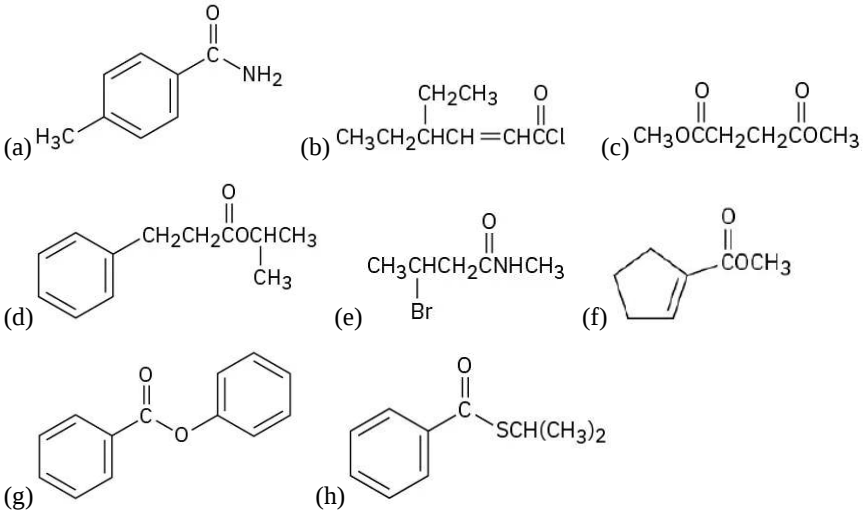
Benzil **Benzylic acid**

PROBLEM 21-44 In the *iodoform reaction*, a triiodomethyl ketone reacts with aqueous NaOH to yield a carboxylate ion and iodoform (triiodomethane). Propose a mechanism for this reaction.



Naming Carboxylic Acid Derivatives

PROBLEM 21-45 Give IUPAC names for the following compounds:



PROBLEM 21-46 Draw structures corresponding to the following names:

(a) *p*-Bromophenylacetamide **(b)** *m*-Benzoylbenzamide **(c)** 2,2-Dimethylhexanamide

(d) Cyclohexyl cyclohexanecarboxylate **(e)** Ethyl 2-cyclobutenecarboxylate **(f)** Succinic anhydride

PROBLEM 21-47 Draw and name compounds that meet the following descriptions:

(a) Three acid chlorides having the formula C_6H_9ClO

(b) Three amides having the formula $C_7H_{11}NO$.

Nucleophilic Acyl Substitution Reactions

PROBLEM 21-48 Predict the product, if any, of reaction between propanoyl chloride and the following reagents:

(a) $Li(Ph)_2Cu$ in ether **(b)** $LiAlH_4$, then H_3O^+ **(c)** CH_3MgBr, then H_3O^+ **(d)** H_3O^+ **(e)** Cyclohexanol **(f)** Aniline **(g)** $CH_3CO_2^-\ Na^+$

PROBLEM 21-49 Answer Problem 21-48 for reaction of the listed reagents with methyl propanoate.

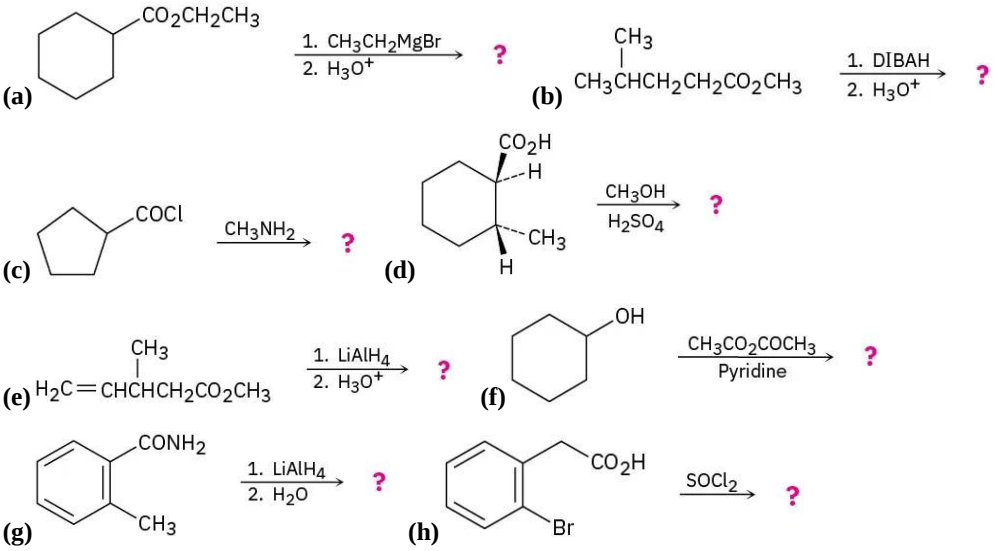
PROBLEM 21-50 Answer Problem 21-48 for reaction of the listed reagents with propanamide.

PROBLEM 21-51 What product would you expect to obtain from Grignard reaction of an excess of phenylmagnesium bromide with dimethyl carbonate, $CH_3OCO_2CH_3$?

PROBLEM 21-52 How might you prepare the following compounds from butanoic acid?

(a) 1-Butanol **(b)** Butanal **(c)** 1-Bromobutane **(d)** Pentanenitrile **(e)** 1-Butene **(f)** *N*-Methylpentanamide **(g)** 2-Hexanone **(h)** Butylbenzene **(i)** Butanenitrile

PROBLEM 21-53 Predict the product(s) of the following reactions:



PROBLEM 21-54 The following reactivity order has been found for the saponification of alkyl acetates by aqueous NaOH. Explain.

$$CH_3CO_2CH_3 > CH_3CO_2CH_2CH_3 > CH_3CO_2CH(CH_3)_2 > CH_3CO_2C(CH_3)_3$$

PROBLEM 21-55 Explain the observation that attempted Fischer esterification of 2,4,6-trimethylbenzoic acid with methanol and HCl is unsuccessful. No ester is obtained, and the acid is recovered unchanged. What alternative method of esterification might be successful?

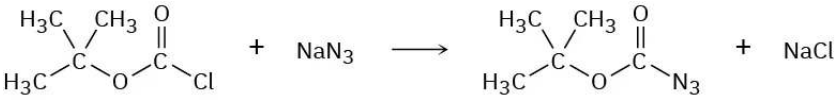
PROBLEM 21-56 Outline methods for the preparation of acetophenone (phenyl methyl ketone) starting from the following:

(a) Benzene **(b)**Bromobenzene **(c)** Methyl benzoate **(d)** Benzonitrile **(e)** Styrene

PROBLEM 21-57 Treatment of 5-aminopentanoic acid with DCC (dicyclohexylcarbodiimide) yields a lactam. Show the structure of the product and the mechanism of the reaction.

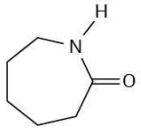
PROBLEM 21-58 When *ethyl* benzoate is heated in methanol containing a small amount of HCl, *methyl* benzoate is formed. Propose a mechanism for the reaction.

PROBLEM 21-59 *tert*-Butoxycarbonyl azide, a reagent used in protein synthesis, is prepared by treating *tert*-butoxycarbonyl chloride with sodium azide. Propose a mechanism for this reaction.



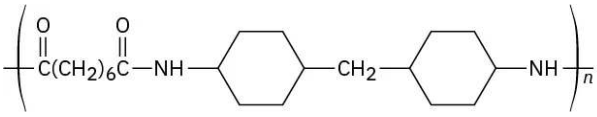
Step-Growth Polymers

PROBLEM 21-60 The step-growth polymer nylon 6 is prepared from caprolactam. The reaction involves initial reaction of caprolactam with water to give an intermediate open-chain amino acid, followed by heating to form the polymer. Propose mechanisms for both steps, and show the structure of nylon 6.



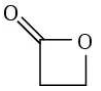
Caprolactam

PROBLEM 21-61 *Qiana*, a polyamide fiber with a silky texture, has the following structure. What are the monomer units used in the synthesis of Qiana?



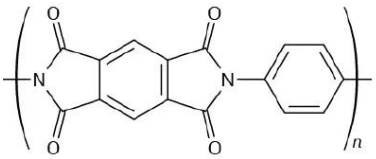
Qiana

PROBLEM 21-62 What is the structure of the polymer produced by treatment of β-propiolactone with a small amount of hydroxide ion?



β-Propiolactone

PROBLEM 21-63 Polyimides with the structure shown are used as coatings on glass and plastics to improve scratch resistance. How would you synthesize a polyimide? (See Problem 21-39.)



A polyimide

PROBLEM 21-64 How would you distinguish spectroscopically between the following isomer pairs? Tell what differences you would expect to see.

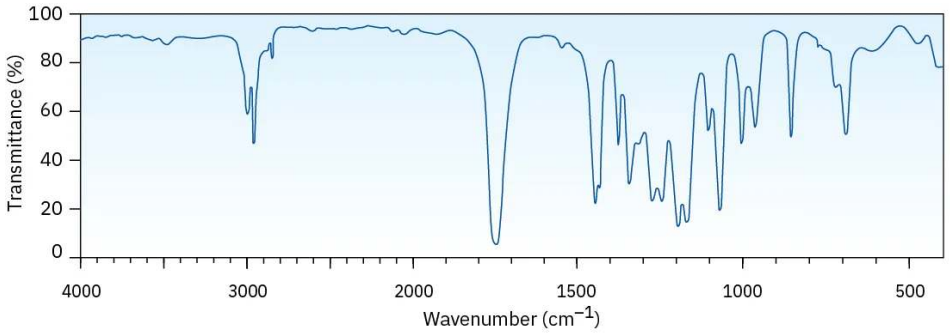
(a)*N*-Methylpropanamide and *N*,*N*-dimethylacetamide

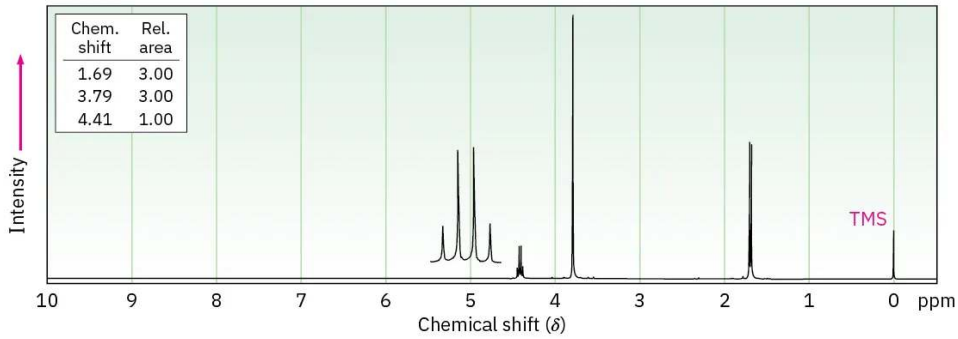
(b) 5-Hydroxypentanenitrile and cyclobutanecarboxamide

(c) 4-Chlorobutanoic acid and 3-methoxypropanoyl chloride

(d) Ethyl propanoate and propyl acetate

PROBLEM 21-65 Propose a structure for a compound, $C_4H_7ClO_2$, that has the following IR and ^1H NMR spectra:

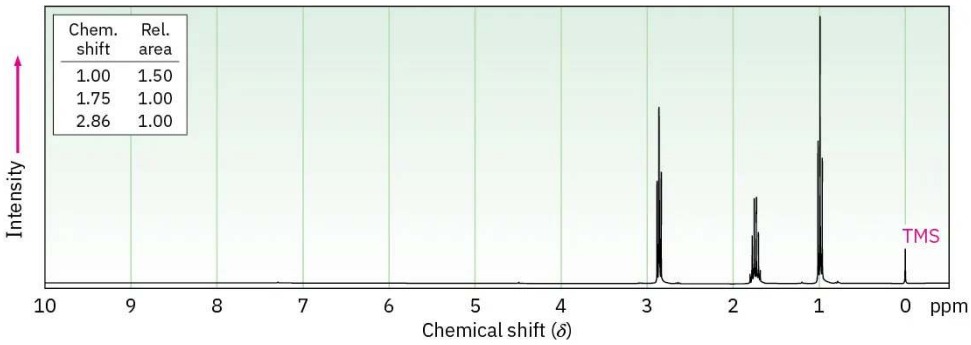




PROBLEM 21-66 Assign structures to compounds with the following <sup">1H NMR spectra:

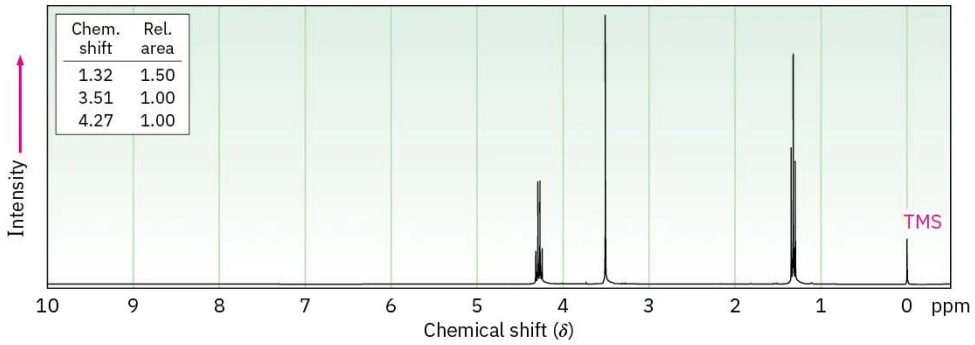
(a)C_4H_7ClO

IR: 1810 cm^{-1}



(b)$C_5H_7NO_2$

IR: 2250, 1735 cm^{-1}

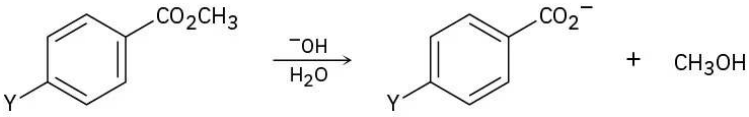


General Problems

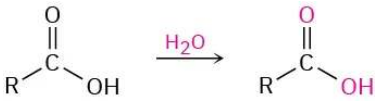
PROBLEM 21-67 The following reactivity order has been found for the basic hydrolysis of *p*-substituted methyl benzoates:

$$Y{=}NO_2 > Br > H > CH_3 > OCH_3$$

How can you explain this reactivity order? Where would you expect Y=C≡ N, Y=CHO, and Y=NH_2 to be in the reactivity list?

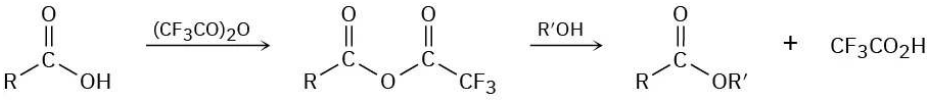


PROBLEM 21-68 When a carboxylic acid is dissolved in isotopically labeled water, the label rapidly becomes incorporated into both oxygen atoms of the carboxylic acid. Explain.



PROBLEM 21-69 We said in Section 21.6 that mechanistic studies on ester hydrolysis have been carried out using ethyl propanoate labeled with ^{18}O in the ether-like oxygen. Assume that ^{18}O-labeled acetic acid is your only source of isotopic oxygen, and then propose a synthesis of the labeled ethyl propanoate.

PROBLEM 21-70 Treatment of a carboxylic acid with trifluoroacetic anhydride leads to an unsymmetrical anhydride that rapidly reacts with alcohol to give an ester.

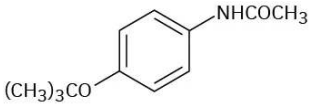


(a)Propose a mechanism for formation of the unsymmetrical anhydride.

(b) Why is the unsymmetrical anhydride unusually reactive?

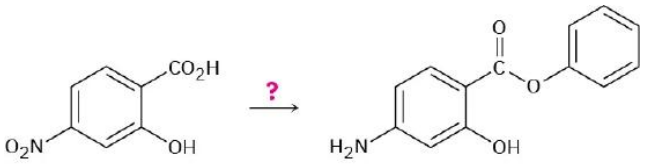
(c) Why does the unsymmetrical anhydride react as indicated rather than giving a trifluoroacetate ester plus carboxylic acid?

PROBLEM 21-71 Butacetin is an analgesic (pain-killing) agent that is synthesized commercially from *p*-fluoronitrobenzene. Propose a synthesis.



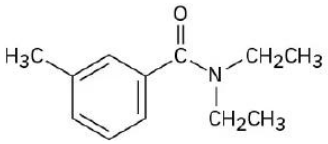
Butacetin

PROBLEM 21-72 Phenyl 4-aminosalicylate is a drug used in the treatment of tuberculosis. Propose a synthesis of this compound starting from 4-nitrosalicylic acid.



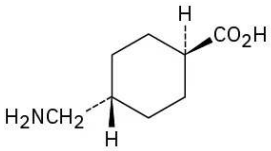
4-Nitrosalicylic acid **Phenyl 4-aminosalicylate**

PROBLEM 21-73 *N*,*N*-Diethyl-*m*-toluamide (DEET) is the active ingredient in many insect-repellent preparations. How might you synthesize this substance from *m*-bromotoluene?



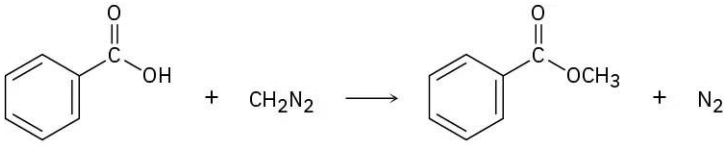
***N*,*N*-Diethyl-*m*-toluamide**

PROBLEM 21-74 Tranexamic acid, a drug useful against blood clotting, is prepared commercially from *p*-methylbenzonitrile. Formulate the steps likely to be used in the synthesis. (Don't worry about cis–trans isomers; heating to 300 °C interconverts the isomers.)



Tranexamic acid

PROBLEM 21-75 One frequently used method for preparing methyl esters is by reaction of carboxylic acids with diazomethane, CH_2N_2.



Benzoic acid **Diazomethane** **Methyl benzoate (100%)**

The reaction occurs in two steps: (**1**) protonation of diazomethane by the carboxylic acid to yield methyldiazonium ion, $CH_3N_2^+$, plus a carboxylate ion; and (**2**) reaction of the carboxylate ion with $CH_3N_2^+$.

(a) Draw two resonance structures of diazomethane, and account for step 1.

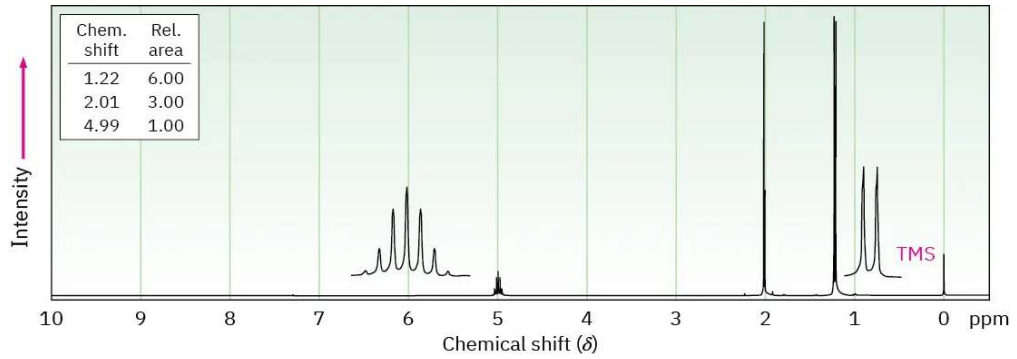
(b) What kind of reaction occurs in step 2?

PROBLEM 21-76 Draw the structure of the polymer you would expect to obtain from reaction of dimethyl terephthalate with a triol such as glycerol. What structural feature would this new polymer have that was not present in Dacron (Table 21.2)? How do you think this new feature might affect the properties of the polymer?

PROBLEM 21-77 Assign structures to compounds with the following ^1H NMR spectra:

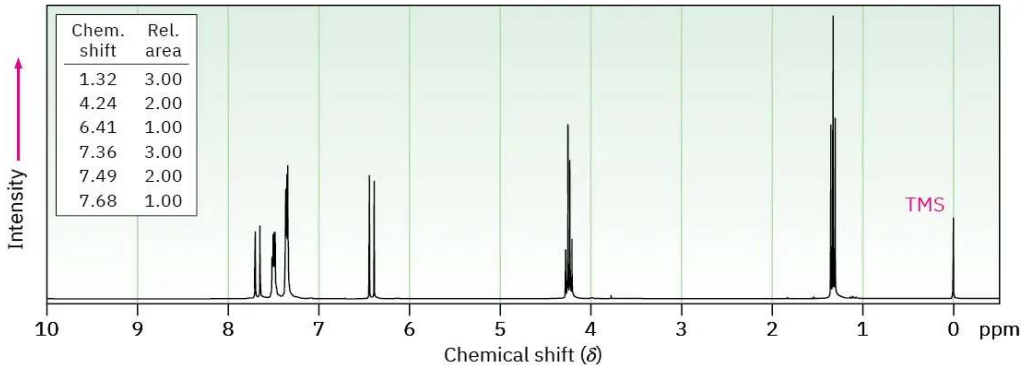
(a)$C_5H_{10}O_2$

IR: 1735 cm^{-1}



(b) $C_{11}H_{12}O_2$

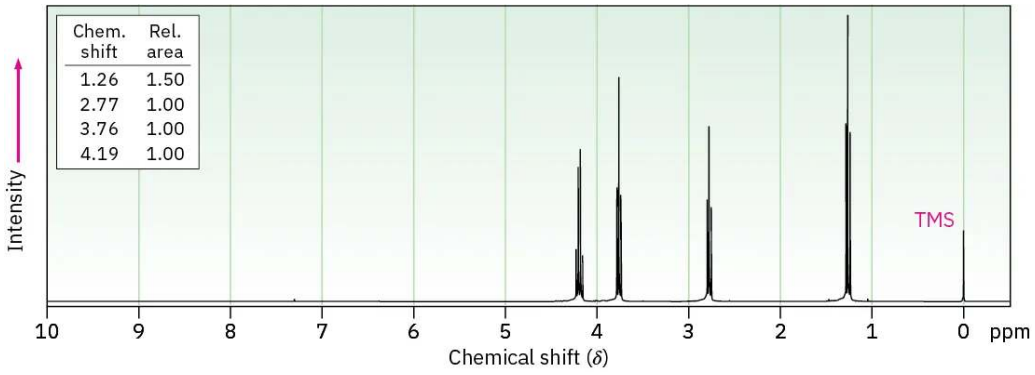
IR: 1710 cm^{-1}



PROBLEM 21-78 Propose structures for compounds with the following ^1H NMR spectra:

(a) $C_5H_9ClO_2$

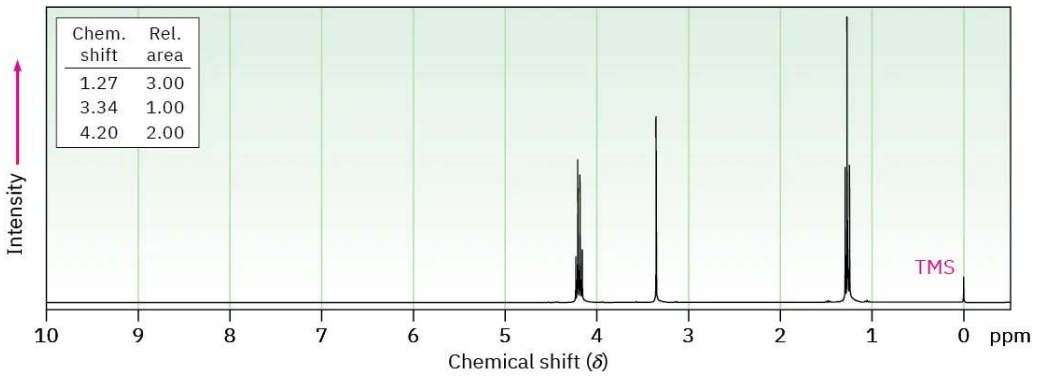
IR: 1735 cm^{-1}



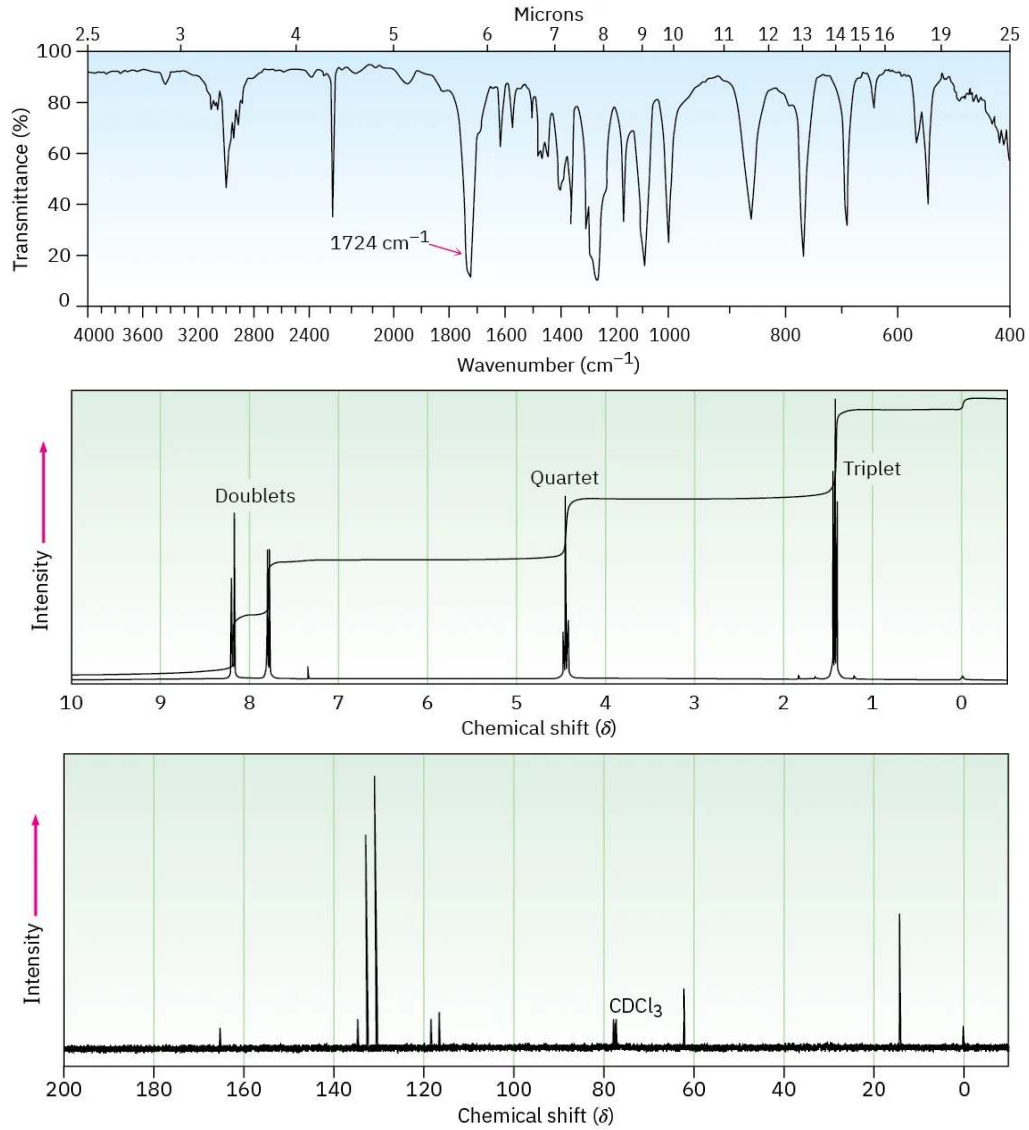
(b) $C_7H_{12}O_4$

IR: 1735 cm^{-1}

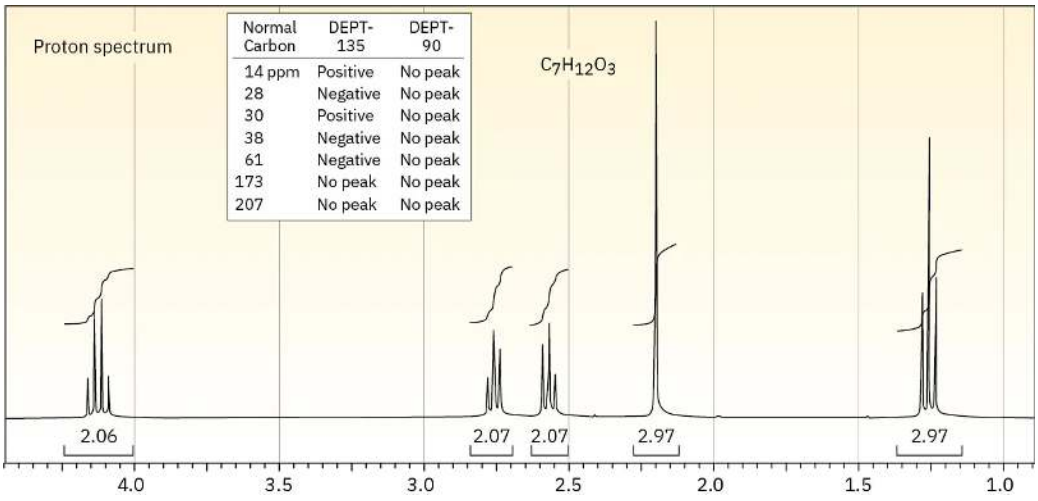
https://chem.libretexts.org/@go/page/564308



PROBLEM 21-79 Propose a structure for the compound with the formula $C_{19}H_9NO_2$ and the following IR and NMR spectra

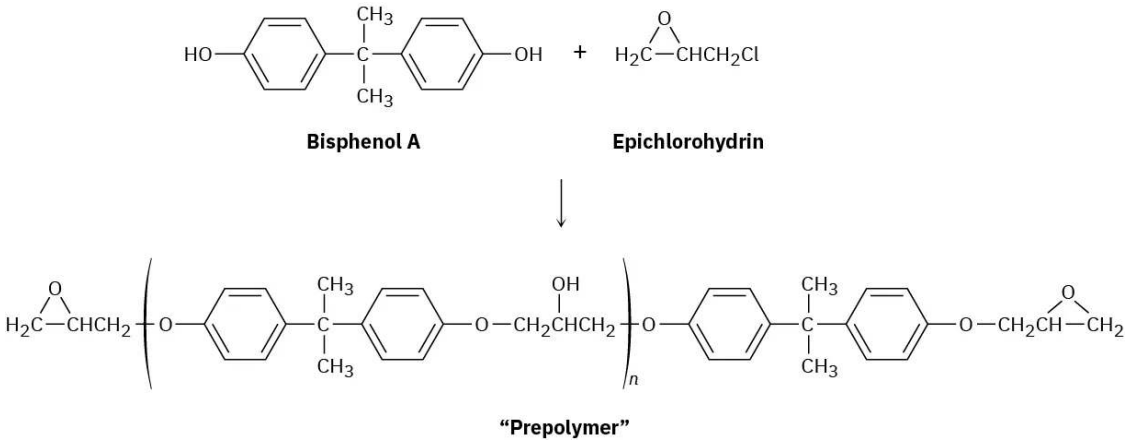


PROBLEM 21-80 Draw the structure of the compound that produced the following spectra. The infrared spectrum has strong bands at 1720 and 1738 cm^{-1}.



PROBLEM 21-81 When an amide is formed from an acid chloride or an anhydride, two equivalents of base are required. However, when an ester is used as the starting material, only one equivalent of base is needed. Explain this reactivity in terms of basicity of the leaving groups.

PROBLEM 21-82 Epoxy adhesives are prepared in two steps. S_N2 reaction of the disodium salt of bisphenol A with epichlorohydrin forms a "prepolymer," which is then "cured" by treatment with a triamine such as $H_2NCH_2CH_2NHCH_2CH_2NH_2$.



Draw structures to show how the addition of triamine results in the strengthening of the polymer.

This page titled 10.16: Additional Problems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **21.15: Additional Problems** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

SECTION OVERVIEW

10.17: Carbonyl Condensation Reactions

Learning Objectives

When you have completed Chapter 23, you should be able to

- fulfill all of the detailed objectives listed under each individual section.
- design multi-step syntheses in which the reactions introduced in this unit are used in conjunction with any of the reactions described in previous units.
- solve road-map problems that require a knowledge of carbonyl condensation reactions.
- define, and use in context, any of the key terms introduced.

In this chapter, we consider the fourth and final general type of reaction that carbonyl compounds undergo—the carbonyl condensation reaction. Carbonyl condensation reactions take place between two carbonyl-containing reactants, one of which must possess an alpha-hydrogen atom. The first step of the reaction involves the removal of an alpha-hydrogen atom by a base. In the second step, the enolate anion that results from this removal attacks the carbonyl-carbon of the second reacting molecule. In the final step of the reaction, a proton is transferred to the tetrahedral intermediate formed in the second step, although in some cases the product that results may subsequently be dehydrated.

This page titled 10.17: Carbonyl Condensation Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

CHAPTER OVERVIEW

11: Carbonyl Alpha-Substitution Reactions

Learning Objectives

When you have completed Chapter 22, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design multi-step syntheses in which the reactions introduced in this unit are used in conjunction with any of the reactions described in previous units.
3. solve road-map problems that require a knowledge of carbonyl alpha-substitution reactions.
4. define, and use in context, the key terms introduced.

Alpha-substitution reactions are the third major type of reaction that you will study in your investigation of the chemistry of carbonyl compounds. As you will see, these reactions proceed through the formation of the enol form of the carbonyl compound.

After a brief review of keto-enol tautomerism, we begin our discussion of alpha-substitution reactions by looking at the methods in which the enol form of the carbonyl compound is directly involved. After discussing the factors that influence the formation and stability of enolate anions, we will examine some halogenation reactions in which an enolate ion is formed as an intermediate.

The chapter concludes with a study of the alkylation of enolate anions. These reactions are of tremendous use in organic syntheses, as they provide a method of forming new carbon-carbon bonds, and hence facilitate the laboratory preparation of increasingly complex compounds.

11.1: Why This Chapter?
11.2: Keto-Enol Tautomerism
11.3: Reactivity of Enols- α-Substitution Reactions
11.4: Alpha Halogenation of Aldehydes and Ketones
11.5: Alpha Bromination of Carboxylic Acids
11.6: Acidity of Alpha Hydrogen Atoms- Enolate Ion Formation
11.7: Reactivity of Enolate Ions
11.8: Alkylation of Enolate Ions
11.9: Chemistry Matters—Barbiturates
11.10: Key Terms
11.11: Summary
11.12: Summary of Reactions
11.13: Additional Problems

This page titled 11: Carbonyl Alpha-Substitution Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

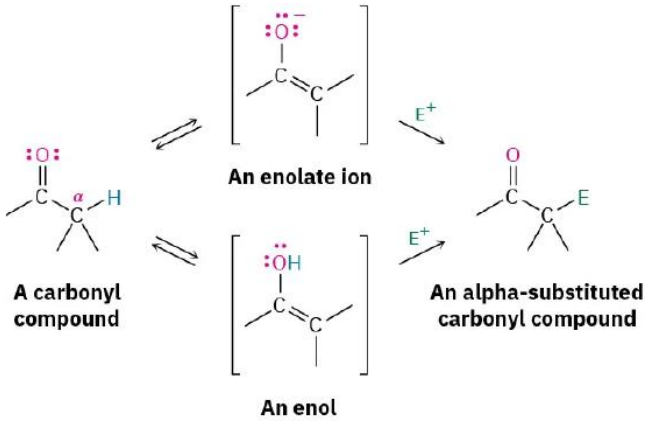
11.1: Why This Chapter?

As with nucleophilic additions and nucleophilic acyl substitutions, many laboratory schemes, pharmaceutical syntheses, and biochemical pathways make frequent use of carbonyl α-substitution reactions. Their great value comes from the fact that they constitute one of the few general methods for forming carbon–carbon bonds, thereby making it possible to build larger molecules from smaller precursors. In this chapter, we'll see how and why these reactions occur.

Figure 11.1.1: Tear gas is a controversial riot-control device used by some military and police forces. It is a simple chloroketone made by a carbonyl α-substitution reaction. (credit: "Tear Gas in CWB Hennessy Road View" by The Stand News/Wikimedia Commons, Public Domain)

We said in the *Preview of Carbonyl Chemistry* that much of the chemistry of carbonyl compounds can be explained by just four fundamental reaction types: nucleophilic additions, nucleophilic acyl substitutions, α substitutions, and carbonyl condensations. Having studied the first two of these reactions in the past three chapters, let's now look in more detail at the third major carbonyl-group process—the α-substitution reaction.

Alpha-substitution reactions occur at the position next to the carbonyl group—the *α position*—and involve the substitution of an α hydrogen atom by an electrophile, E, through either an enol or enolate ion intermediate. Let's begin by learning more about these two species.

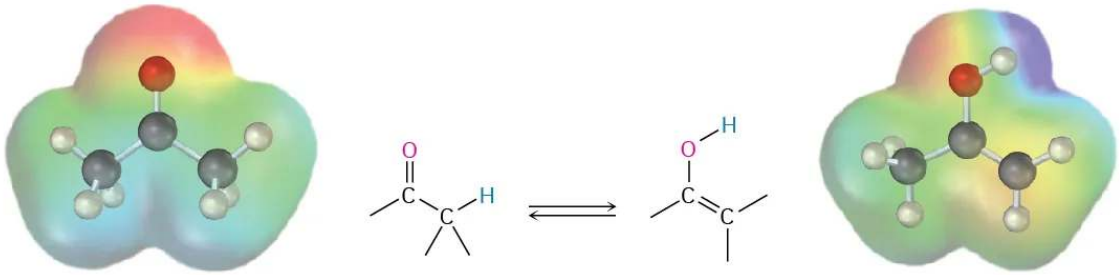


This page titled 11.1: Why This Chapter? is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **22.0: Why This Chapter?** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

11.2: Keto-Enol Tautomerism

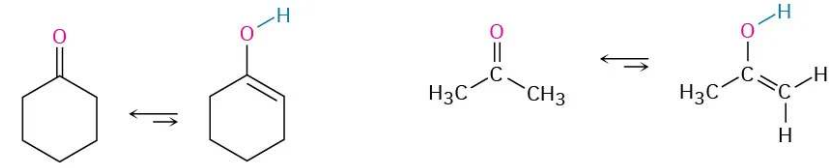
A carbonyl compound with a hydrogen atom on its α carbon is in equilibrium with its corresponding enol isomer (Section 9.4). This spontaneous interconversion between two isomers, usually with the change in position of a hydrogen, is called *tautomerism*, from the Greek *tauto*, meaning "the same," and *meros*, meaning "part." The individual keto and enol isomers are called tautomers.



Keto tautomer **Enol tautomer**

Note the difference between tautomers and resonance forms. Tautomers are constitutional isomers—different compounds with different structures—while resonance forms are different representations of a single compound. Tautomers have their *atoms* arranged differently, while resonance forms differ only in the position of their π and nonbonding *electrons*.

Most monocarbonyl compounds exist almost entirely in their keto form at equilibrium, and it's usually difficult to isolate the pure enol. Cyclohexanone, for example, contains only about 0.0001% of its enol tautomer at room temperature. The percentage of enol tautomer is even lower for carboxylic acids, esters, and amides. The enol can only predominate when stabilized by conjugation or intramolecular hydrogen bonding. Thus, 2,4-pentanedione is about 76% enol tautomer. Although enols are scarce at equilibrium, they are nevertheless responsible for much of the chemistry of carbonyl compounds because they are so reactive.



99.999 9% 0.000 1% 99.999 999 9% 0.000 000 1%

Cyclohexanone **Acetone**

Keto–enol tautomerism of carbonyl compounds is catalyzed by both acids and bases. Acid catalysis occurs by protonation of the carbonyl oxygen atom to give an intermediate cation that loses H^+ from its α carbon to yield a neutral enol (Figure 11.2.1*a*). This proton loss from the cation intermediate is similar to what occurs during an E1 reaction when a carbocation loses H^+ to form an alkene (Section 11.10).

Base-catalyzed enol formation occurs because the presence of a carbonyl group makes the hydrogens on the α carbon weakly acidic. Thus, a carbonyl compound can act as an acid and donate one of its α hydrogens to a sufficiently strong base. The resultant resonance-stabilized anion, an enolate ion, is then protonated to yield a neutral compound. If protonation of the enolate ion takes place on the α carbon, the keto tautomer is regenerated and no net change occurs. If, however, protonation takes place on the oxygen atom, an enol tautomer is formed (Figure 11.2.1*b*).

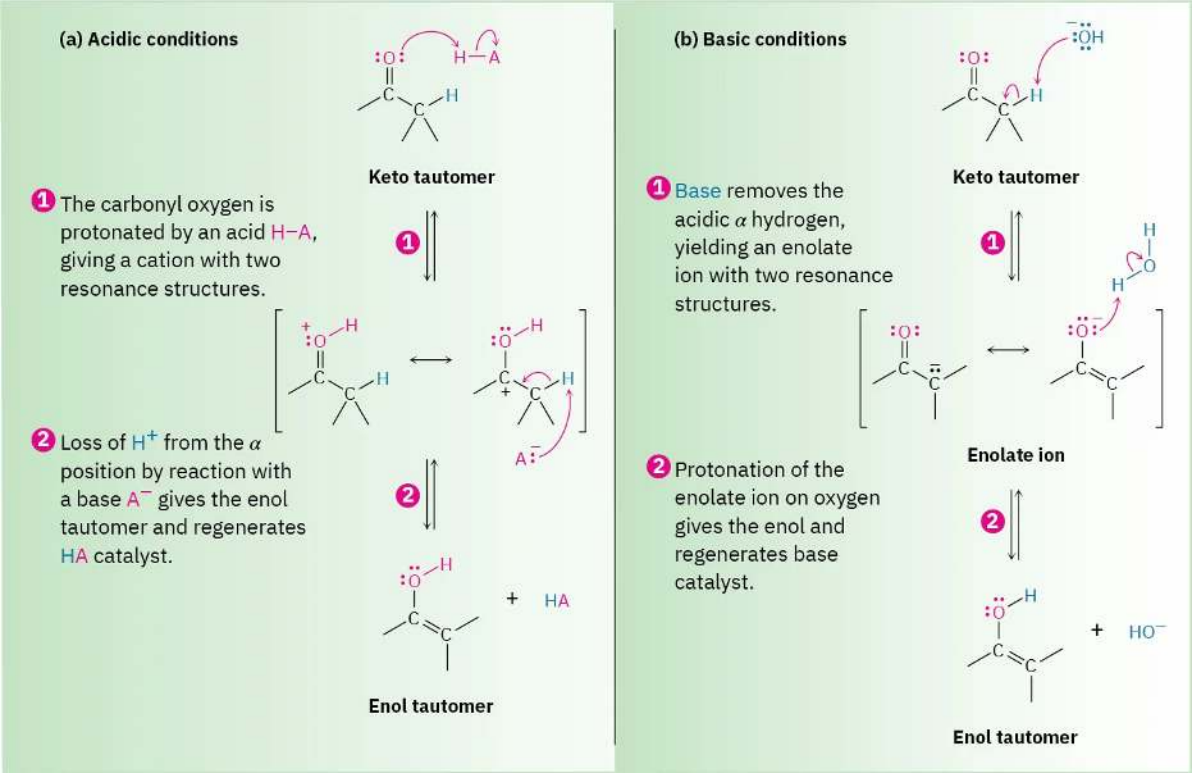
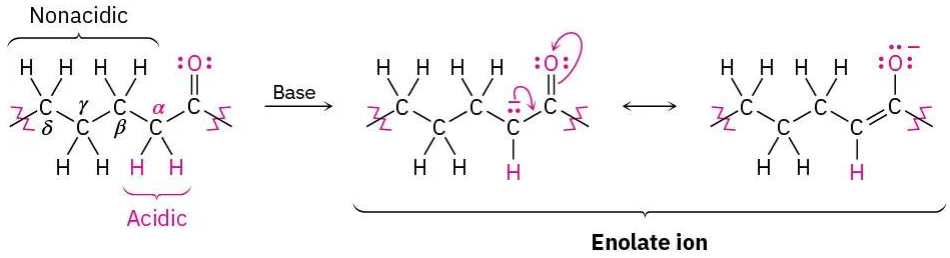


Figure 11.2.1: Mechanism of enol formation under both acid-catalyzed and base-catalyzed conditions. (a) Acid catalysis involves (1) initial protonation of the carbonyl oxygen followed by (2) removal of H^+ from the α position. (b) Base catalysis involves (1) initial deprotonation of the α position to give an enolate ion, followed by (2) reprotonation on oxygen.

Note that only the hydrogens on the α position of carbonyl compounds are acidic. Hydrogens at β, γ, δ, and so on, aren't acidic and can't be removed by base because the resulting anions can't be resonance-stabilized by the carbonyl group.

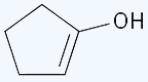


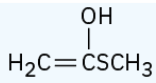
Exercise 11.2.1

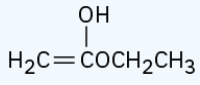
Draw structures for the enol tautomers of the following compounds:

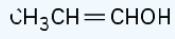
a. Cyclopentanone
b. Methyl thioacetate
c. Ethyl acetate
d. Propanal
e. Acetic acid
f. Phenylacetone

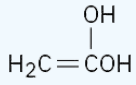
Answer

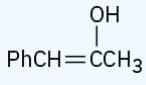
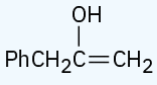
a. 

b. 

c. 

d. 

e. 

f.  or 

? Exercise 11.2.2

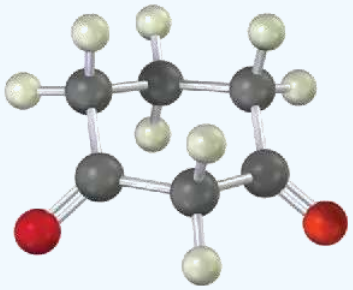
How many acidic hydrogens does each of the molecules listed in ? Exercise 11.2.2 have? Identify them.

Answer

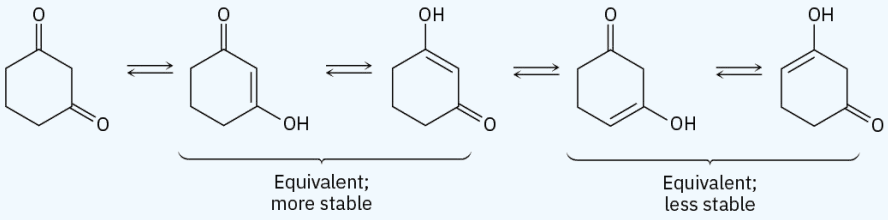
a. 4
b. 3
c. 3
d. 2
e. 4
f. 5

? Exercise 11.2.3

Draw structures for all monoenol forms of the following molecule. Which would you expect to be most stable? Explain.



Answer

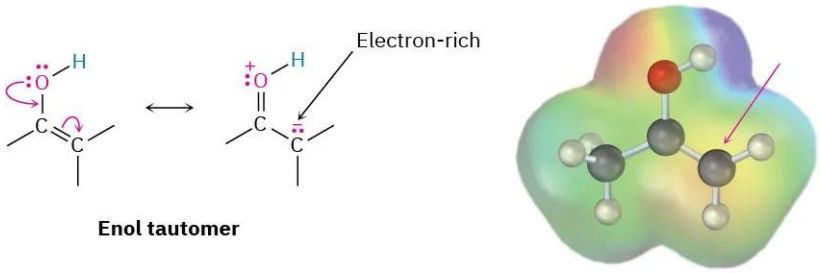


This page titled 11.2: Keto-Enol Tautomerism is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **22.1: Keto-Enol Tautomerism** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

11.3: Reactivity of Enols- α-Substitution Reactions

What kind of chemistry do enols have? Because their double bonds are electron-rich, enols behave as nucleophiles and react with electrophiles in much the same way that alkenes do. But because of resonance-electron donation of a lone pair of electrons on the neighboring oxygen, enols are more electron-rich and correspondingly more reactive than alkenes. Notice in the following electrostatic potential map of ethenol ($H_2C{=}CHOH$) how there is a substantial electron density (yellow-red) on the α carbon.



When an *alkene* reacts with an electrophile, E^+, initial addition gives an intermediate cation and subsequent reaction with a nucleophile, such as a halide ion, yields an addition product (Section 7.7). When an *enol* reacts with an electrophile, however, only the initial addition step is the same (Figure 11.3.1). Instead of reacting with a nucleophile to give an addition product, the intermediate cation loses the –OH proton to give an *α*-substituted carbonyl compound.

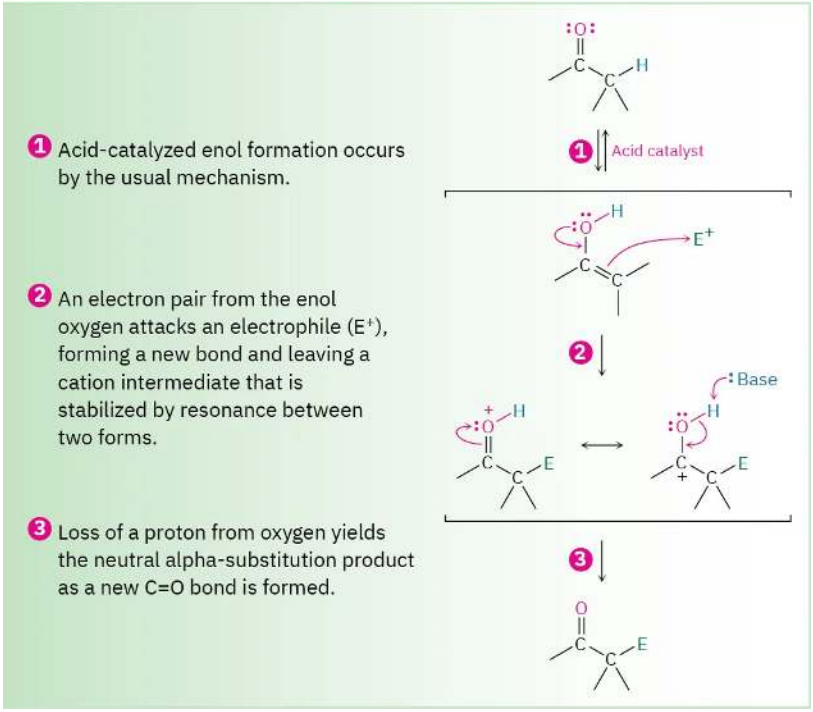


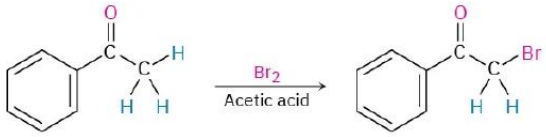
Figure 11.3.1: General mechanism of a carbonyl α-substitution reaction. In step 3, the initially formed cation loses H^+ to regenerate a carbonyl compound.

This page titled 11.3: Reactivity of Enols- α-Substitution Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **22.2: Reactivity of Enols- α-Substitution Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

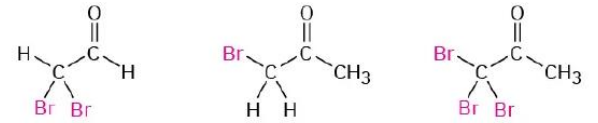
11.4: Alpha Halogenation of Aldehydes and Ketones

A particularly common α-substitution reaction in the laboratory is the halogenation of aldehydes and ketones at their α positions by reaction with Cl_2, Br_2, or I_2 in acidic solution. Bromine in acetic acid solvent is often used.



Acetophenone **α-Bromoacetophenone (72%)**

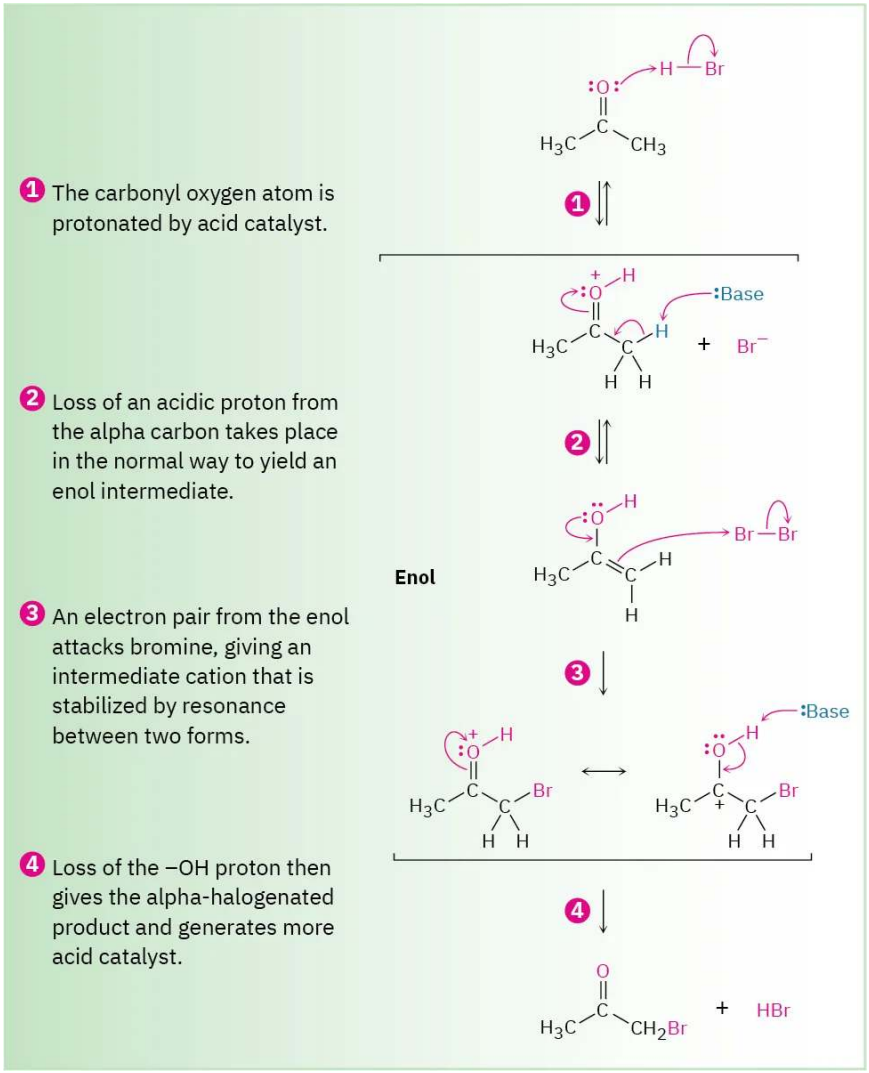
Remarkably, ketone halogenation also occurs in biological systems, particularly in marine alga, where dibromoacetaldehyde, bromoacetone, 1,1,1-tribromoacetone, and other related compounds have been found.



From the Hawaiian alga *Asparagopsis taxiformis*

This form of halogenation is a typical α-substitution reaction that proceeds by acid-catalyzed formation of an enol intermediate, as shown in Figure 11.4.1.

Figure 11.4.1: Mechanism of the acid-catalyzed bromination of acetone.

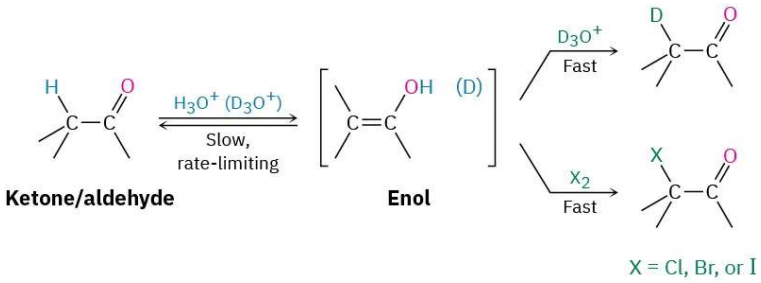


Evidence for the mechanism shown in Figure 11.4.1 includes the observation that acid-catalyzed halogenations show second-order kinetics and follow the rate law.

$$\text{Reaction rate} = k[\text{ Ketone }][\text{H}^+]$$

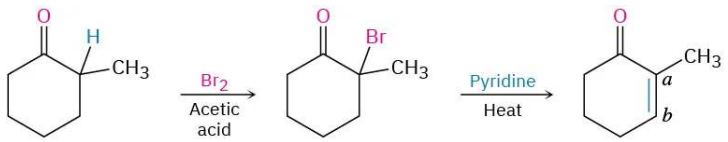
In other words, the rate of halogenation depends only on the concentrations of ketone and acid and is independent of halogen concentration. Since halogen is not involved in the rate-limiting step, chlorination, bromination, and iodination of a given substrate all occur at the same rate.

Furthermore, if an aldehyde or ketone is treated with D_3O^+, the acidic α hydrogens are replaced by deuterium. For a given ketone, the rate of deuterium exchange is identical to the rate of halogenation, implying that a common intermediate—presumably the enol—is involved in both processes.



https://chem.libretexts.org/@go/page/564314

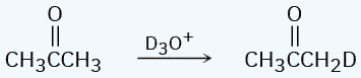
α-Bromo ketones are useful in the laboratory because they can be dehydrobrominated by base treatment to yield α,β-unsaturated ketones. For example, 2-methylcyclohexanone gives 2-bromo-2-methylcyclohexanone on halogenation, and the α-bromo ketone gives 2-methyl-2-cyclohexenone when heated in pyridine. The reaction takes place by an E2 elimination pathway (Section 11.8) and is a good method for introducing a C═CSection 7.6).



2-Methylcyclo-hexanone → **2-Bromo-2-methyl-cyclohexanone** → **2-Methyl-2-cyclo-hexenone (63%)**

Exercise 11.4.1

Write the complete mechanism for the deuteration of acetone on treatment with D_3O^+.



Answer

Acid-catalyzed formation of an enol is followed by deuteronation of the enol double bond and de-deuteronation of oxygen.

Exercise 11.4.2

Show how you might prepare 1-penten-3-one from 3-pentanone.

Answer

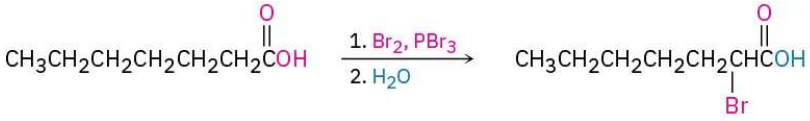
A1. Br_2; 2. Pyridine, heat

This page titled 11.4: Alpha Halogenation of Aldehydes and Ketones is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **22.3: Alpha Halogenation of Aldehydes and Ketones** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

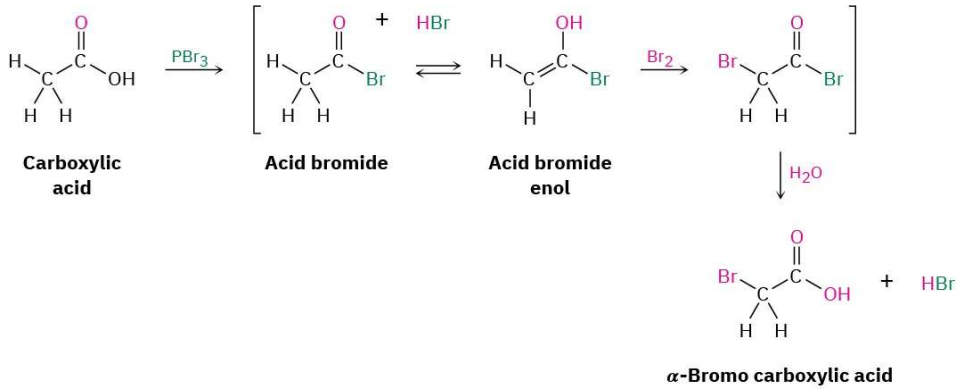
11.5: Alpha Bromination of Carboxylic Acids

The α bromination of carbonyl compounds by Br_2 in acetic acid is limited to aldehydes and ketones because acids, esters, and amides don't enolize to a sufficient extent. Carboxylic acids, however, can be α brominated by a mixture of Br_2 and PBr_3 in the *Hell–Volhard–Zelinskii (HVZ) reaction.*



Heptanoic acid **2-Bromoheptanoic acid (90%)**

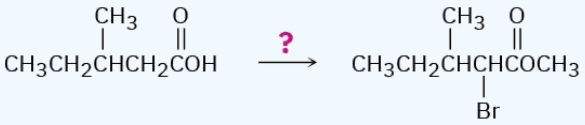
The Hell–Volhard–Zelinskii reaction is a bit more complex than it looks and actually involves α substitution of an acid bromide enol rather than a carboxylic acid enol. The process begins by reaction of the carboxylic acid with PBr_3 to form an acid bromide plus HBr (Section 21.4). The HBr then catalyzes enolization of the acid bromide, and the resultant enol reacts with Br_2 in an α-substitution reaction to give an α-bromo acid bromide. Addition of water hydrolyzes the acid bromide in a nucleophilic acyl substitution reaction and yields the α-bromo carboxylic acid product.



Carboxylic acid **Acid bromide** **Acid bromide enol** **α-Bromo carboxylic acid**

? Exercise 11.5.1

If methanol rather than water is added at the end of a Hell–Volhard–Zelinskii reaction, an ester rather than an acid is produced. Show how you would carry out the following transformation, and propose a mechanism for the ester-forming step.



Answer

The intermediate α-bromo acid bromide undergoes a nucleophilic acyl substitution reaction with methanol to give an α-bromo ester.

This page titled 11.5: Alpha Bromination of Carboxylic Acids is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **22.4: Alpha Bromination of Carboxylic Acids** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

11.6: Acidity of Alpha Hydrogen Atoms- Enolate Ion Formation

As noted in Section 22.1, a hydrogen on the α position of a carbonyl compound is weakly acidic and can be removed by a strong base to yield an enolate ion. In comparing acetone (pK_a = 19.3) with ethane ($pK_a \approx 60$), for instance, the presence of a neighboring carbonyl group increases the acidity of the ketone over the alkane by a factor of 10^{40}.

Acetone (pK_a = 19.3) **Ethane** ($pK_a \approx 60$)

Proton abstraction from a carbonyl compound occurs when the α C–H bond is oriented roughly parallel to the p orbitals of the carbonyl group. The α carbon atom of the enolate ion is sp^2-hybridized and has a p orbital that overlaps the neighboring carbonyl p orbitals. Thus, the negative charge is shared by the electronegative oxygen atom, and the enolate ion is stabilized by resonance (Figure 11.6.1).

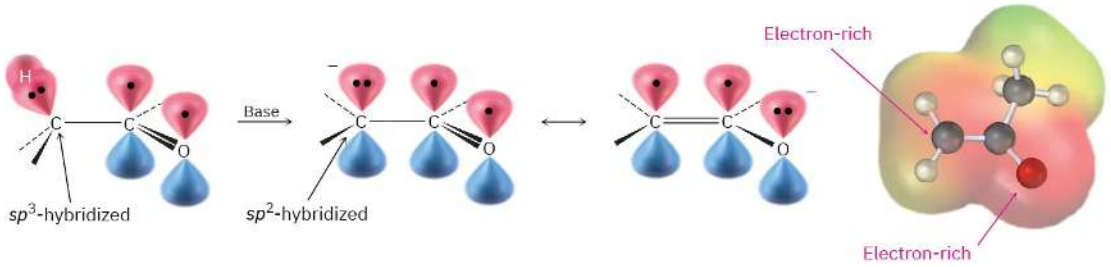
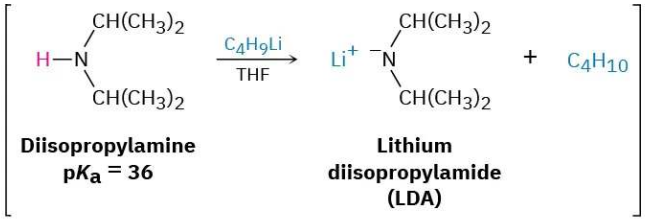


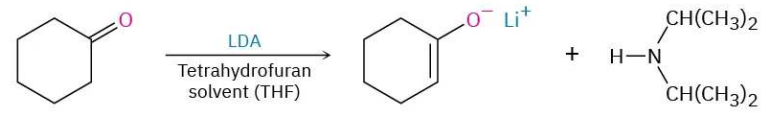
Figure 11.6.1: Mechanism of enolate-ion formation by abstraction of an α proton from a carbonyl compound. The enolate ion is stabilized by resonance, and the negative charge (red) is shared by the oxygen and the α carbon atom, as indicated in the electrostatic potential map.

Because carbonyl compounds are only weakly acidic, a strong base is needed for the formation of an enolate-ion. If an alkoxide ion, such as sodium ethoxide, is used as base, deprotonation of acetone only takes place to the extent of about 0.1% because acetone is a weaker acid than ethanol (pK_a = 16). If, however, a more powerful base is used, then a carbonyl compound is completely converted into its enolate ion.

In practice, the strong base lithium diisopropylamide [$LiN(i\text{-}C_3H_7)_2$; abbreviated LDA] is commonly used for making enolate ions. As the lithium salt of the weak acid diisopropylamine, pK_a = 36, LDA can readily deprotonate most carbonyl compounds. It is easily prepared by reaction of butyllithium with diisopropylamine and is soluble in organic solvents because of its two alkyl groups.



Diisopropylamine (pK_a = 36) **Lithium diisopropylamide (LDA)**

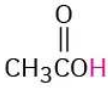
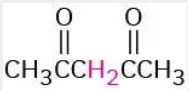
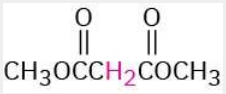
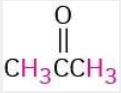
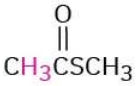


Cyclohexanone **Cyclohexanone enolate ion** **Diisopropylamine**

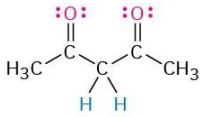
Many types of carbonyl compounds, including aldehydes, ketones, esters, thioesters, acids, and amides, can be converted into enolate ions by reaction with LDA. Table 11.6.1 lists the approximate pK_a values of different types of carbonyl compounds and

shows how these values compare to other acidic substances we've seen. Note that nitriles, too, are acidic and can be converted into enolate-like anions.

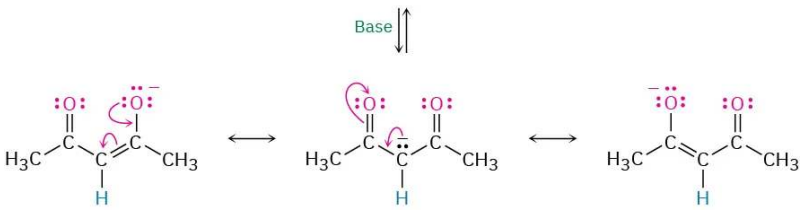
Table 11.6.1 Acidity Constants for Some Organic Compounds

Functional group	Example	pK_a
Carboxylic acid		5
1,3-Diketone		9
3-Keto ester		11
1,3-Diester		13
Alcohol	CH_3OH	16
Acid chloride		16
Aldehyde		17
Ketone		19
Thioester		21
Ester		25
Nitrile		25
N,*N*-Dialkylamide		30
Dialkylamine	$HN(i\text{-}C_3H_7)_2$	36

When a hydrogen atom is flanked by two carbonyl groups, its acidity is enhanced further. Table 11.6.1 thus shows that 1,3-diketones (*β*-diketones), 3-oxo esters (*β*-keto esters), and 1,3-diesters (malonic esters) are more acidic than water. The enolate ions derived from these *β*-dicarbonyl compounds are stabilized by sharing the negative charge of the two neighboring carbonyl oxygens. The enolate ion of 2,4-pentanedione, for instance, has three resonance forms. Similar resonance forms can be drawn for other doubly stabilized enolate ions.

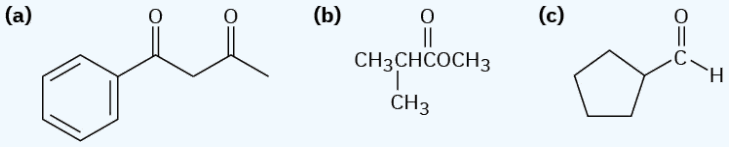


2,4-Pentanedione (pK_a = 9)



Worked Example 11.6.1: Identifying the Acidic Hydrogens in a Compound

Identify the most acidic hydrogens in each of the following compounds, and rank the compounds in order of increasing acidity:

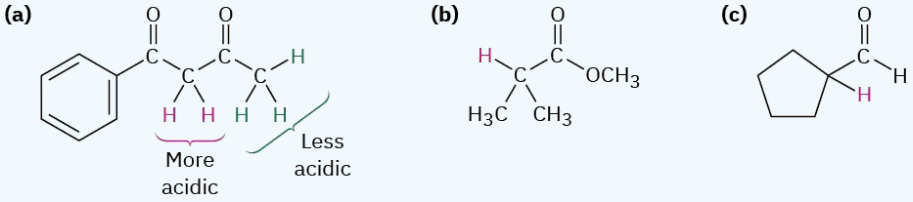


Strategy

Hydrogens on carbon next to a carbonyl group are acidic. In general, a β-dicarbonyl compound is most acidic, a ketone or aldehyde is next most acidic, and a carboxylic acid derivative is least acidic. Remember that alcohols, phenols, and carboxylic acids are also acidic because of their –OH hydrogens.

Solution

The acidity order is (**a**) > (**c**) > (**b**). Acidic hydrogens are shown in red.



Exercise 11.6.1

Identify the most acidic hydrogens in each of the following molecules:

a. CH_3CH_2CHO
b. $(CH_3)_3C{-}COCH_3$
c. CH_3CO_2H
d. Benzamide
e. $CH_3CH_2CH_2CN$
f. $CH_3CON(CH_3)_2$

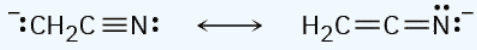
Answer

a. CH_3CH_2CHO
b. $(CH_3)_3CCOCH_3$
c. CH_3CO_2H
d. $PhCONH_2$
e. $CH_3CH_2CH_2CN$
f. $CH_3CON(CH_3)_2$

Exercise 11.6.2

Draw a resonance structure of the acetonitrile anion, $^{-}$:$CH_2C{\equiv}N$, and account for the acidity of nitriles.

Answer



This page titled 11.6: Acidity of Alpha Hydrogen Atoms- Enolate Ion Formation is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **22.5: Acidity of Alpha Hydrogen Atoms- Enolate Ion Formation** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

11.7: Reactivity of Enolate Ions

Enolate ions are more useful than enols for two reasons. First, pure enols can't normally be isolated but are instead generated only as short-lived intermediates in low concentration. By contrast, stable solutions of pure enolate ions are easily prepared from most carbonyl compounds by reaction with a strong base. Second, enolate ions are more reactive than enols and undergo many reactions that enols don't. Whereas enols are neutral, enolate ions are negatively charged, making them much better nucleophiles.

Because they are resonance hybrids of two nonequivalent forms, enolate ions can be looked at either as vinylic alkoxides (C═C−O−) or as α-keto carbanions (−C−C═O). Thus, enolate ions can react with electrophiles either on oxygen or on carbon. Reaction on oxygen yields an enol derivative, while reaction on carbon yields an α-substituted carbonyl compound (Figure 11.7.1). Both kinds of reactivity are known, but reaction on carbon is more common.

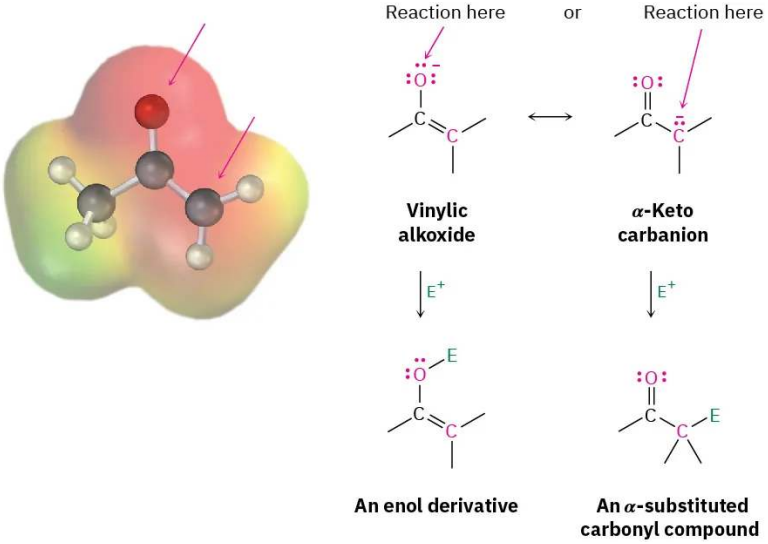
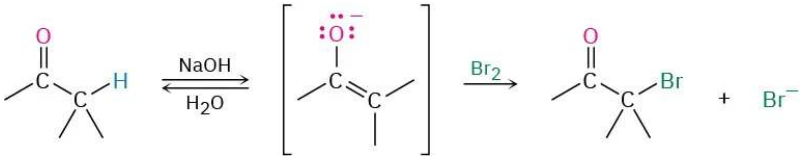


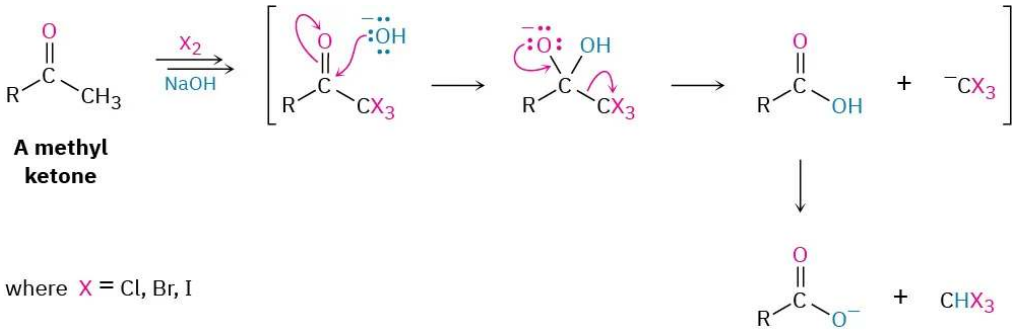
Figure 11.7.1: The electrostatic potential map of acetone enolate ion shows how the negative charge is delocalized over both the oxygen and the α carbon. As a result, two modes of reaction of an enolate ion with an electrophile E^+ are possible. Reaction on carbon to yield an α-substituted carbonyl product is more common.

As an example of enolate ion reactivity, aldehydes and ketones undergo base-promoted α halogenation. Even relatively weak bases such as hydroxide ion are effective for halogenation because it's not necessary to convert the ketone completely into its enolate ion. As soon as a small amount of enolate is generated, halogen reacts with it immediately, removing it from the reaction and driving the equilibrium toward further enolate ion formation.



Base-promoted halogenation of aldehydes and ketones is seldom used in practice because it's difficult to stop the reaction at the monosubstituted product. An α-halogenated ketone is generally more acidic than the starting, unsubstituted ketone because of the electron-withdrawing inductive effect of the halogen atom. Thus, the monohalogenated products are themselves rapidly turned into enolate ions and further halogenated.

If excess base and halogen are used, a methyl ketone is triply halogenated and then cleaved by base in the **haloform reaction.** The products are a carboxylic acid plus a so-called haloform (chloroform, $CHCl_3$; bromoform, $CHBr_3$; or iodoform, CHI_3). Note that the second step of the reaction is a nucleophilic acyl substitution of $^-CX_3$ by ^-OH. That is, a halogen-stabilized carbanion acts as a leaving group.



? Exercise 11.7.1

Why do you suppose ketone halogenations in acidic media are referred to as being acid-*catalyzed*, whereas halogenations in basic media are base-*promoted*? In other words, why is a full equivalent of base required for halogenation?

Answer

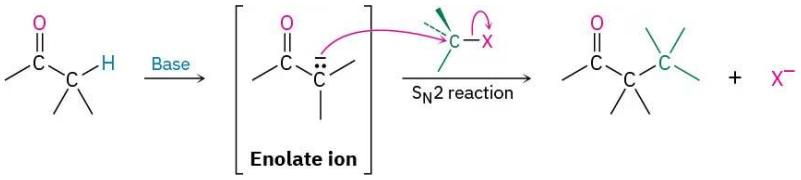
a. 1. $Na^+ {}^-OEt$; 2. $PhCH_2Br$; 3. H_3O^+
b. 1. $Na^+ {}^-OEt$; 2. $CH_3CH_2CH_2Br$; 3. $Na^+ {}^-OEt$; 4. CH_3Br; 5. H_3O^+
c. 1. $Na^+ {}^-OEt$; 2. $(CH_3)_2CHCH_2Br$; 3. H_3O^+

This page titled 11.7: Reactivity of Enolate Ions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

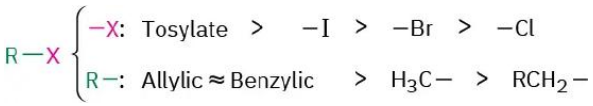
- **22.6: Reactivity of Enolate Ions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

11.8: Alkylation of Enolate Ions

Perhaps the most useful reaction of enolate ions is their alkylation by treatment with an alkyl halide, thereby forming a new C−C bond and joining two smaller pieces into one larger molecule. Alkylation occurs when the nucleophilic enolate ion reacts with the electrophilic alkyl halide in an S_N2 reaction and displaces the leaving group by backside attack.

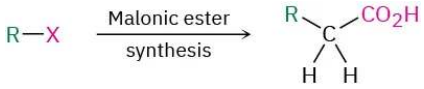


Alkylation reactions are subject to the same constraints that affect all S_N2 reactions (Section 11.3). Thus, the leaving group X in the alkylating agent R−X can be chloride, bromide, or iodide. The alkyl group R should be primary or methyl, and preferably should be allylic or benzylic. Secondary halides react poorly, and tertiary halides don't react at all because a competing E2 elimination of HX occurs instead. Vinylic and aryl halides are also unreactive because a backside approach is sterically prevented.

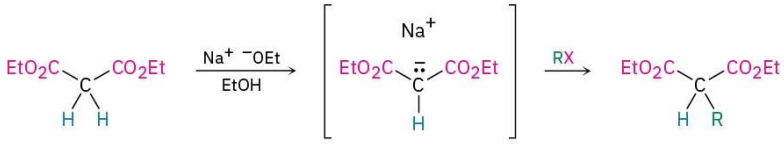


The Malonic Ester Synthesis

One of the oldest and best known carbonyl alkylation reactions is the malonic ester synthesis, a method for preparing a carboxylic acid from an alkyl halide while lengthening the carbon chain by two atoms.

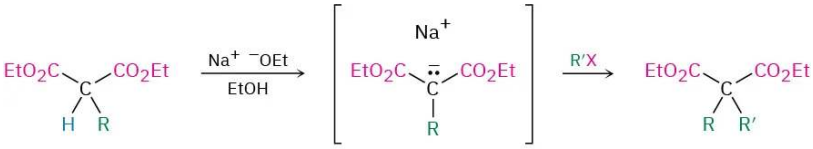


Diethyl propanedioate, commonly called diethyl malonate, or *malonic ester,* is relatively acidic (pK_a = 13) because its *α* hydrogens are flanked by two carbonyl groups. Thus, malonic ester is easily converted into its enolate ion by reaction with sodium ethoxide in ethanol. The enolate ion, in turn, is a good nucleophile that reacts rapidly with an alkyl halide to give an *α*-substituted malonic ester. Note in the following examples that the abbreviation "Et" is used for an ethyl group, $–CH_2CH_3$.



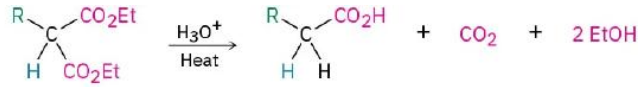
Diethyl propanedioate (malonic ester) | **Sodio malonic ester** | **An alkylated malonic ester**

The product of a malonic ester alkylation has one acidic *α* hydrogen remaining, so the alkylation process can be repeated to yield a dialkylated malonic ester.



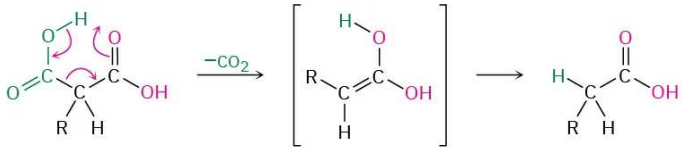
An alkylated malonic ester | **A dialkylated malonic ester**

On heating with aqueous hydrochloric acid, the alkylated (or dialkylated) malonic ester undergoes hydrolysis of its two ester groups followed by *decarboxylation* (loss of CO_2) to yield a substituted monocarboxylic acid.

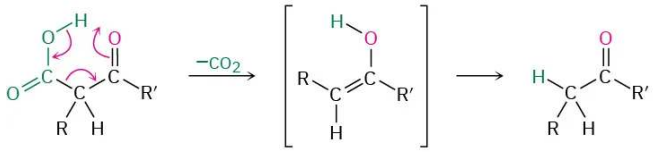


An alkylated malonic ester **A carboxylic acid**

Decarboxylation is not a general reaction of carboxylic acids. Rather, it is unique to compounds that have a second carbonyl group two atoms away from the $-CO_2H$. That is, only substituted malonic acids and β-keto acids undergo loss of CO_2 on heating. The decarboxylation reaction occurs by a cyclic mechanism and involves initial formation of an enol, thereby accounting for the need to have a second carbonyl group appropriately positioned.

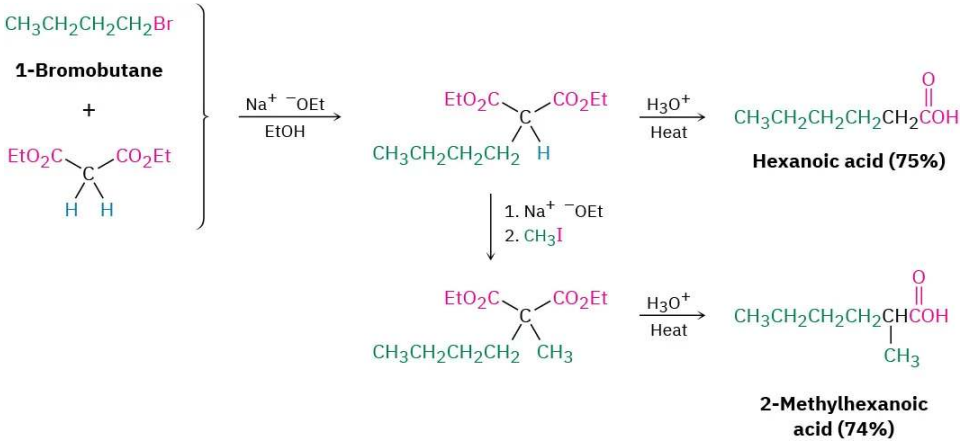


A diacid **An acid enol** **A carboxylic acid**

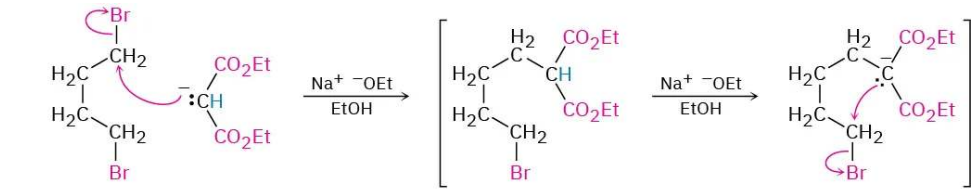


A β-keto acid **An enol** **A ketone**

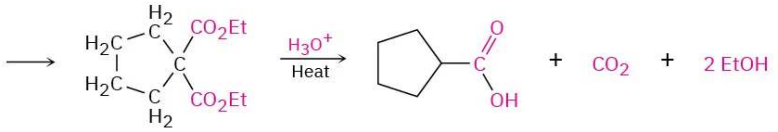
As noted previously, the overall effect of malonic ester synthesis is to convert an alkyl halide into a carboxylic acid while lengthening the carbon chain by two atoms ($RX \rightarrow RCH_2CO_2H$).



A malonic ester synthesis can also be used to prepare *cyclo*alkanecarboxylic acids. For example, when 1,4-dibromobutane is treated with diethyl malonate in the presence of two equivalents of sodium ethoxide base, the second alkylation step occurs intramolecularly to yield a cyclic product. Hydrolysis and decarboxylation then give cyclopentanecarboxylic acid. Three-, four-, five-, and six-membered rings can be prepared in this way, but yields decrease for larger ring sizes.



1,4-Dibromobutane



Cyclopentane-carboxylic acid

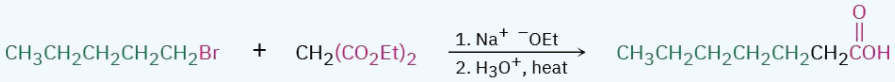
Worked Example 11.8.1: Using Malonic Ester Synthesis to Prepare a Carboxylic Acid

How would you prepare heptanoic acid using a malonic ester synthesis?

Strategy

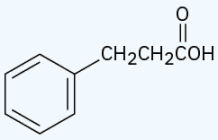
A malonic ester synthesis converts an alkyl halide into a carboxylic acid having two more carbons. Thus, a seven-carbon acid chain must be derived from the five-carbon alkyl halide 1-bromopentane.

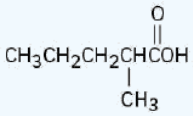
Solution

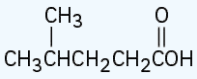


Exercise 11.8.1

How could you use a malonic ester synthesis to prepare the following compounds? Show all steps.

a. 

b. 

c. 

Answer

a. 1. $Na^+ {}^-OEt$; 2. $PhCH_2Br$; 3. H_3O^+
b. 1. $Na^+ {}^-OEt$; 2. $CH_3CH_2CH_2Br$; 3. $Na^+ {}^-OEt$; 4. CH_3Br; 5. H_3O^+
c. 1. $Na^+ {}^-OEt$; 2. $(CH_3)_2CHCH_2Br$; 3. H_3O^+

Exercise 11.8.2

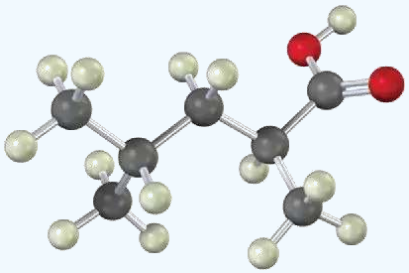
Monoalkylated and dialkylated acetic acids can be prepared by malonic ester synthesis, but trialkylated acetic acids ($R_3C–CO_2H$) can't be prepared. Explain.

Answer

Malonic ester has only two acidic hydrogens to be replaced.

? Exercise 11.8.3

How could you use a malonic ester synthesis to prepare the following compound?

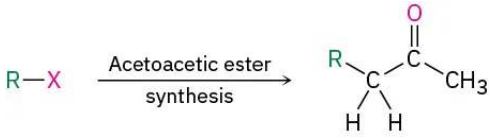


Answer

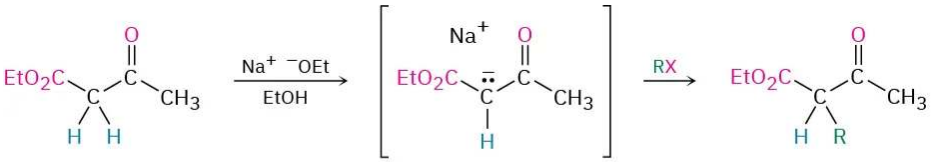
1. $Na^+ {}^-OEt$; 2. $(CH_3)_2CHCH_2Br$; 3. $Na^+ {}^-OEt$; 4. CH_3Br; 5. H_3O^+

The Acetoacetic Ester Synthesis

Just as the malonic ester synthesis converts an alkyl halide into a carboxylic acid, the acetoacetic ester synthesis converts an alkyl halide into a methyl ketone having three more carbons.



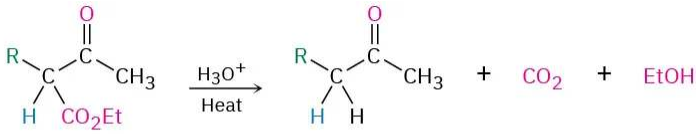
Ethyl 3-oxobutanoate, commonly called ethyl acetoacetate, or *acetoacetic ester*, is much like malonic ester in that its α hydrogens are flanked by two carbonyl groups. It is therefore readily converted into its enolate ion, which can be alkylated by reaction with an alkyl halide. A second alkylation can also be carried out if desired, since acetoacetic ester has two acidic α hydrogens.



Ethyl acetoacetate (acetoacetic ester) — **Sodio acetoacetic ester** — **A monoalkylated acetoacetic ester**

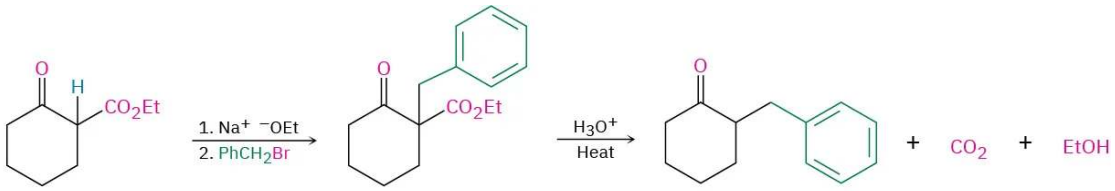
A monoalkylated acetoacetic ester — **A dialkylated acetoacetic ester**

On heating with aqueous HCl, the alkylated (or dialkylated) acetoacetic ester is hydrolyzed to a β-keto acid, which then undergoes decarboxylation to yield a ketone product. The decarboxylation occurs in the same way as in the malonic ester synthesis and involves a ketone enol as the initial product.



An alkylated acetoacetic ester — **A methyl ketone**

The three-step sequence of (**1**) enolate ion formation, (**2**) alkylation, and (**3**) hydrolysis/decarboxylation is applicable to all β-keto esters with acidic α hydrogens, not just to acetoacetic ester itself. For example, cyclic β-keto esters, such as ethyl 2-oxocyclohexanecarboxylate, can be alkylated and decarboxylated to give 2-substituted cyclohexanones.



Ethyl 2-oxocyclohexane-carboxylate (a cyclic β-keto ester)

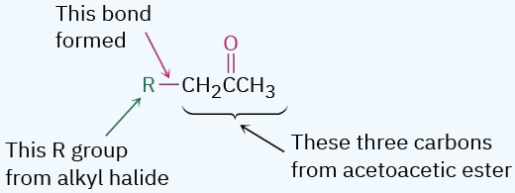
2-Benzylcyclohexanone (77%)

Worked Example 11.8.1: Using Acetoacetic Ester Synthesis to Prepare a Ketone

How would you prepare 2-pentanone by an acetoacetic ester synthesis?

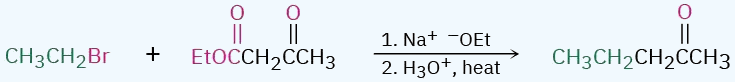
Strategy

An acetoacetic ester synthesis yields a methyl ketone by adding three carbons to an alkyl halide.



Thus, the acetoacetic ester synthesis of 2-pentanone must involve reaction of bromoethane.

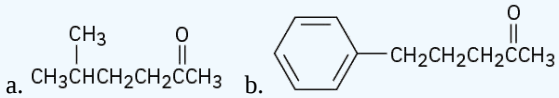
Solution



2-Pentanone

Exercise 11.8.4

What alkyl halides would you use to prepare the following ketones by an acetoacetic ester synthesis?



Answer

a. $(CH_3)_2CHCH_2Br$ b. $PhCH_2CH_2Br$

Exercise 11.8.5

Which of the following compounds can't be prepared by an acetoacetic ester synthesis? Explain.

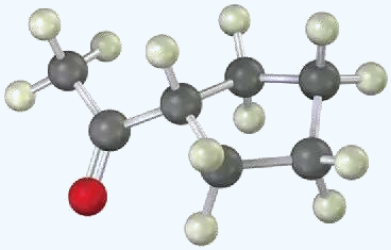
a. Phenylacetone
b. Acetophenone
c. 3,3-Dimethyl-2-butanone

Answer

None can be prepared.

? Exercise 11.8.6

How would you prepare the following compound using an acetoacetic ester synthesis?



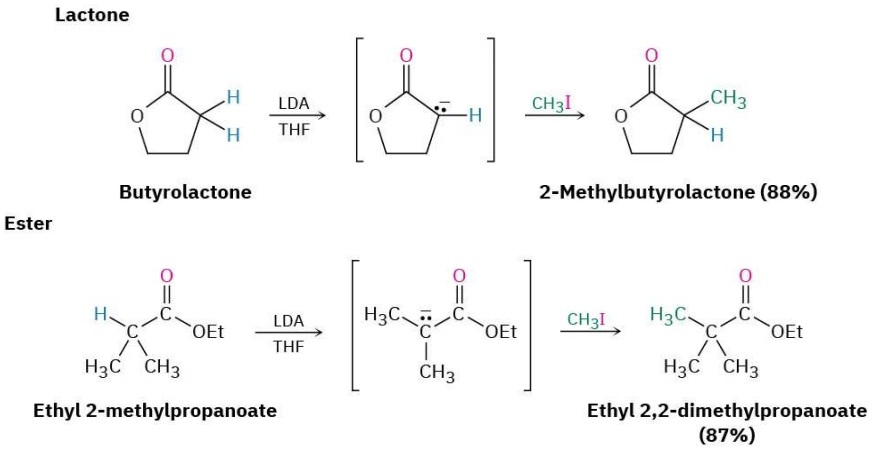
Answer

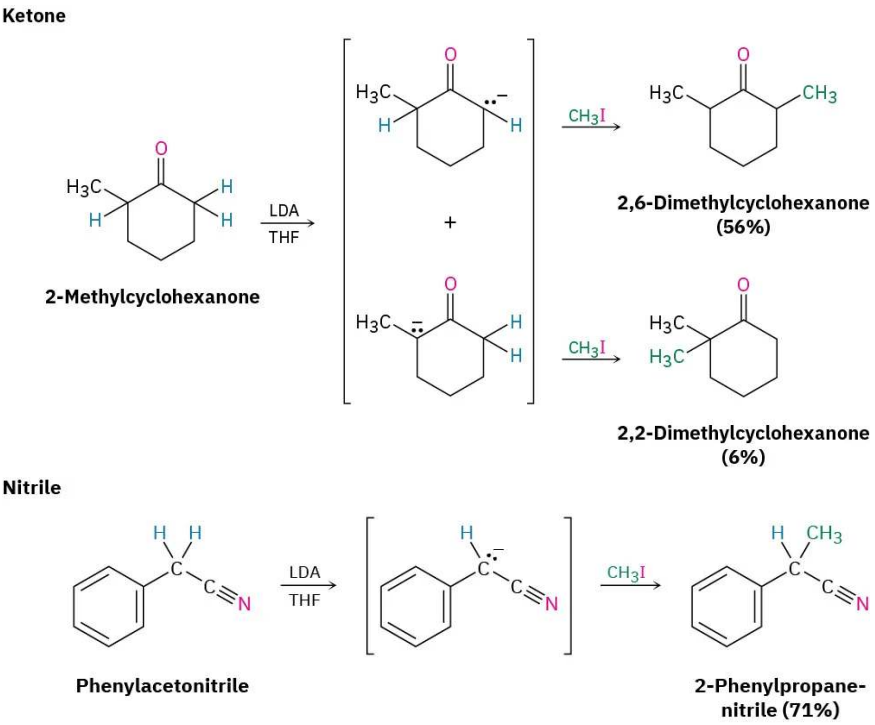
1. 2 $Na^+ {}^-OEt$; 2. $BrCH_2CH_2CH_2CH_2Br$; 3. H_3O^+

Direct Alkylation of Ketones, Esters, and Nitriles

Both the malonic ester synthesis and the acetoacetic ester synthesis are easy to carry out because they involve relatively acidic dicarbonyl compounds. As a result, sodium ethoxide in ethanol can be used to prepare the necessary enolate ions. Alternatively, however, it's also possible in many cases to directly alkylate the *α* position of *mono*carbonyl compounds. A strong, sterically hindered base such as LDA is needed so that complete conversion to the enolate ion takes place rather than a nucleophilic addition, and a nonprotic solvent must be used.

Ketones, esters, and nitriles can all be alkylated using LDA or related dialkylamide bases in tetrahydrofuran (THF). Aldehydes, however, rarely give high yields of pure products because their enolate ions undergo carbonyl condensation reactions instead of alkylation. (We'll study this condensation reaction in the next chapter.) Some specific examples of alkylation reactions are shown.

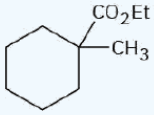




Note in the ketone example that alkylation of 2-methylcyclohexanone leads to a mixture of products because both possible enolate ions are formed. In general, the major product in such cases occurs by alkylation at the less hindered, more accessible position. Thus, alkylation of 2-methylcyclohexanone occurs primarily at C6 (secondary) rather than C2 (tertiary).

Worked Example 11.8.2: Using an Alkylation Reaction to Prepare a Substituted Ester

How might you use an alkylation reaction to prepare ethyl 1-methylcyclohexanecarboxylate?

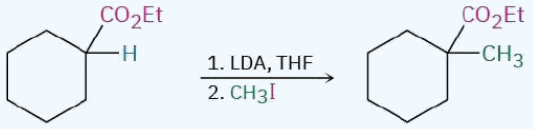


Ethyl 1-methylcyclohexanecarboxylate

Strategy

An alkylation reaction is used to introduce a methyl or primary alkyl group onto the α position of a ketone, ester, or nitrile by S_N2 reaction of an enolate ion with an alkyl halide. Thus, we need to look at the target molecule and identify any methyl or primary alkyl groups attached to an α carbon. In the present instance, the target has an α methyl group, which might be introduced by alkylation of an ester enolate ion with iodomethane.

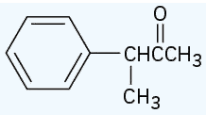
Solution

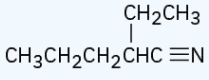


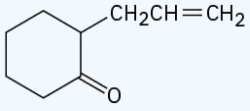
Ethyl cyclohexane-carboxylate **Ethyl 1-methylcyclo-hexanecarboxylate**

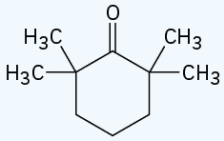
Exercise 11.8.7

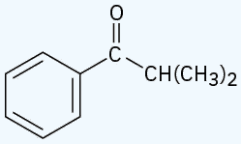
Show how you might prepare the following compounds using an alkylation reaction as the key step:

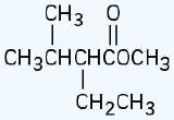
a. 

b. 

c. 

d. 

e. 

f. 

Answer

a. Alkylate phenylacetone with CH_3I
b. Alkylate pentanenitrile with CH_3CH_2I
c. Alkylate cyclohexanone with $H_2C{=}{=}CHCH_2Br$
d. Alkylate cyclohexanone with excess CH_3I
e. Alkylate $C_6H_5COCH_2CH_3$ with CH_3I
f. Alkylate methyl 3-methylbutanoate with CH_3CH_2I

Biological Alkylations

Alkylations are rare but not unknown in biological chemistry. One example occurs during biosynthesis of the antibiotic indolmycin from indolylpyruvate when a base abstracts an acidic hydrogen from an α position and the resultant enolate ion carries out an S_N2 alkylation reaction on the methyl group of *S*-adenosylmethionine (SAM; Section 11.6). Although it's convenient to speak of "enolate ion" intermediates in biological pathways, it's unlikely that they exist for long in an aqueous cellular environment. Rather, proton removal and alkylation probably occur at essentially the same time (Figure 11.8.1).

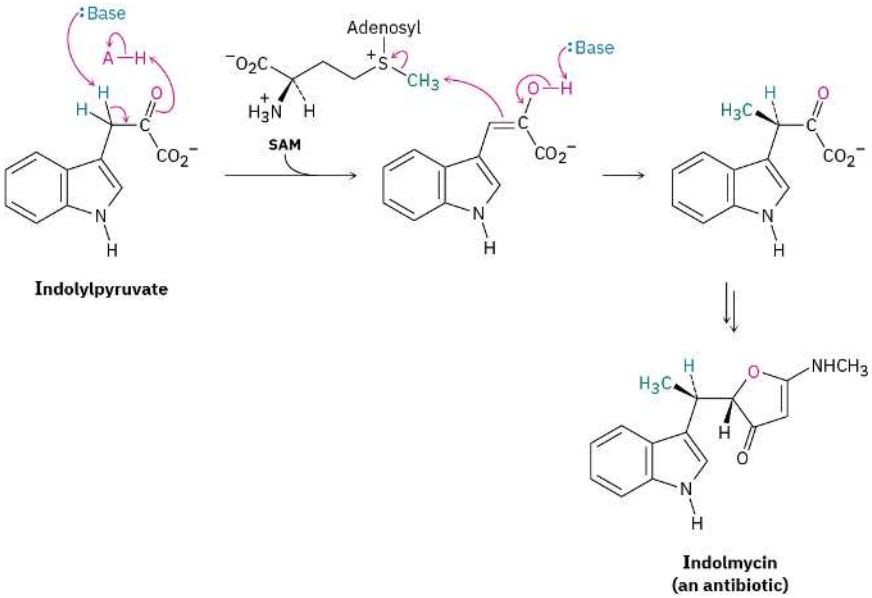


Figure 11.8.1: The biosynthesis of indolmycin from indolylpyruvate occurs through a pathway that includes an alkylation reaction of a short-lived enolate ion intermediate.

This page titled 11.8: Alkylation of Enolate Ions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **22.7: Alkylation of Enolate Ions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

11.9: Chemistry Matters—Barbiturates

The use of herbal remedies to treat illness and disease goes back thousands of years, but the medical use of chemicals prepared in the laboratory has a much shorter history. Barbiturates, a large class of drugs with a wide variety of uses, constitute one of the earliest successes of medicinal chemistry. The synthesis and medical use of barbiturates goes back to 1904 when Bayer, a German chemical company, first marketed a compound called barbital, trade named Veronal, as a treatment for insomnia. Since that time, more than 2500 different barbiturate analogs have been synthesized by drug companies, more than 50 have been used medicinally, and about a dozen are still in use as anesthetics, anticonvulsants, sedatives, and anxiolytics.

Figure 11.9.1: Different barbiturates come in a multitude of colors, giving rise to similarly colorful street names when the drugs are abused. (credit: “Medications” by freestocks.org/Flickr, Public Domain)

The synthesis of barbiturates is relatively simple and relies on reactions that are now familiar: enolate alkylations and nucleophilic acyl substitutions. Starting with diethyl malonate, alkylation of the corresponding enolate ion with simple alkyl halides provides a wealth of different disubstituted malonic esters. Reaction with urea, $(H_2N)_2C{=}O$, then gives the product barbiturates by a twofold nucleophilic acyl substitution reaction of the ester groups with the $-NH_2$ groups of urea (Figure 11.9.2). Amobarbital (Amytal), pentobarbital (Nembutal), and secobarbital (Seconal) are typical examples.

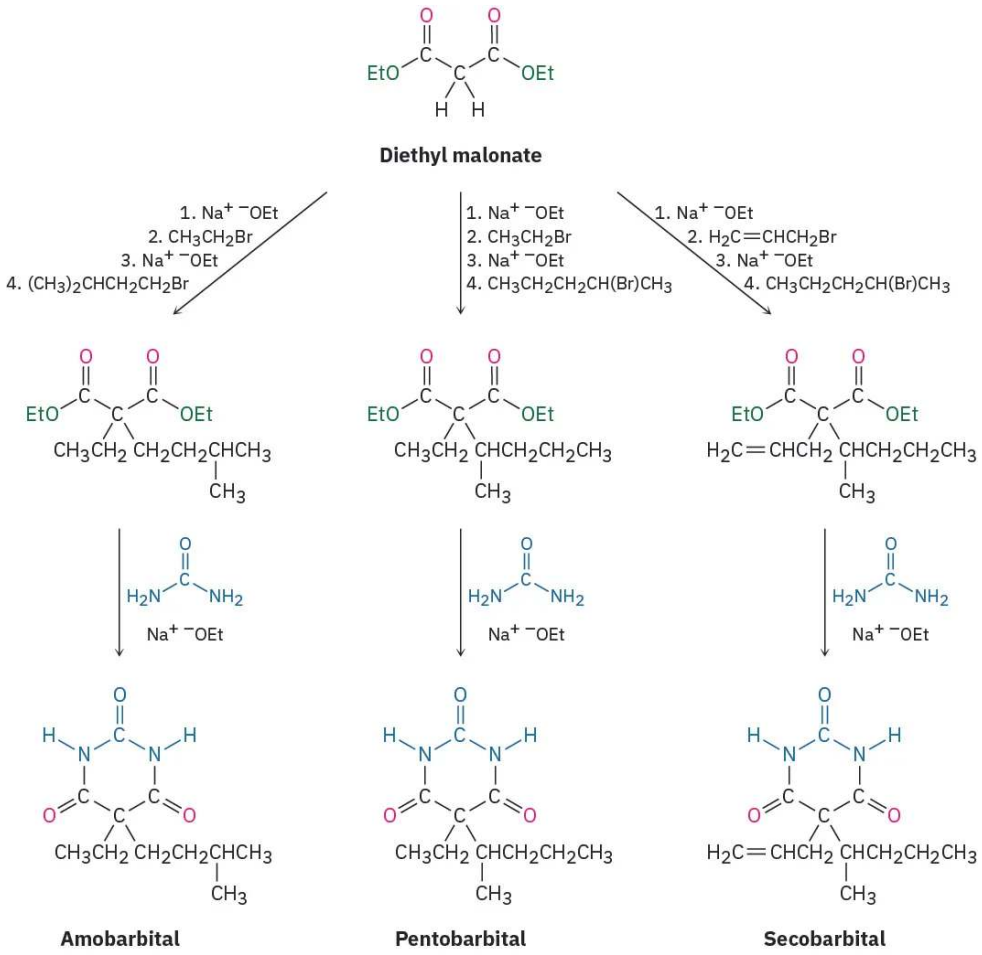
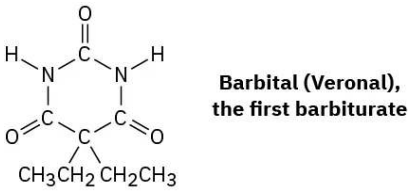


Figure 11.9.2: The synthesis of barbiturates relies on malonic ester alkylations and nucleophilic acyl substitution reactions. More than 2500 different barbiturates have been synthesized over the past 100 years.



In addition to their prescribed medical uses, many barbiturates have also found widespread illegal use as street drugs. Each barbiturate often comes as a tablet of regulated size, shape, and color. Although still used today, most barbiturates have been replaced by safer, more potent alternatives with markedly different structures.

This page titled 11.9: Chemistry Matters—Barbiturates is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **22.8: Chemistry Matters—Barbiturates** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

11.10: Key Terms

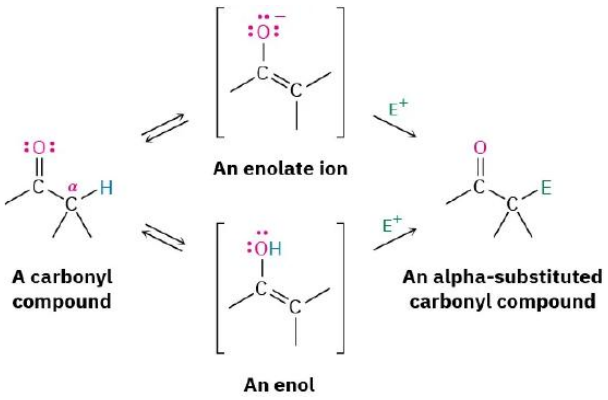
- acetoacetic ester synthesis
- α-substitution reaction
- decarboxylation
- enol
- enolate ion
- malonic ester synthesis
- tautomer

This page titled 11.10: Key Terms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **22.9: Key Terms** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

11.11: Summary

The α-substitution reaction of a carbonyl compound through either an **enol** or **enolate ion** intermediate is one of the four fundamental reaction types in carbonyl-group chemistry.



Carbonyl compounds are in an equilibrium with their enols, a process called keto–enol tautomerism. Although enol **tautomers** are normally present to only a small extent at equilibrium and can't usually be isolated in pure form, they nevertheless contain a highly nucleophilic double bond and react with electrophiles in an ***α*-substitution reaction**. An example is the α halogenation of ketones on treatment with Cl_2, Br_2, or I_2 in acid solution. Alpha bromination of carboxylic acids can be similarly accomplished by the Hell–Volhard–Zelinskii (HVZ) reaction, in which an acid is treated with Br_2 and PBr_3. The α-halogenated products can then undergo base-induced E2 elimination to yield α,β-unsaturated carbonyl compounds.

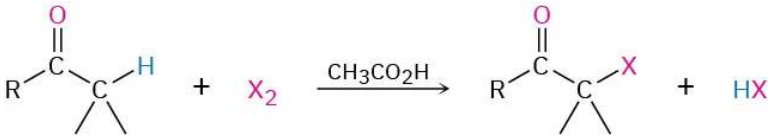
Alpha hydrogen atoms of carbonyl compounds are weakly acidic and can be removed by strong bases, such as lithium diisopropylamide (LDA), to yield nucleophilic enolate ions. The most useful reaction of enolate ions is their S_N2 alkylation with alkyl halides. The **Malonic ester synthesis** converts an alkyl halide into a carboxylic acid with the addition of two carbon atoms ($RX \rightarrow RCH_2CO_2H$). Similarly, the **acetoacetic ester synthesis** converts an alkyl halide into a methyl ketone with the addition of three carbon atoms ($RX \rightarrow RCH_2COCH_3$). In addition, many carbonyl compounds, including ketones, esters, and nitriles, can be directly alkylated by treatment with LDA and an alkyl halide.

This page titled 11.11: Summary is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

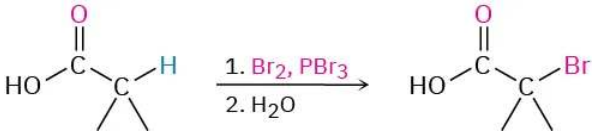
- **22.10: Summary** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

11.12: Summary of Reactions

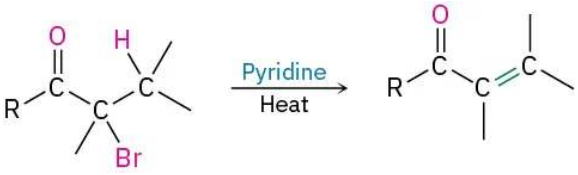
1. Aldehyde/ketone halogenation (Section 22.3)



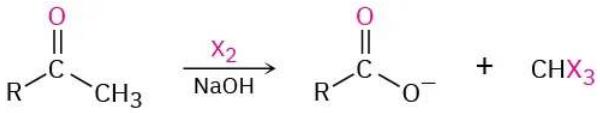
- Hell–Volhard–Zelinskii bromination of acids (Section 22.4)



- Dehydrobromination of α-bromo ketones (Section 22.3)

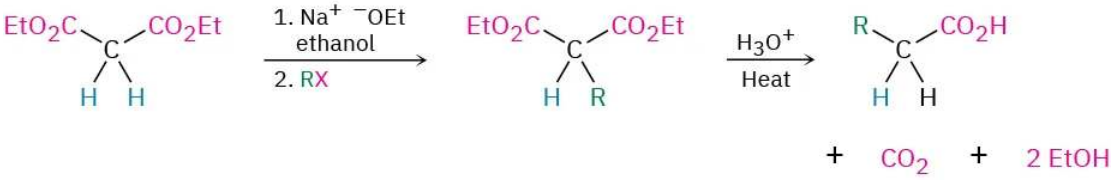


- Haloform reaction (Section 22.6)

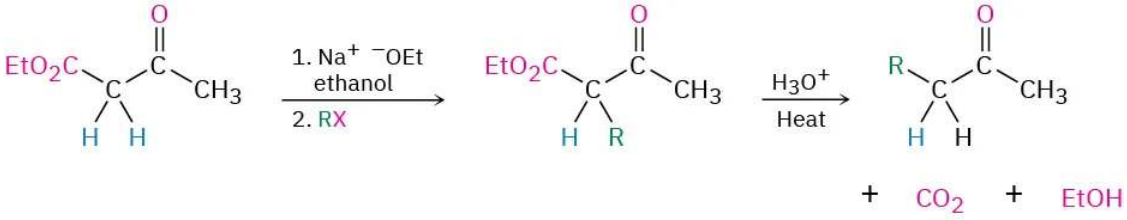


- Alkylation of enolate ions (Section 22.7)

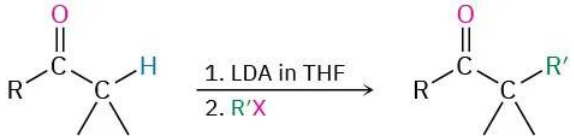
a. Malonic ester synthesis



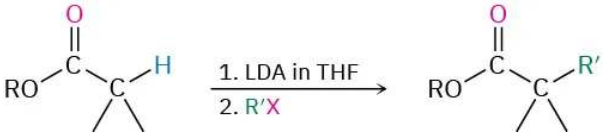
b. Acetoacetic ester synthesis



c. Direct alkylation of ketones



d. Direct alkylation of esters



e. Direct alkylation of nitriles

https://chem.libretexts.org/@go/page/564322

This page titled 11.12: Summary of Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

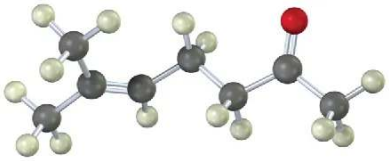
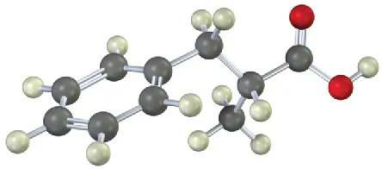
- **22.11: Summary of Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

11.13: Additional Problems

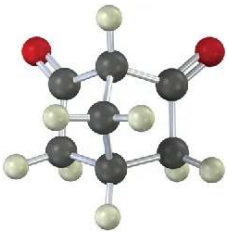
22 • Additional Problems

Visualizing Chemistry

PROBLEM 22-17 Show the steps in preparing each of the following substances using either a malonic ester synthesis or an acetoacetic ester synthesis:

(a)  (b) 

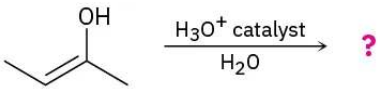
PROBLEM 22-18 Unlike most β-diketones, the following β-diketone has no detectable enol content and is about as acidic as acetone. Explain.

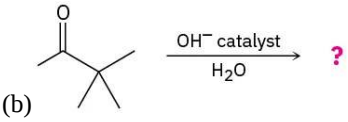


PROBLEM 22-19 For a given α-hydrogen atom to be acidic, the C–H bond must be parallel to the p orbitals of the C Math input error

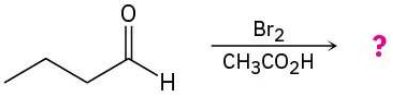
Mechanism Problems

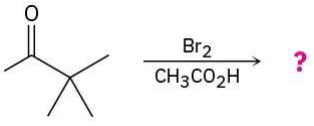
PROBLEM 22-20 Draw the corresponding keto or enol tautomer for each of the following molecules.

(a) 

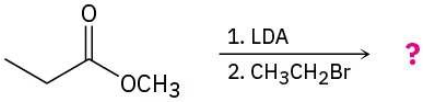
(b) 

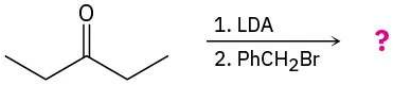
PROBLEM 22-21 Predict the product(s) and show the mechanism for each of the following reactions:

(a) 

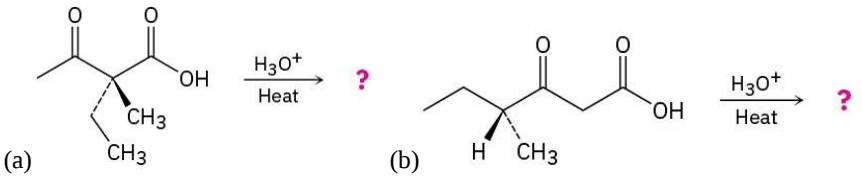
(b) 

PROBLEM 22-22 Predict the product(s) and show the mechanism for each of the following reactions:

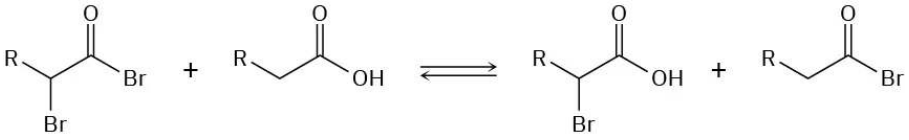
(a) 

(b) 

PROBLEM 22-23 The following two optically active β-keto acids were decarboxylated under the conditions typically used for the acetoacetic ester synthesis. Will the ketone products be optically active? Explain.

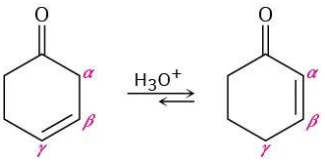


PROBLEM 22-24 In the Hell–Volhard–Zelinskii reaction, only a catalytic amount of PBr_3 is necessary because of the following equilibrium. Propose a mechanism for formation of the equilibrium.

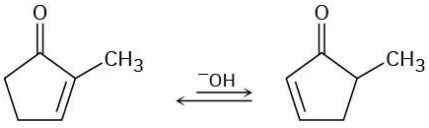


PROBLEM 22-25 When a ketone is treated with a halogen under acidic conditions, the α-monohalogenated product can be obtained in high yield. Under basic conditions however it is difficult to isolate the monohalogenated product. Explain.

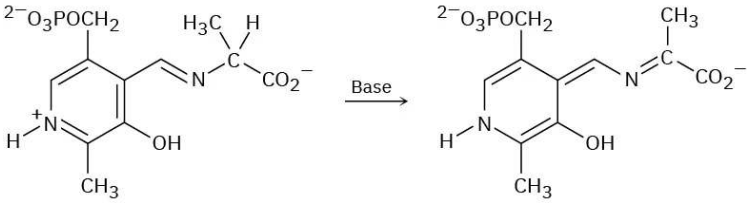
PROBLEM 22-26 Nonconjugated β,γ-unsaturated ketones, such as 3-cyclohexenone, are in an acid-catalyzed equilibrium with their conjugated α,β-unsaturated isomers. Propose a mechanism for the isomerization.



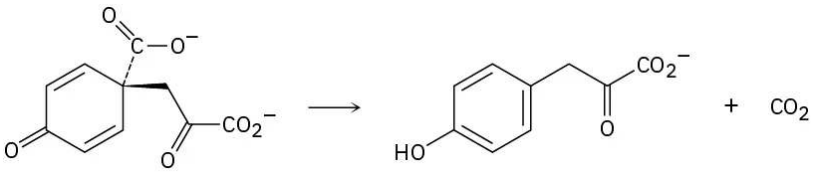
PROBLEM 22-27 2-substituted 2-cyclopentenones can be interconverted with 5-substituted 2-cyclopentenones under basic conditions. Propose a mechanism for this isomerization.



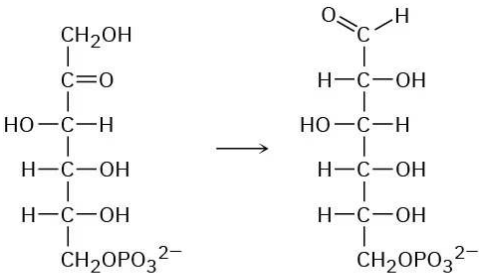
PROBLEM 22-28 Using curved arrows, propose a mechanism for the following reaction, one of the steps in the metabolism of the amino acid alanine.



PROBLEM 22-29 Using curved arrows, propose a mechanism for the following reaction, one of the steps in the biosynthesis of the amino acid tyrosine.

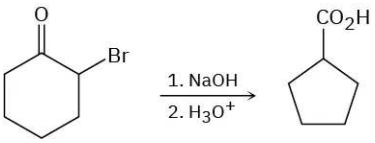


PROBLEM 22-30 One of the later steps in glucose biosynthesis is the isomerization of fructose 6-phosphate to glucose 6-phosphate. Propose a mechanism, using acid or base catalysis as needed.

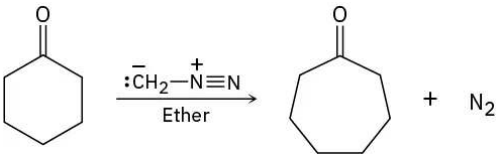


Fructose 6-phosphate **Glucose 6-phosphate**

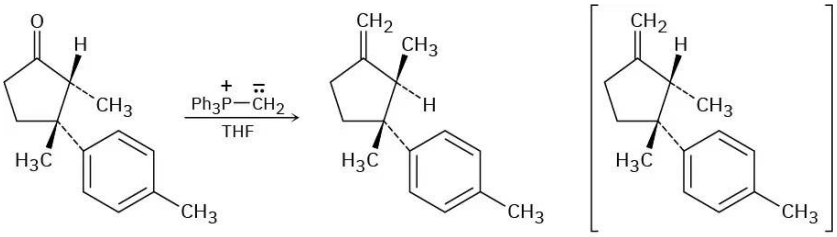
PROBLEM 22-31 The *Favorskii reaction* involves treatment of an α-bromo ketone with base to yield a ring-contracted product. For example, reaction of 2-bromocyclohexanone with aqueous NaOH yields cyclopentanecarboxylic acid. Propose a mechanism.



PROBLEM 22-32 Treatment of a cyclic ketone with diazomethane is a method for accomplishing a ring-expansion reaction. For example, treatment of cyclohexanone with diazomethane yields cycloheptanone. Propose a mechanism.

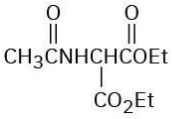


PROBLEM 22-33 The final step in an attempted synthesis of laurene, a hydrocarbon isolated from the marine alga *Laurencia glandulifera*, involved the Wittig reaction shown. The product obtained, however, was not laurene but an isomer. Propose a mechanism to account for the unexpected results.



Laurene
(Not formed)

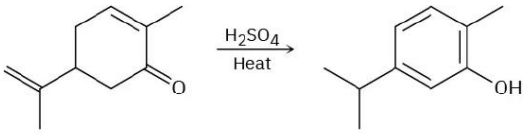
PROBLEM 22-34 Amino acids can be prepared by reaction of alkyl halides with diethyl acetamidomalonate, followed by heating the initial alkylation product with aqueous HCl. Show how you would prepare alanine, $CH_3CH(NH_2)CO_2H$, one of the twenty amino acids found in proteins, and propose a mechanism for acid-catalyzed conversion of the initial alkylation product to the amino acid.



Diethyl acetamidomalonate

PROBLEM 22-35 Amino acids can also be prepared by a two-step sequence that involves Hell–Volhard–Zelinskii reaction of a carboxylic acid followed by treatment with ammonia. Show how you would prepare leucine, $(CH_3)_2CHCH_2CH(NH_2)CO_2H$, and identify the mechanism of the second step.

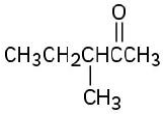
PROBLEM 22-36 Heating carvone with aqueous sulfuric acid converts it into carvacrol. Propose a mechanism for the isomerization.



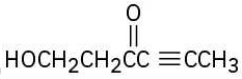
Carvone **Carvacrol**

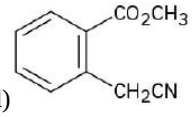
Acidity of Carbonyl Compounds

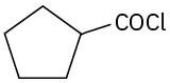
PROBLEM 22-37 Identify all the acidic hydrogens (p<i">K_a < 25) in the following molecules:

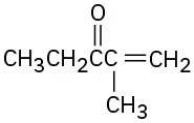
(a) 

(b)

(c) 

(d) 

(e) 

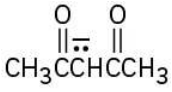
(f) 

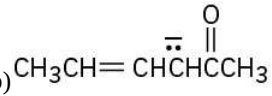
PROBLEM 22-38 Rank the following compounds in order of increasing acidity:

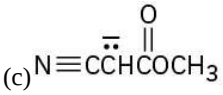
(a) $CH_3CH_2CO_2H$ **(b)** CH_3CH_2OH **(c)** $(CH_3CH_2)_2NH$

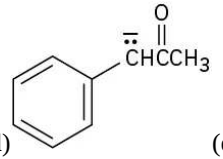
(d) CH_3COCH_3 **(e)** $CH_3CCH_2CCH_3$ **(f)** CCl_3CO_2H

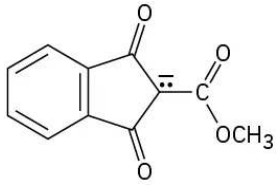
PROBLEM 22-39 Write resonance structures for the following anions:

(a) 

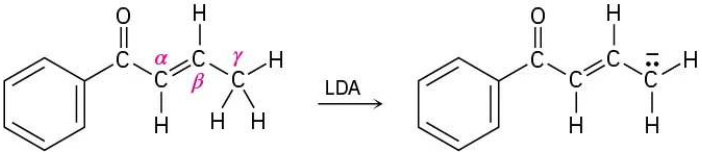
(b) 

(c) 

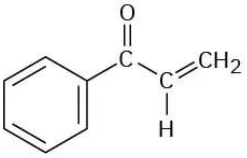
(d) 

(e) 

PROBLEM 22-40 Base treatment of the following α,β-unsaturated carbonyl compound yields an anion by removal of H^+ from the γ carbon. Why are hydrogens on the γ carbon atom acidic?



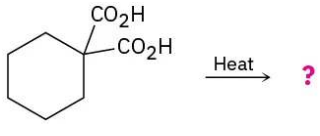
PROBLEM 22-41 Treatment of 1-phenyl-2-propenone with a strong base such as LDA does not yield an anion, even though it contains a hydrogen on the carbon atom next to the carbonyl group. Explain.

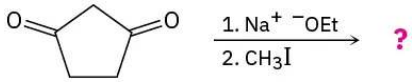


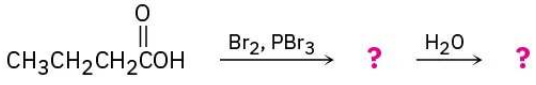
1-Phenyl-2-propenone

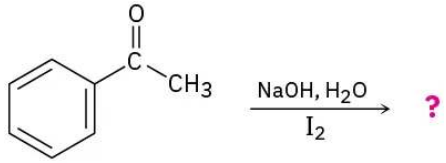
α-Substitution Reactions

PROBLEM 22-42 Predict the product(s) of the following reactions:

(a) 

(b) 

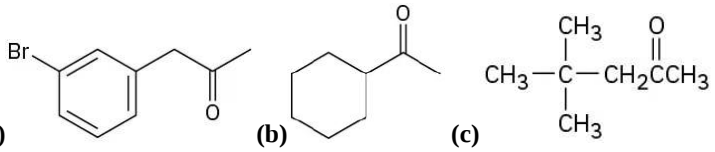
(c) 

(d) 

PROBLEM 22-43 Which, if any, of the following compounds can be prepared by a malonic ester synthesis? Show the alkyl halide you would use in each case.

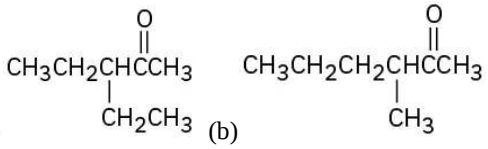
(a) Ethyl pentanoate **(b)** Ethyl 3-methylbutanoate **(c)** Ethyl 2-methylbutanoate **(d)** Ethyl 2,2-dimethylpropanoate

PROBLEM 22-44 Which, if any, of the following compounds can be prepared by an acetoacetic ester synthesis? Explain.



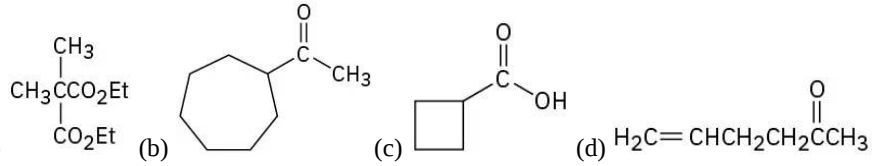
(a) **(b)** **(c)**

PROBLEM 22-45 How would you prepare the following ketones using an acetoacetic ester synthesis?



(a) (b)

PROBLEM 22-46 How would you prepare the following compounds using either an acetoacetic ester synthesis or a malonic ester synthesis? (a)

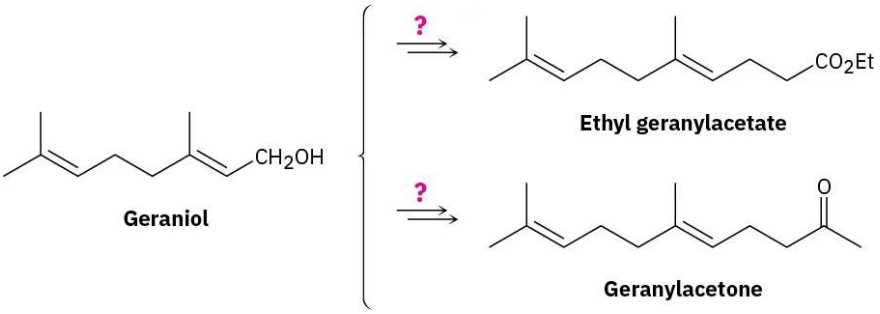


(a) (b) (c) (d)

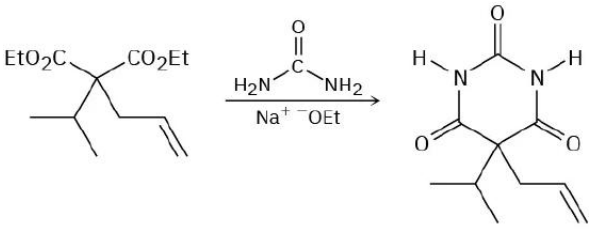
PROBLEM 22-47 Which of the following substances would undergo the haloform reaction?

(a) CH_3COCH_3 **(b)** Acetophenone **(c)** CH_3CH_2CHO **(d)** CH_3CO_2H **(e)** $CH_3C{\equiv}N$

PROBLEM 22-48 How might you convert geraniol into either ethyl geranylacetate or geranylacetone?



PROBLEM 22-49 Aprobarbital, a barbiturate once used in treating insomnia, is synthesized in three steps from diethyl malonate. Show how you would synthesize the necessary dialkylated intermediate, and then propose a mechanism for the reaction of this intermediate with urea to give aprobarbital.



General Problems

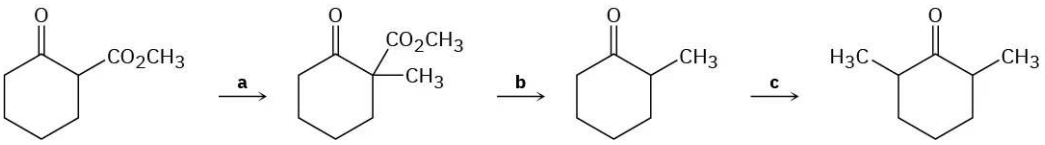
PROBLEM 22-50 One way to determine the number of acidic hydrogens in a molecule is to treat the compound with NaOD in D_2O, isolate the product, and determine its molecular weight by mass spectrometry. For example, if cyclohexanone is treated with NaOD in D_2O, the product has MW = 102. Explain how this method works.

PROBLEM 22-51 When optically active (*R*)-2-methylcyclohexanone is treated with either aqueous base or acid, racemization occurs. Explain.

PROBLEM 22-52 Would you expect optically active (*S*)-3-methylcyclohexanone to be racemized on acid or base treatment in the same way as 2-methylcyclohexanone (Problem 22-51)? Explain.

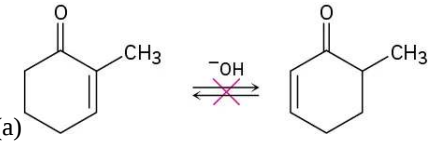
PROBLEM 22-53 When an optically active carboxylic acid such as (*R*)-2-phenylpropanoic acid is brominated under Hell–Volhard–Zelinskii conditions, is the product optically active or racemic? Explain.

PROBLEM 22-54 Fill in the reagents **a**–**c** that are missing from the following scheme:

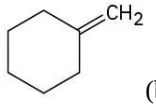


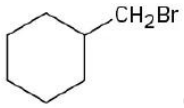
PROBLEM 22-55 Although 2-substituted 2-cyclopentenones are in a base-catalyzed equilibrium with their 5-substituted 2-cyclopentenone isomers, the analogous isomerization is not observed for 2-substituted 2-cyclohexenones. Explain.

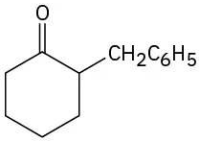
(a)

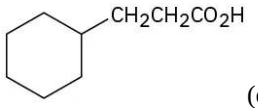


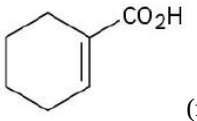
PROBLEM 22-56 How would you synthesize the following compounds from cyclohexanone? More than one step may be required.

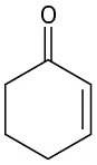
(a) 

(b) 

(c) 

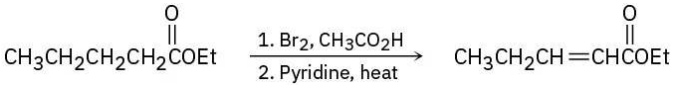
(d) 

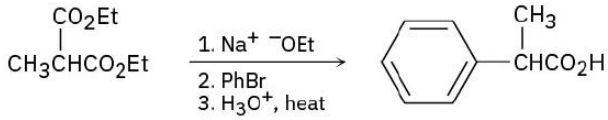
(e) 

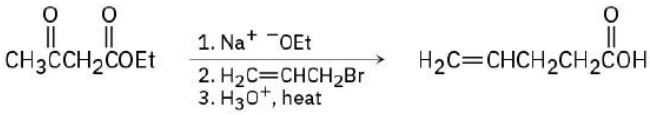
(f) 

PROBLEM 22-57 The two isomers *cis*- and *trans*-4-*tert*-butyl-2-methylcyclohexanone are interconverted by base treatment. Which isomer do you think is more stable, and why?

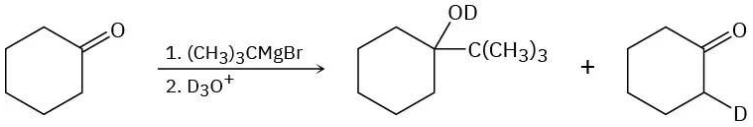
PROBLEM 22-58 The following synthetic routes are incorrect. What is wrong with each?

(a) 

(b) 

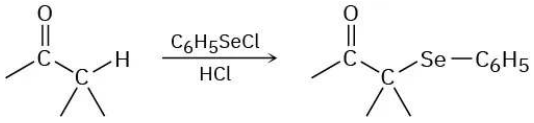
(c) 

PROBLEM 22-59 Attempted Grignard reaction of cyclohexanone with *tert*-butylmagnesium bromide yields only about 1% of the expected addition product along with 99% unreacted cyclohexanone. If D_3O^+ is added to the reaction mixture after a suitable period, however, the "unreacted" cyclohexanone is found to have one deuterium atom incorporated into it. Explain.

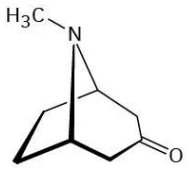


1% **99%**

PROBLEM 22-60 Ketones react slowly with benzeneselenenyl chloride in the presence of HCl to yield α-phenylseleno ketones. Propose a mechanism for this acid-catalyzed α-substitution reaction.



PROBLEM 22-61 South American Incas chewed the leaves of the coca bush, *Erythroxylon coca*, to combat fatigue. Chemical studies of *Erythroxylon coca* by Friedrich Wöhler in 1862 resulted in the discovery of *cocaine*, $C_{17}H_{21}NO_4$, as the active component. Basic hydrolysis of cocaine leads to methanol, benzoic acid, and another compound called *ecgonine*, $C_9H_{15}NO_3$. Oxidation of ecgonine with CrO_3 yields a keto acid that readily loses CO_2 on heating, giving tropinone.



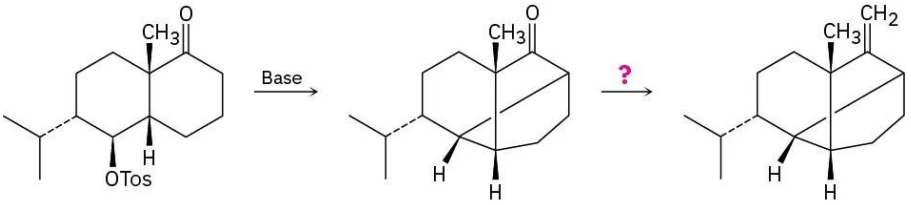
Tropinone

(a) What is a likely structure for the keto acid?

(b) What is a likely structure for ecgonine, neglecting stereochemistry?

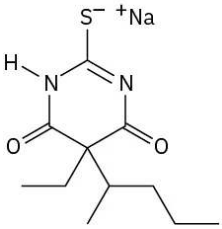
(c) What is a likely structure for cocaine, neglecting stereochemistry?

PROBLEM 22-62 The key step in a reported laboratory synthesis of sativene, a hydrocarbon isolated from the mold *Helminthosporium sativum*, involves the following base treatment of a keto tosylate. What kind of reaction is occurring? How would you complete the synthesis?



A keto tosylate **Sativene**

PROBLEM 22-63 Sodium pentothal is a short-acting barbiturate derivative used as a general anesthetic and known in popular culture as a truth serum. It is synthesized like other barbiturates (see the *Chemistry Matters* at the end of this chapter), using thiourea, $(H_2N)_2C$Math input error



Sodium pentothal

This page titled 11.13: Additional Problems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **22.12: Additional Problems** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

CHAPTER OVERVIEW

12: Carbonyl Condensation Reactions

Learning Objectives

When you have completed Chapter 23, you should be able to

- fulfill all of the detailed objectives listed under each individual section.
- design multi-step syntheses in which the reactions introduced in this unit are used in conjunction with any of the reactions described in previous units.
- solve road-map problems that require a knowledge of carbonyl condensation reactions.
- define, and use in context, any of the key terms introduced.

In this chapter, we consider the fourth and final general type of reaction that carbonyl compounds undergo—the carbonyl condensation reaction. Carbonyl condensation reactions take place between two carbonyl-containing reactants, one of which must possess an alpha-hydrogen atom. The first step of the reaction involves the removal of an alpha-hydrogen atom by a base. In the second step, the enolate anion that results from this removal attacks the carbonyl-carbon of the second reacting molecule. In the final step of the reaction, a proton is transferred to the tetrahedral intermediate formed in the second step, although in some cases the product that results may subsequently be dehydrated.

12.1: Why This Chapter?
12.2: Carbonyl Condensations - The Aldol Reaction
12.3: Carbonyl Condensations versus Alpha Substitutions
12.4: Dehydration of Aldol Products - Synthesis of Enones
12.5: Using Aldol Reactions in Synthesis
12.6: Mixed Aldol Reactions
12.7: Intramolecular Aldol Reactions
12.8: The Claisen Condensation Reaction
12.9: Mixed Claisen Condensations
12.10: Intramolecular Claisen Condensations - The Dieckmann Cyclization
12.11: Conjugate Carbonyl Additions - The Michael Reaction
12.12: Carbonyl Condensations with Enamines - The Stork Enamine Reaction
12.13: The Robinson Annulation Reaction
12.14: Some Biological Carbonyl Condensation Reactions
12.15: Chemistry Matters - A Prologue to Metabolism
12.16: Key Terms
12.17: Summary
12.18: Summary of Reactions
12.19: Additional Problems

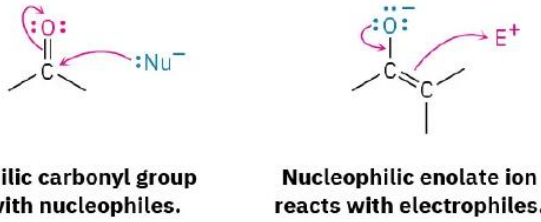
This page titled 12: Carbonyl Condensation Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

12.1: Why This Chapter?

We'll see later in this chapter and again in Chapter 29 that carbonyl condensation reactions occur in a large number of metabolic pathways. In fact, almost all classes of biomolecules—carbohydrates, lipids, proteins, nucleic acids, and many others—are biosynthesized through pathways that involve carbonyl condensation reactions. As with the α-substitution reaction discussed in the previous chapter, the great value of carbonyl condensations is that they are one of the few general methods for forming carbon–carbon bonds, thereby making it possible to build larger molecules from smaller precursors. In this chapter, we'll see how and why these reactions occur.

Figure 12.1.1: Many of the molecules needed by all growing organisms are biosynthesized using carbonyl condensation reactions. (credit: modification of work "Newborn Sea Lion" by Steven Bedard/Flickr, CC BY 2.0)

We've now studied three of the four general kinds of carbonyl-group reactions and have seen two general kinds of behavior. In nucleophilic addition and nucleophilic acyl substitution reactions, a carbonyl compound behaves as an electrophile when an electron-rich reagent adds to it. In α-substitution reactions, however, a carbonyl compound behaves as a nucleophile when it is converted into its enol or enolate ion. In the carbonyl condensation reactions that we'll study in this chapter, the carbonyl compound behaves *both* as an electrophile and as a nucleophile.



Electrophilic carbonyl group reacts with nucleophiles. **Nucleophilic enolate ion reacts with electrophiles.**

This page titled 12.1: Why This Chapter? is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **23.0: Why This Chapter?** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

12.2: Carbonyl Condensations - The Aldol Reaction

Carbonyl condensation reactions take place between two carbonyl partners and involve a combination of nucleophilic addition and α-substitution steps. One partner is converted into an enolate-ion nucleophile and adds to the electrophilic carbonyl group of the second partner. In so doing, the nucleophilic partner undergoes an α-substitution reaction and the electrophilic partner undergoes a nucleophilic addition. The general mechanism of the process is shown in Figure 12.2.1.

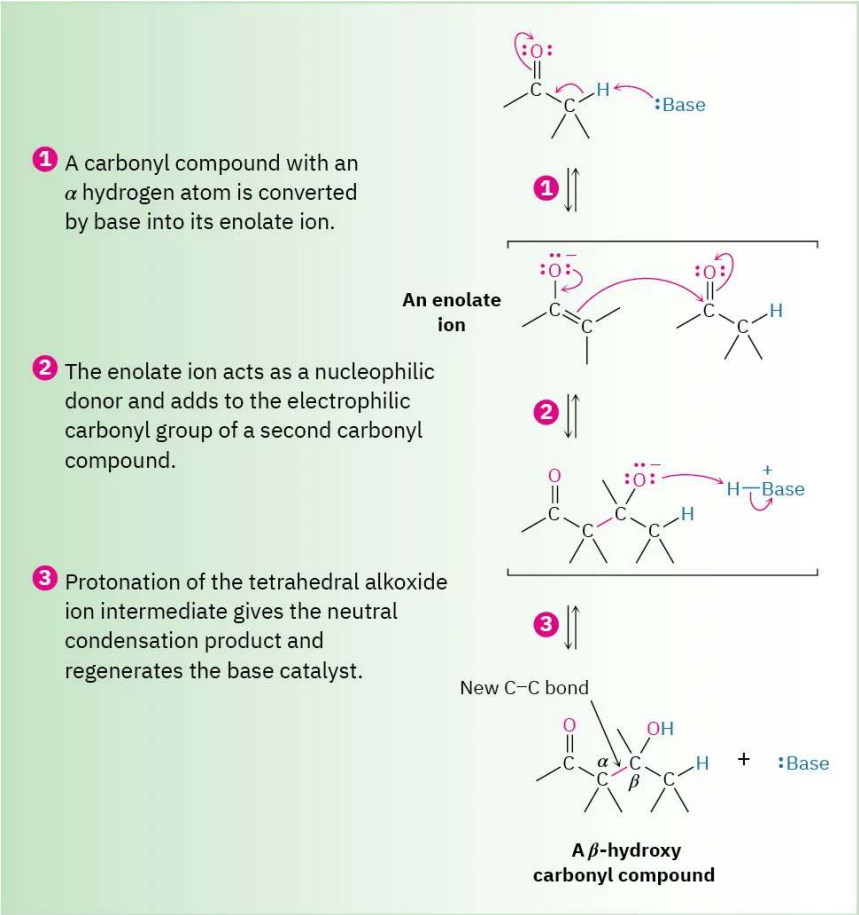
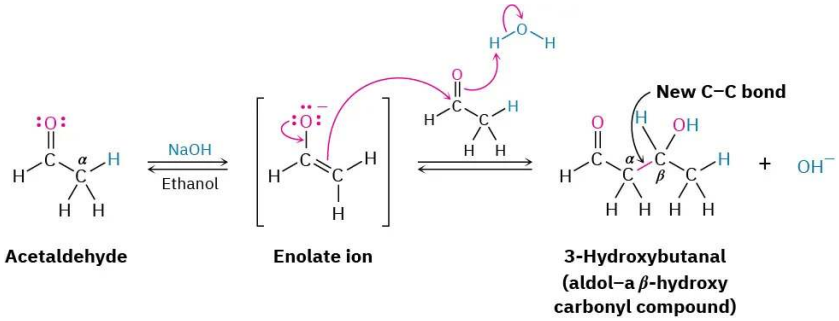


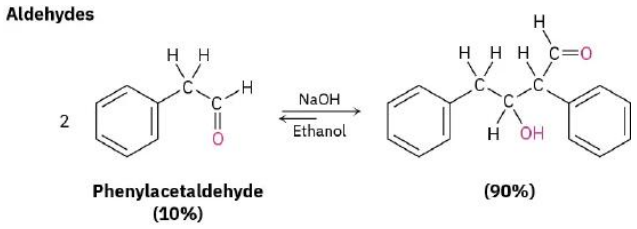
Figure 12.2.1: The general mechanism of a carbonyl condensation reaction. One partner becomes a nucleophilic donor and adds to the second partner as an electrophilic acceptor. After protonation, the final product is a β-hydroxy carbonyl compound.

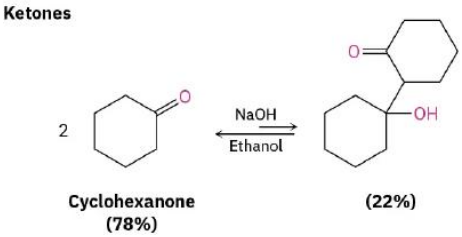
Aldehydes and ketones with an α hydrogen atom undergo a base-catalyzed carbonyl condensation reaction called the aldol reaction. For example, treatment of acetaldehyde with a base such as sodium ethoxide or sodium hydroxide in a protic solvent leads to rapid and reversible formation of 3-hydroxybutanal, known commonly as *aldol* (*ald*ehyde + alcoh*ol*), hence the general name of the reaction.



The exact position of the aldol equilibrium depends both on reaction conditions and on substrate structure. The equilibrium generally favors the condensation product in the case of aldehydes with no α substituent (RCH_2CHO) but favors the reactant for

disubstituted aldehydes (R_2CHCHO) and for most ketones. Steric factors are probably responsible for these trends, since increased substitution near the reaction site increases steric congestion in the aldol product.





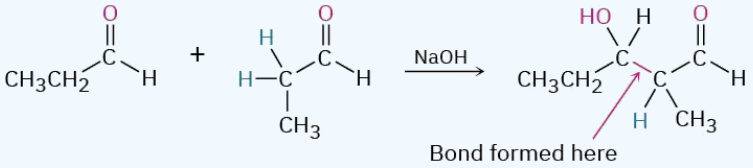
Worked Example 12.2.1: Predicting the Product of an Aldol Reaction

What is the structure of the aldol product from propanal?

Strategy

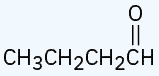
An aldol reaction combines two molecules of reactant by forming a bond between the α carbon of one partner and the carbonyl carbon of the second partner. The product is a β-hydroxy aldehyde or ketone, meaning that the two oxygen atoms in the product have a 1,3 relationship.

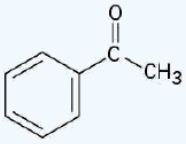
Solution

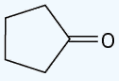


Exercise 12.2.1

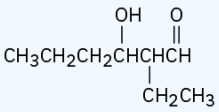
Predict the aldol reaction product of the following compounds:

a. 

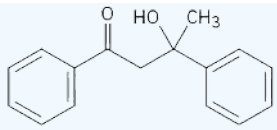
b. 

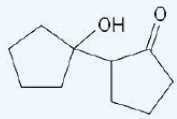
c. 

Answer

a. 

https://chem.libretexts.org/@go/page/564326

b. 

c. 

? Exercise 12.2.2

Using curved arrows to indicate the electron flow in each step, show how the base-catalyzed reverse-aldol reaction of 4-hydroxy-4-methyl-2-pentanone takes place to yield 2 equivalents of acetone.

Answer

The reverse reaction is the exact opposite of the forward reaction shown in Figure 12.2.1.

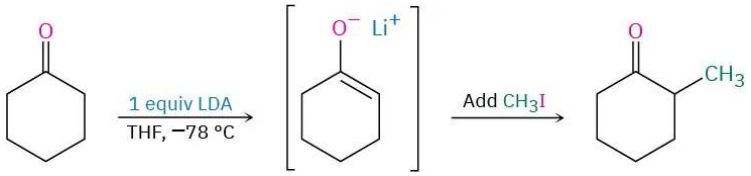
This page titled 12.2: Carbonyl Condensations - The Aldol Reaction is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **23.1: Carbonyl Condensations - The Aldol Reaction** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

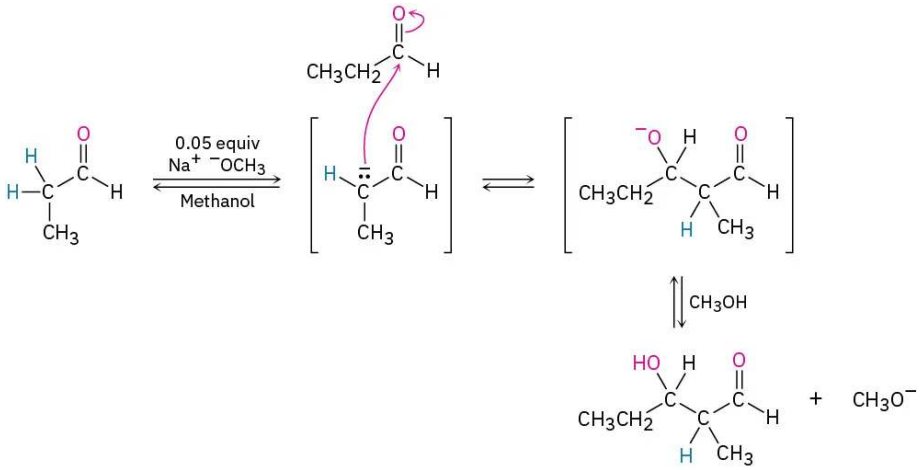
12.3: Carbonyl Condensations versus Alpha Substitutions

Two of the four general carbonyl-group reactions—carbonyl condensations and α substitutions—take place under basic conditions and involve enolate-ion intermediates. Because the experimental conditions for the two reactions are similar, how can we predict which will occur in a given case? When we generate an enolate ion with the intention of carrying out an α alkylation, how can we be sure that a carbonyl condensation reaction won't occur instead?

There is no simple answer to this question, but the exact experimental conditions usually have much to do with the result. Alpha-substitution reactions require a full equivalent of strong base and are normally carried out so that the carbonyl compound is rapidly and completely converted into its enolate ion at a low temperature. An electrophile is then added rapidly to ensure that the reactive enolate ion is quenched quickly. In a ketone alkylation reaction, for instance, we might use 1 equivalent of lithium diisopropylamide (LDA) in tetrahydrofuran solution at –78 °C. Rapid and complete generation of the ketone enolate ion would occur, and no unreacted ketone would remain, meaning that no condensation reaction could take place. We would then immediately add an alkyl halide to complete the alkylation reaction.



On the other hand, carbonyl condensation reactions require only a catalytic amount of a relatively weak base, rather than a full equivalent, so that a small amount of enolate ion is generated in the presence of unreacted carbonyl compound. Once a condensation occurs, the basic catalyst is regenerated. To carry out an aldol reaction on propanal, for instance, we might dissolve the aldehyde in methanol, add 0.05 equivalent of sodium methoxide, and then warm the mixture to give the aldol product.

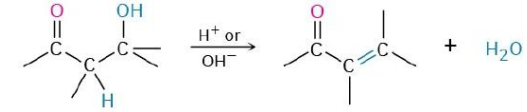


This page titled 12.3: Carbonyl Condensations versus Alpha Substitutions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **23.2: Carbonyl Condensations versus Alpha Substitutions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

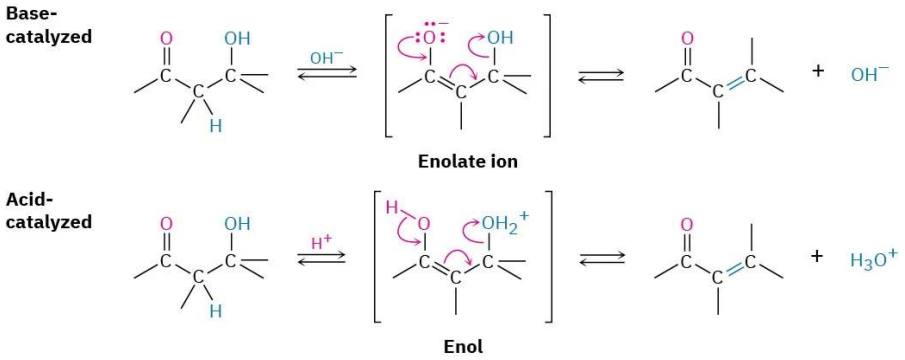
12.4: Dehydration of Aldol Products - Synthesis of Enones

When heated under either acidic or basic conditions, the β-hydroxy aldehydes or ketones formed in aldol reactions can be dehydrated to yield α,β-unsaturated products, or conjugated enones (ene + ketone). In fact, it's this loss of water that gives the carbonyl *condensation* reaction its name, because water condenses out when an enone product forms.



A β-hydroxy ketone or aldehyde **A conjugated enone**

Most alcohols are resistant to dehydration by base (Section 17.6) because hydroxide ion is a poor leaving group, but aldol products dehydrate easily because of their carbonyl group. Under basic conditions, an acidic α hydrogen is removed, yielding an enolate ion that expels the nearby $^{-}$OH leaving group in an E1cB reaction (Section 11.10). Under acidic conditions, an enol is formed, the –OH group is protonated, and water is expelled in an E1 or E2 reaction.



The reaction conditions needed for aldol dehydration are often only a bit more vigorous (slightly higher temperature, for instance) than the conditions needed for the aldol formation itself. As a result, conjugated enones are usually obtained directly from aldol reactions without isolating the intermediate β-hydroxy carbonyl compounds.

Conjugated enones are more stable than nonconjugated enones for the same reason that conjugated dienes are more stable than nonconjugated dienes (Section 14.1). Interaction between the π electrons of the C═CFigure 23.3).

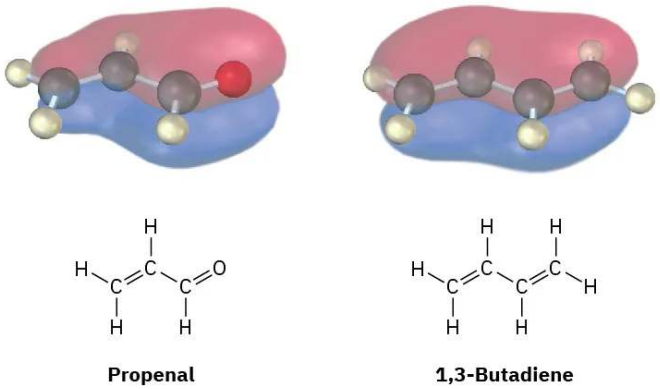
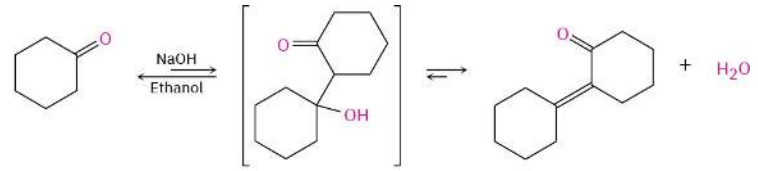


Figure 12.4.1: The π bonding molecular orbitals of a conjugated enone (propenal) and a conjugated diene (1,3-butadiene) are similar in shape and are spread over the entire π system.

The real value of aldol dehydration is that removal of water from the reaction mixture can be used to drive the aldol equilibrium toward the product. Even though the initial aldol step itself may be unfavorable, as it usually is for ketones, the subsequent dehydration step nevertheless allows many aldol condensations to be carried out in good yield. Cyclohexanone, for example, gives cyclohexylidenecyclohexanone in 92% yield, even though the initial equilibrium is unfavorable.



Cyclohexanone

Cyclohexylidenecyclohexanone
(92%)

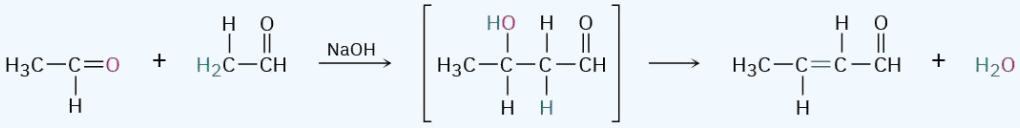
Worked Example 12.4.1: Predicting the Product of an Aldol Reaction

What is the structure of the enone obtained from aldol condensation of acetaldehyde?

Strategy

In the aldol reaction, H_2O is eliminated and a double bond is formed by removing two hydrogens from the acidic α position of one partner and the carbonyl oxygen from the second partner. The product is thus an α,β-unsaturated aldehyde or ketone.

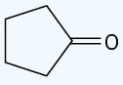
Solution

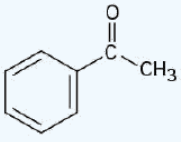


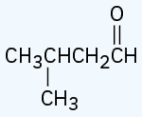
2-Butenal

Exercise 12.4.1

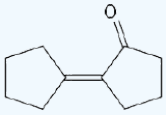
What enone product would you expect from aldol condensation of each of the following compounds?

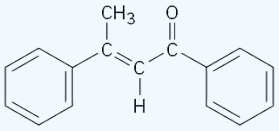
a.


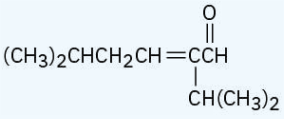
b.


c.


Answer

a.


b.


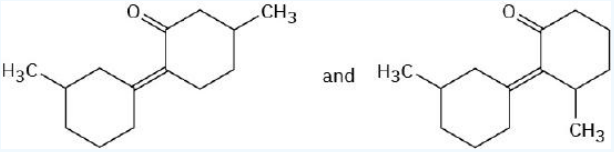
c.


https://chem.libretexts.org/@go/page/564328

Exercise 12.4.2

Aldol condensation of 3-methylcyclohexanone leads to a mixture of two enone products, not counting double-bond isomers. Draw them.

Answer

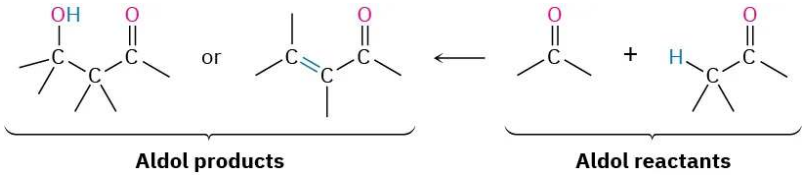


This page titled 12.4: Dehydration of Aldol Products - Synthesis of Enones is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

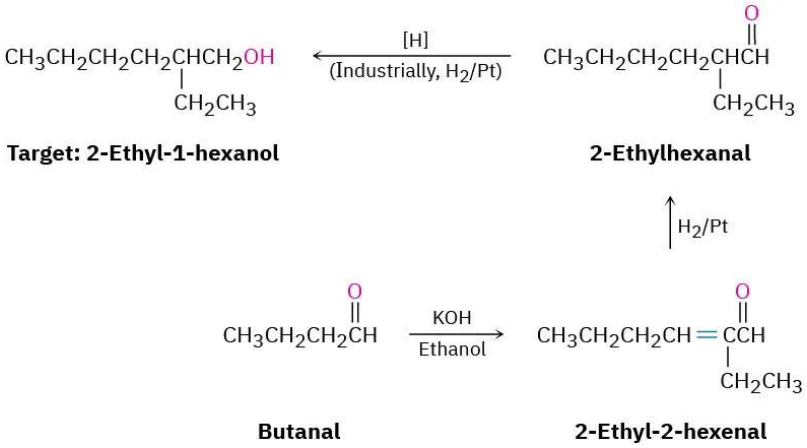
- **23.3: Dehydration of Aldol Products - Synthesis of Enones** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

12.5: Using Aldol Reactions in Synthesis

The aldol reaction yields either a β-hydroxy aldehyde/ketone or an α,β-unsaturated aldehyde/ketone, depending on the experimental conditions. By learning how to work backward, it's possible to predict when the aldol reaction might be useful in synthesis. Whenever the target molecule contains either a β-hydroxy aldehyde/ketone or a conjugated enone functional group, it might come from an aldol reaction.



We can extend this kind of reasoning even further by imagining that subsequent transformations might be carried out on the aldol products. For example, a saturated ketone might be prepared by catalytic hydrogenation of the enone product. A good example can be found in the industrial preparation of 2-ethyl-1-hexanol, an alcohol used in the synthesis of plasticizers for polymers. Although 2-ethyl-1-hexanol bears little resemblance to an aldol product at first glance, it is in fact prepared commercially from butanal by an aldol reaction. Working backward, we can reason that 2-ethyl-1-hexanol might come from 2-ethylhexanal by a reduction. 2-Ethylhexanal, in turn, might be prepared by catalytic reduction of 2-ethyl-2-hexenal, which is the aldol condensation product of butanal. The reactions that follow show the sequence in reverse order.



? Exercise 12.5.1

Which of the following compounds are aldol condensation products? What is the aldehyde or ketone precursor of each?

a. 2-Hydroxy-2-methylpentanal
b. 5-Ethyl-4-methyl-4-hepten-3-one

Answer

a. Not an aldol product
b. 3-Pentanone

? Exercise 12.5.2

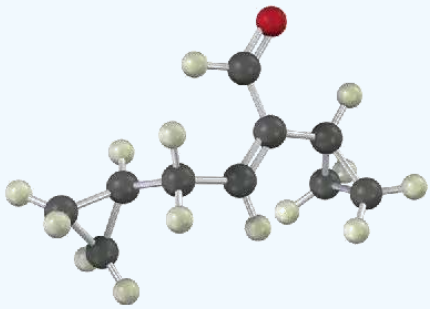
1-Butanol is prepared commercially by a route that begins with an aldol reaction. Show the steps that are likely to be involved.

Answer

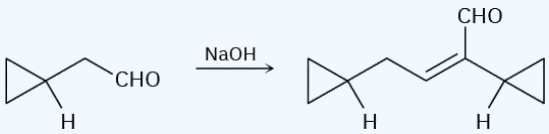
1. NaOH; 2. $LiAlH_4$; 3. H_2/Pd

Exercise 12.5.3

Show how you would synthesize the following compound using an aldol reaction:



Answer



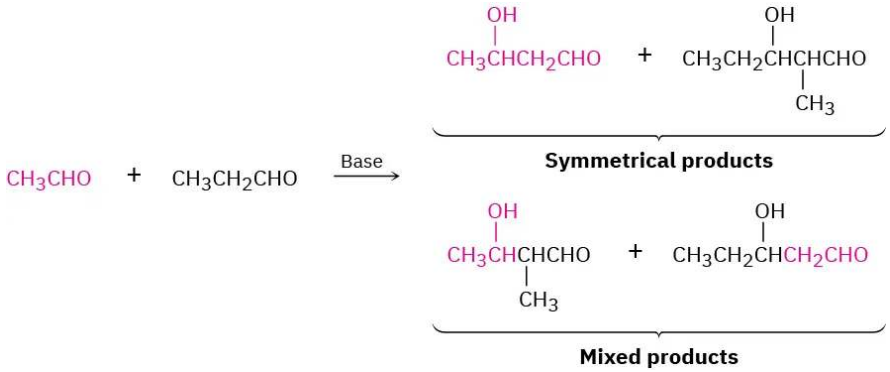
This page titled 12.5: Using Aldol Reactions in Synthesis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **23.4: Using Aldol Reactions in Synthesis** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

12.6: Mixed Aldol Reactions

Until now, we've considered only symmetrical aldol reactions, in which the two carbonyl components have been the same. What would happen, though, if an aldol reaction were carried out between two different carbonyl partners?

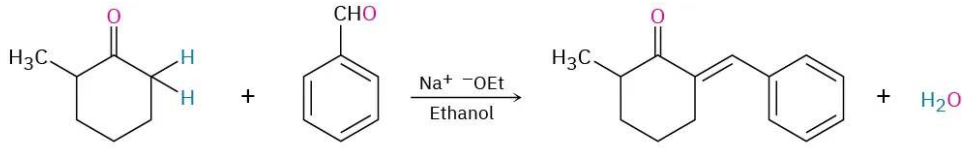
In general, a mixed aldol reaction between two similar aldehyde or ketone partners leads to a mixture of four possible products. For example, base treatment of a mixture of acetaldehyde and propanal gives a complex product mixture containing two "symmetrical" aldol products and two "mixed" aldol products. Clearly, such a reaction is of no practical value.



On the other hand, mixed aldol reactions can lead cleanly to a single product if either of two conditions is met:

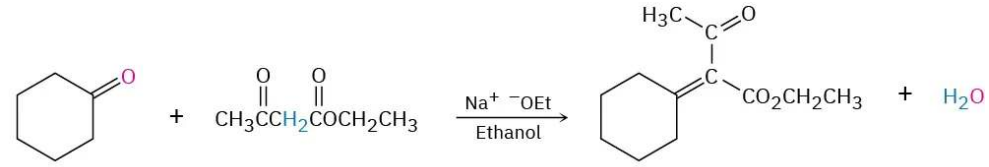
- If one of the carbonyl partners contains no α hydrogens (and thus can't form an enolate ion to become a donor), but does contain an unhindered carbonyl group (and so is a good acceptor of nucleophiles), then a mixed aldol reaction is likely to be successful. This is the case, for instance, when either benzaldehyde or formaldehyde is used as one of the carbonyl partners.

Neither benzaldehyde nor formaldehyde can form an enolate ion to add to another partner, yet both compounds have an unhindered carbonyl group. The ketone 2-methylcyclohexanone, for instance, gives the mixed aldol product in reaction with benzaldehyde.



2-Methylcyclohexanone (donor) **Benzaldehyde (acceptor)** **78%**

- If one of the carbonyl partners is much more acidic than the other, and is thus transformed into its enolate ion in preference to the other, then a mixed aldol reaction is likely to be successful. Ethyl acetoacetate, for instance, is completely converted into its enolate ion in preference to enolate ion formation from monocarbonyl partners. Thus, aldol condensations of monoketones with ethyl acetoacetate occur preferentially to give the mixed product.

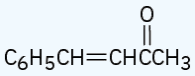


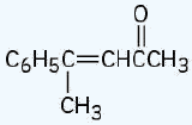
Cyclohexanone (acceptor) **Ethyl acetoacetate (donor)** **80%**

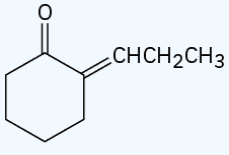
The situation can be summarized by saying that a mixed aldol reaction leads to a mixture of products unless one of the partners either has no α hydrogens but is a good electrophilic acceptor (such as benzaldehyde) or is an unusually acidic nucleophilic donor (such as ethyl acetoacetate).

Exercise 12.6.1

Which of the following compounds can probably be prepared by a mixed aldol reaction? Show the reactants you would use in each case.

a. 

b. 

c. 

Answer

a. $C_6H_5CHO + CH_3COCH_3$

b. Not easily prepared

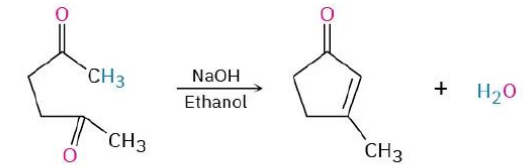
c. Not easily prepared

This page titled 12.6: Mixed Aldol Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

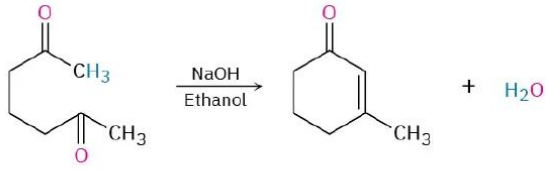
- **23.5: Mixed Aldol Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

12.7: Intramolecular Aldol Reactions

The aldol reactions we've seen thus far have all been *intermolecular*, meaning that they have taken place between two different molecules. When certain *di*carbonyl compounds are treated with base, however, an *intramolecular* aldol reaction can occur, leading to the formation of a cyclic product. For example, base treatment of a 1,4-diketone such as 2,5-hexanedione yields a cyclopentenone product, and base treatment of a 1,5-diketone such as 2,6-heptanedione yields a cyclohexenone.



2,5-Hexanedione (a 1,4-diketone) **3-Methyl-2-cyclopentenone**



2,6-Heptanedione (a 1,5-diketone) **3-Methyl-2-cyclohexenone**

The mechanism of intramolecular aldol reactions is similar to that of intermolecular reactions. The only difference is that both the nucleophilic carbonyl anion donor and the electrophilic carbonyl acceptor are now in the same molecule. One complication, however, is that intramolecular aldol reactions might lead to a mixture of products, depending on which enolate ion is formed. For example, 2,5-hexanedione might yield either the five-membered-ring product 3-methyl-2-cyclopentenone or the three-membered-ring product (2-methylcyclopropenyl) ethanone (Figure 12.7.1). In practice, though, only the cyclopentenone is formed.

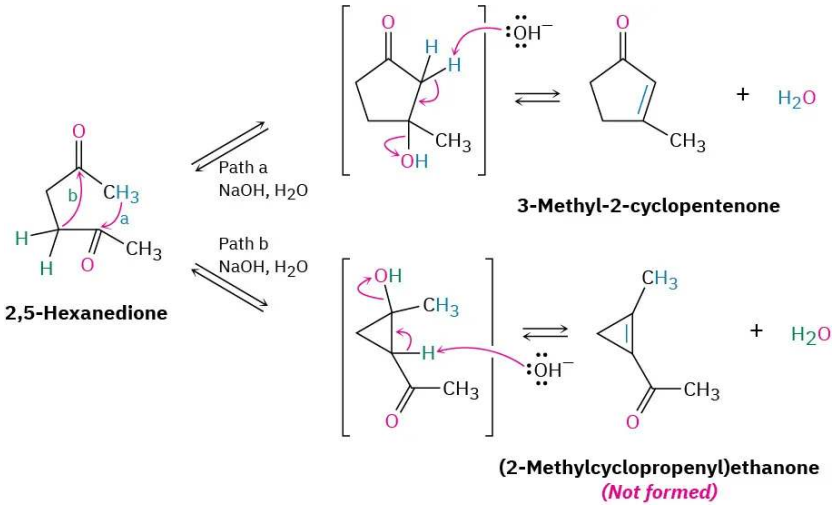


Figure 12.7.1: Intramolecular aldol reaction of 2,5-hexanedione yields 3-methyl-2-cyclopentenone rather than the alternative cyclopropene.

The selectivity observed in the intramolecular aldol reaction of 2,5-hexanedione is due to the fact that all steps in the mechanism are reversible, so an equilibrium is reached. Thus, the relatively strain-free cyclopentenone product is considerably more stable than the highly strained cyclopropene alternative. For similar reasons, intramolecular aldol reactions of 1,5-diketones lead only to cyclohexenone products rather than to the more strained acylcyclobutenes.

Exercise 12.7.1

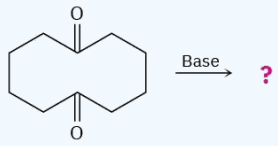
Treatment of a 1,3-diketone such as 2,4-pentanedione with base does not give an aldol condensation product. Explain.

Answer

The CH_2 position between the two carbonyl groups is so acidic that it is completely deprotonated to give a stable enolate ion.

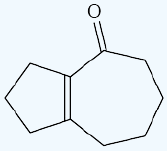
Exercise 12.7.2

What product would you expect to obtain from base treatment of 1,6-cyclodecanedione?



1,6-Cyclodecanedione

Answer

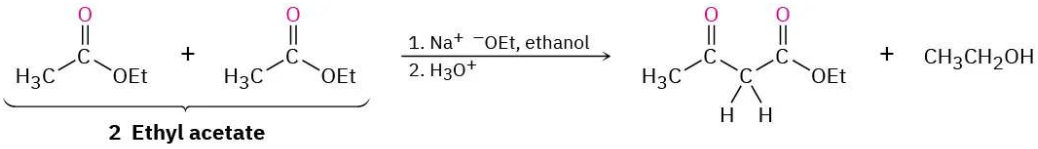


This page titled 12.7: Intramolecular Aldol Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **23.6: Intramolecular Aldol Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

12.8: The Claisen Condensation Reaction

\Esters, like aldehydes and ketones, are weakly acidic. When an ester with an α hydrogen is treated with 1 equivalent of a base such as sodium ethoxide, a reversible carbonyl condensation reaction occurs to yield a β-keto ester. For instance, ethyl acetate yields ethyl acetoacetate on base treatment. This reaction between two ester molecules is known as the Claisen condensation reaction. (We'll use ethyl esters, abbreviated "Et," for consistency, but other esters will also work.)



2 Ethyl acetate

Ethyl acetoacetate, a β-keto ester (75%)

The mechanism of the Claisen condensation is similar to that of the aldol condensation and involves the nucleophilic addition of an ester enolate ion to the carbonyl group of a second ester molecule (Figure 12.8.1). The only difference between the aldol condensation of an aldehyde or ketone and the Claisen condensation of an ester involves the fate of the initially formed tetrahedral intermediate. The tetrahedral intermediate in the aldol reaction is protonated to give an alcohol product—exactly the behavior previously seen for aldehydes and ketones (Section 19.4). The tetrahedral intermediate in the Claisen reaction, however, expels an alkoxide leaving group to yield an acyl substitution product—as previously seen for esters (Section 21.6).

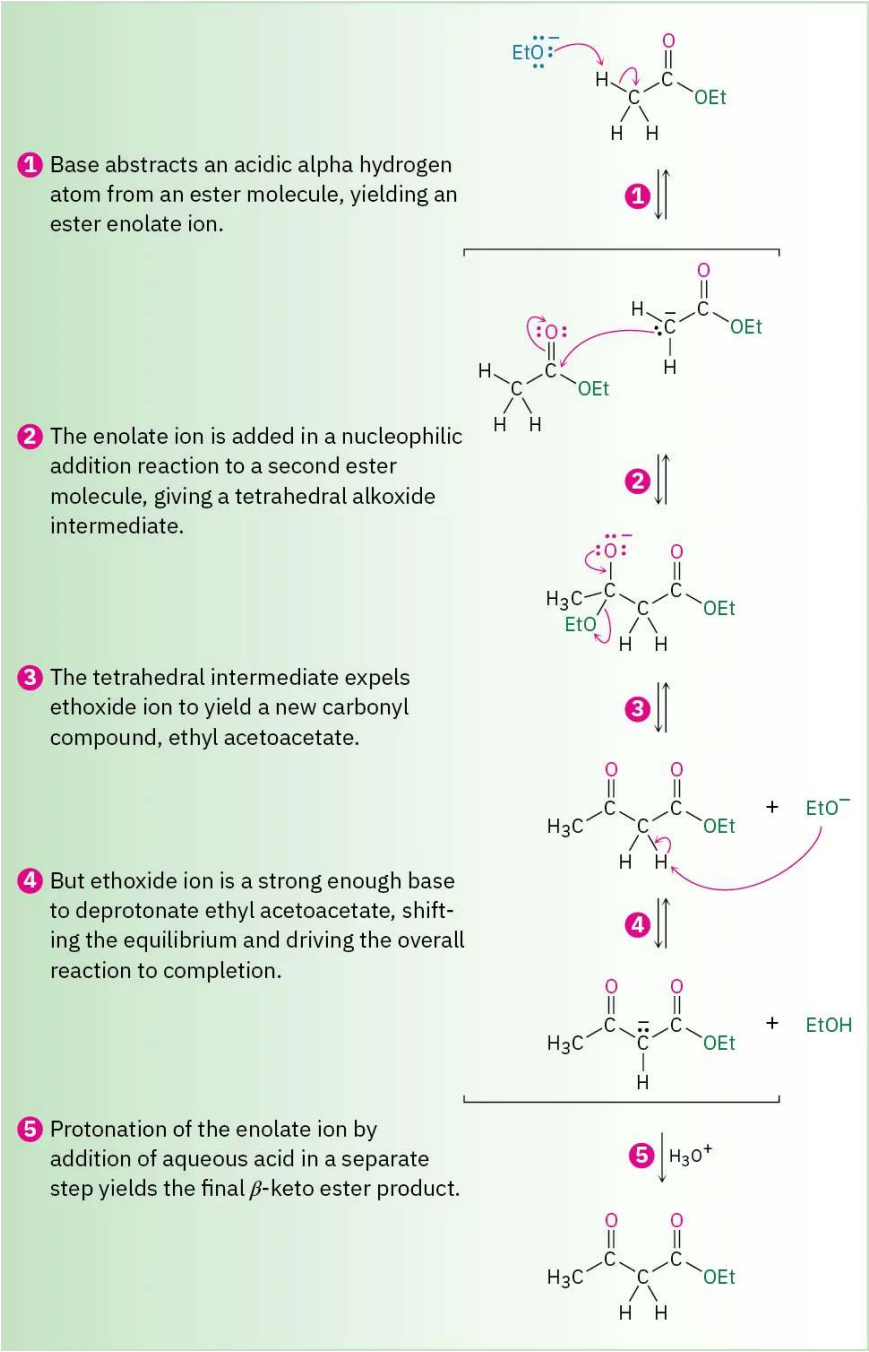


Figure 12.8.1: Mechanism of the Claisen condensation reaction.

If the starting ester has more than one acidic α hydrogen, the product β-keto ester has a highly acidic, doubly activated hydrogen atom that can be abstracted by base. This deprotonation of the product requires the use of a full equivalent of base rather than a catalytic amount. Furthermore, the deprotonation serves to drive the equilibrium completely to the product side so that high yields are usually obtained in Claisen condensations.

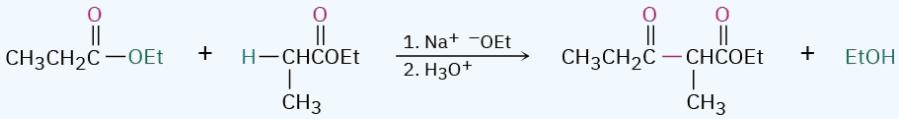
✔ Worked Example 12.8.1: Predicting the Product of a Claisen Condensation Reaction

What product would you obtain from Claisen condensation of ethyl propanoate?

Strategy

The Claisen condensation of an ester results in loss of one molecule of alcohol and formation of a product in which an acyl group of one reactant bonds to the α carbon of the second reactant. The product is a β-keto ester.

Solution



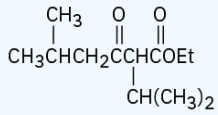
2 Ethyl propanoate **Ethyl 2-methyl-3-oxopentanoate**

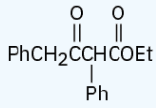
Exercise 12.8.1

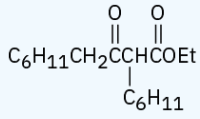
Add exercises text here.

a. $(CH_3)_2CHCH_2CO_2Et$
b. Ethyl phenylacetate
c. Ethyl cyclohexylacetate

Answer

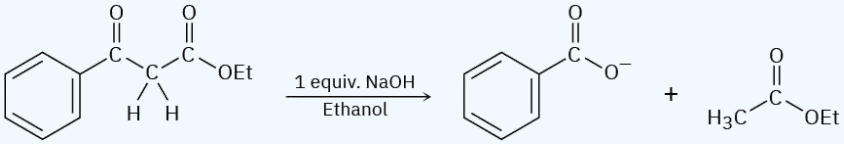
a. 

b. 

c. 

Exercise 12.8.2

As shown in Figure 12.8.1, the Claisen reaction is reversible. That is, a β-keto ester can be cleaved by base into two fragments. Using curved arrows to indicate electron flow, show the mechanism by which this cleavage occurs.



Answer

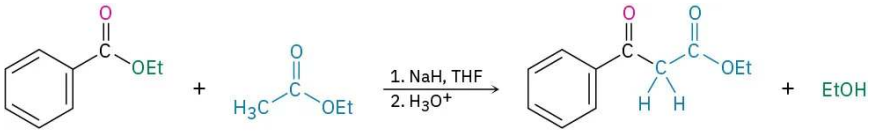
The cleavage reaction is the exact reverse of the forward reaction.

This page titled 12.8: The Claisen Condensation Reaction is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **23.7: The Claisen Condensation Reaction** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

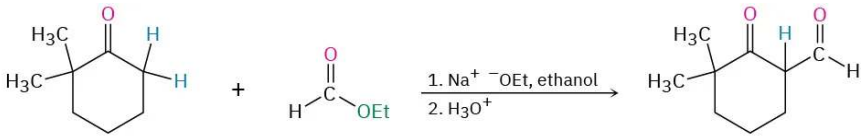
12.9: Mixed Claisen Condensations

The mixed Claisen condensation of two different esters is similar to the mixed aldol condensation of two different aldehydes or ketones (Section 23.5). Mixed Claisen reactions are successful only when one of the two ester components has no α hydrogens and thus can't form an enolate ion. For example, ethyl benzoate and ethyl formate can't form enolate ions and thus can't serve as donors. They can, however, act as the electrophilic acceptor components in reactions with other ester anions to give mixed β-keto ester products.



Ethyl benzoate (acceptor) **Ethyl acetate (donor)** **Ethyl benzoylacetate**

Mixed Claisen-like reactions can also be carried out between an ester and a ketone, resulting in the synthesis of a β-diketone. The reaction works best when the ester component has no α-hydrogens and thus can't act as the nucleophilic donor. For example, ethyl formate gives high yields in mixed Claisen condensations with ketones.



2,2-Dimethylcyclohexanone (donor) **Ethyl formate (acceptor)** **A *b*-keto aldehyde (91%)**

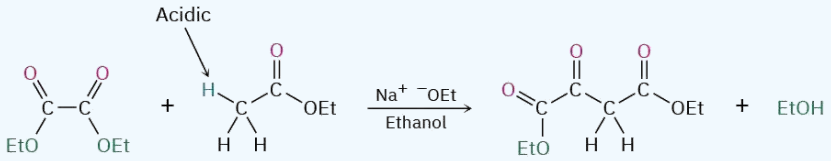
Worked Example 12.9.1: Predicting the Product of a Mixed Claisen Condensation Reaction

Diethyl oxalate, $(CO_2Et)_2$, often gives high yields in mixed Claisen reactions. What product would you expect to obtain from a mixed Claisen reaction of ethyl acetate with diethyl oxalate?

Strategy

A mixed Claisen reaction is effective when only one of the two partners has an acidic α hydrogen atom. In the present case, ethyl acetate can be converted into its enolate ion, but diethyl oxalate cannot. Thus, ethyl acetate acts as the donor and diethyl oxalate as the acceptor.

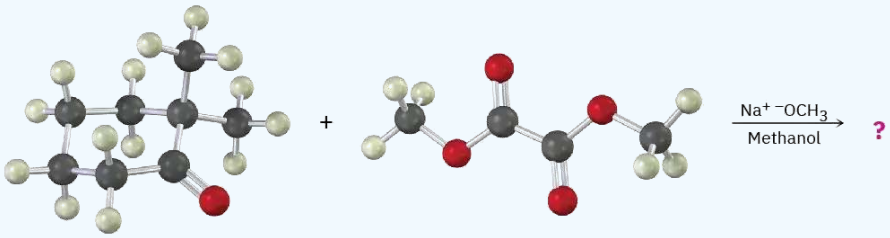
Solution



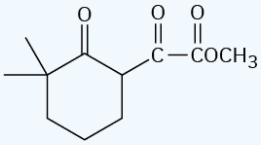
Diethyl oxalate **Ethyl acetate**

Exercise 12.9.1

What product would you expect from the following mixed Claisen-like reaction?



Answer

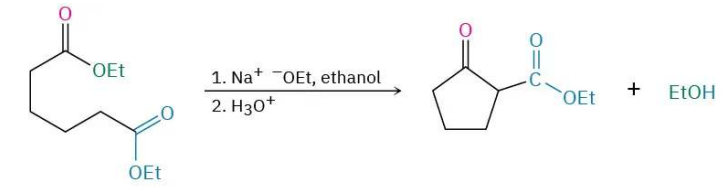


This page titled 12.9: Mixed Claisen Condensations is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

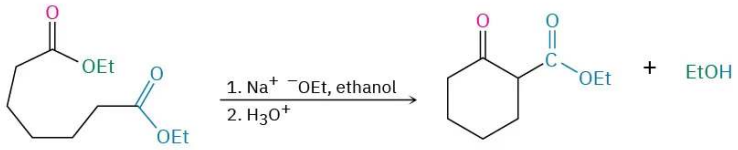
- **23.8: Mixed Claisen Condensations** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

12.10: Intramolecular Claisen Condensations - The Dieckmann Cyclization

Intramolecular Claisen condensations can be carried out with diesters, just as intramolecular aldol condensations can be carried out with diketones (Section 23.6). Called the Dieckmann cyclization, this reaction works best on 1,6-diesters and 1,7-diesters. Intramolecular Claisen cyclization of a 1,6-diester gives a five-membered cyclic β-keto ester, and cyclization of a 1,7-diester gives a six-membered cyclic β-keto ester.



Diethyl hexanedioate (a 1,6-diester) → **Ethyl 2-oxocyclopentanecarboxylate (82%)**



Diethyl heptanedioate (a 1,7-diester) → **Ethyl 2-oxocyclohexanecarboxylate**

The mechanism of the Dieckmann cyclization, shown in Figure 12.10.1, is the same as that of the Claisen condensation. One of the two ester groups is converted into an enolate ion, which carries out a nucleophilic acyl substitution on the second ester group at the other end of the molecule. A cyclic β-keto ester product results.

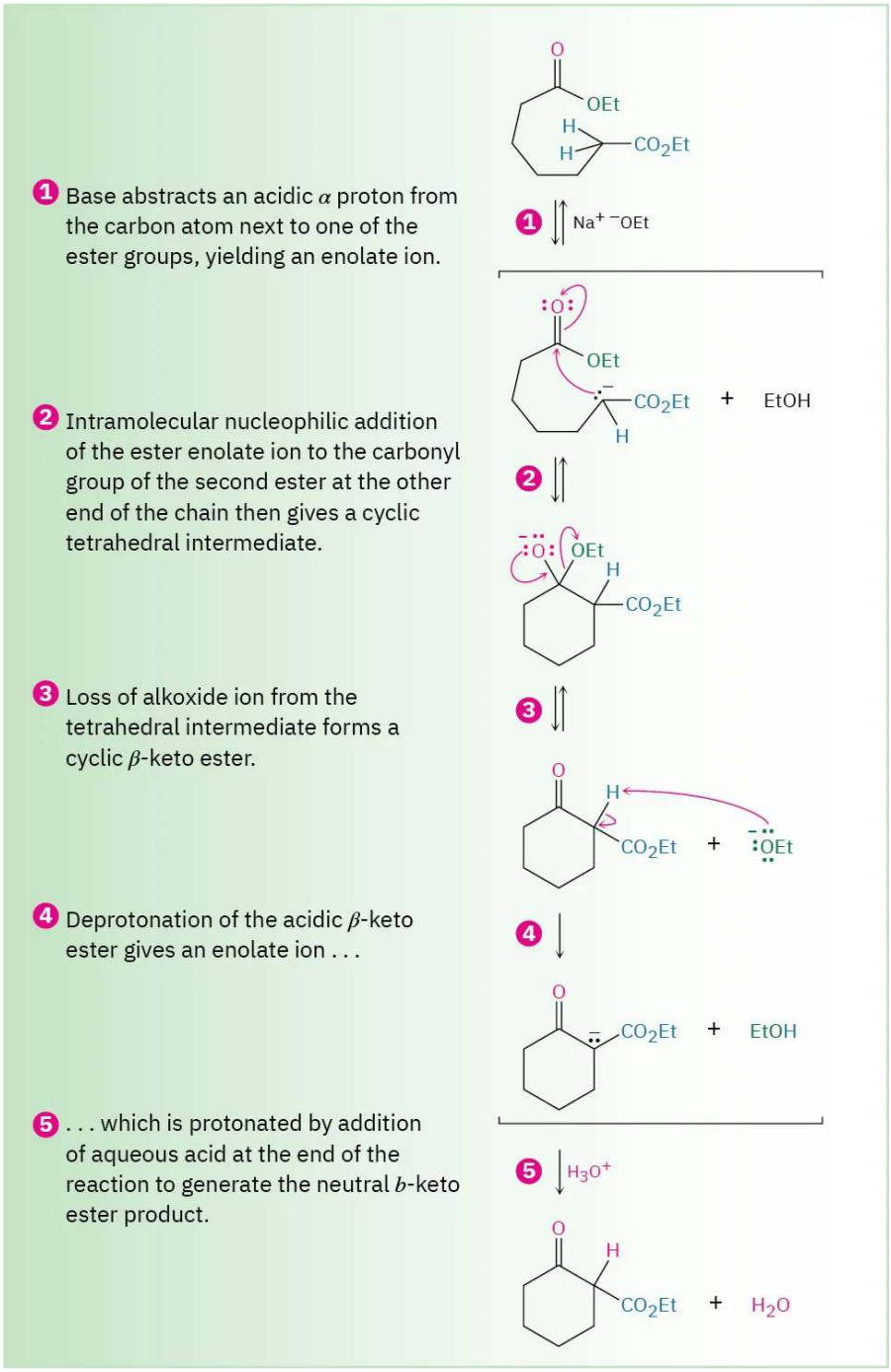
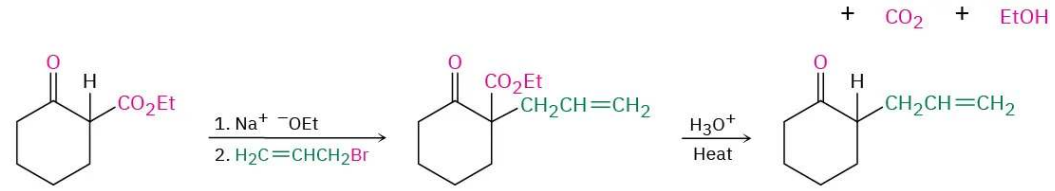


Figure 12.10.1: Mechanism of the Dieckmann cyclization of a 1,7-diester to yield a cyclic β-keto ester product.

The cyclic β-keto ester produced in a Dieckmann cyclization can be further alkylated and decarboxylated by a series of reactions analogous to those used in the acetoacetic ester synthesis (Section 22.7). Alkylation and subsequent decarboxylation of ethyl 2-oxocyclohexanecarboxylate, for instance, yields a 2-alkylcyclohexanone. The overall sequence of (**1**) Dieckmann cyclization, (**2**) β-keto ester alkylation, and (**3**) decarboxylation is a powerful method for preparing 2-substituted cyclopentanones and cyclohexanones.

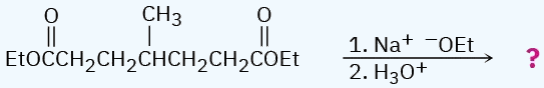


Ethyl 2-oxocyclo-hexanecarboxylate

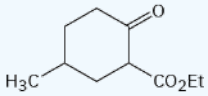
2-Allylcyclohexanone (83%)

Exercise 12.10.1

What product would you expect from the following reaction?



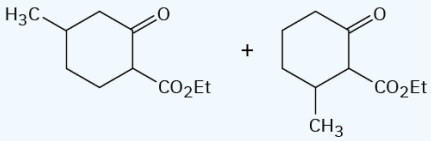
Answer



Exercise 12.10.2

Dieckmann cyclization of diethyl 3-methylheptanedioate gives a mixture of two β-keto ester products. What are their structures, and why is a mixture formed?

Answer



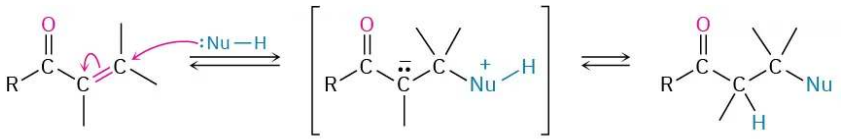
Each has the ability to act as a Claisen donor and a Claisen acceptor. The reaction should produce a roughly 50/50 mixture where each ester acts as a Claisen acceptor.

This page titled 12.10: Intramolecular Claisen Condensations - The Dieckmann Cyclization is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **23.9: Intramolecular Claisen Condensations - The Dieckmann Cyclization** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

12.11: Conjugate Carbonyl Additions - The Michael Reaction

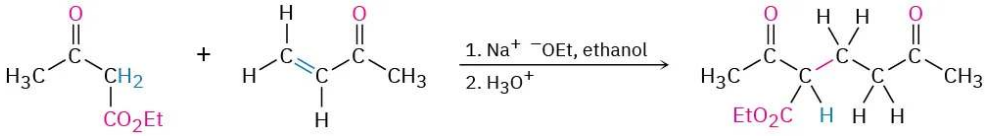
We saw in Section 19.13 that certain nucleophiles, such as amines, react with *α*,*β*-unsaturated aldehydes and ketones to give a conjugate addition product, rather than a direct addition product.



Conjugate addition product

Exactly the same kind of conjugate addition can occur when a nucleophilic enolate ion reacts with an *α*,*β*-unsaturated carbonyl compound—a process known as the Michael reaction after Arthur Michael at Tufts College and Harvard University.

The best Michael reactions are those that take place when a particularly stable enolate ion, such as that derived from a *β*-keto ester or other 1,3-dicarbonyl compound, adds to an unhindered *α*,*β*-unsaturated ketone. For example, ethyl acetoacetate reacts with 3-buten-2-one in the presence of sodium ethoxide to yield the conjugate addition product.



Ethyl acetoacetate **3-Buten-2-one**

Michael reactions take place by addition of a nucleophilic enolate ion donor to the *β* carbon of an *α*,*β*-unsaturated carbonyl acceptor, according to the mechanism shown in Figure 12.11.1.

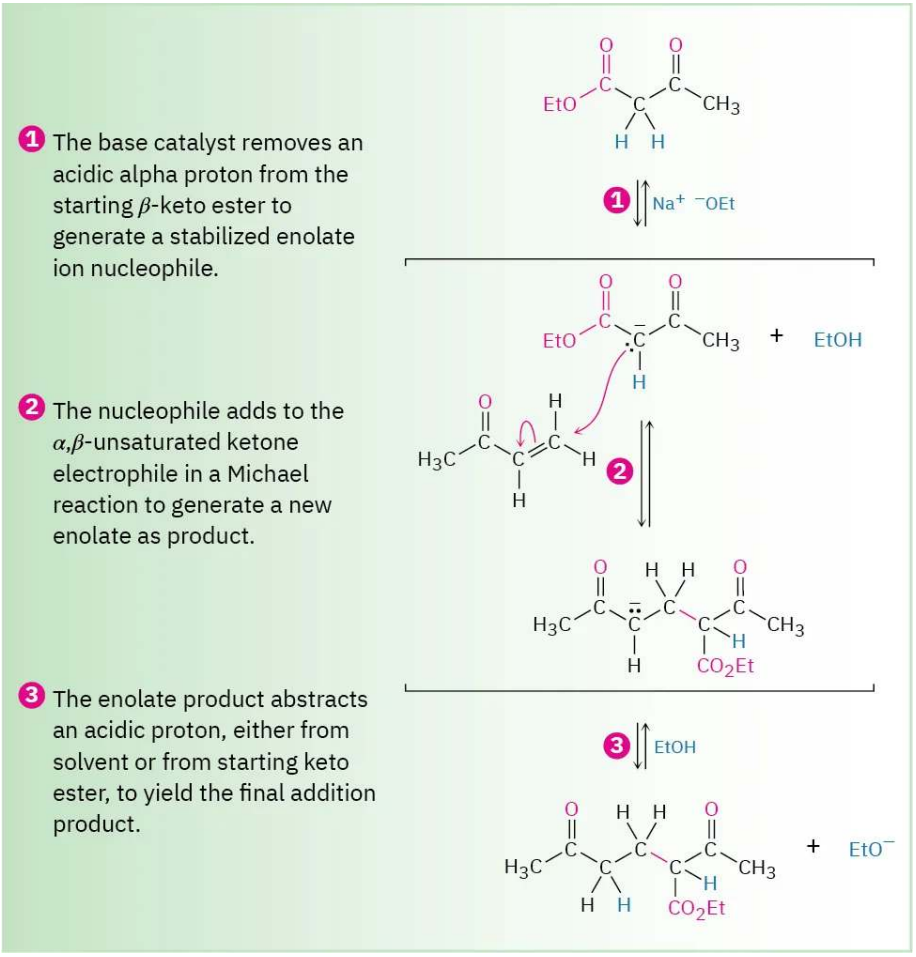
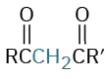
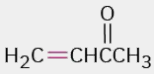
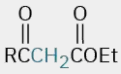
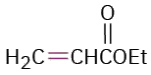
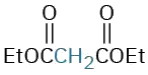
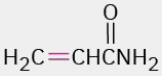
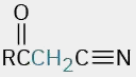
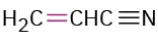
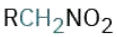
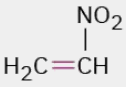


Figure 12.11.1: Mechanism of the Michael reaction between a β-keto ester and an α,β-unsaturated ketone. The reaction is a conjugate addition of an enolate ion to the unsaturated carbonyl compound.

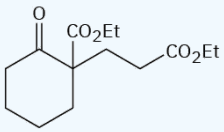
The Michael reaction occurs with a variety of α,β-unsaturated carbonyl compounds, not just conjugated ketones. Unsaturated aldehydes, esters, thioesters, nitriles, amides, and nitro compounds can all act as the electrophilic acceptor component in Michael reactions (Table 12.11.1). Similarly, a variety of different donors can be used, including β-diketones, β-keto esters, malonic esters, β-keto nitriles, and nitro compounds.

Table 12.11.1: Some Michael Acceptors and Michael Donors

Michael acceptors		Michael donors	
CH_2=CH-CH=O	Propenal		β-Diketone
	3-Buten-2-one		β-Keto ester
	Ethyl propenoate		Diethyl malonate
	Propenamide		β-Keto nitrile
	Propenenitrile		Nitro compound
	Nitroethylene		

Worked Example 12.11.1: Using the Michael Reaction

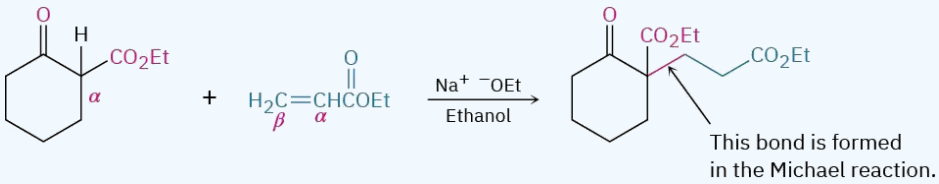
How might you obtain the following compound using a Michael reaction?



Strategy

A Michael reaction involves the conjugate addition of a stable enolate ion donor to an α,β-unsaturated carbonyl acceptor, yielding a 1,5-dicarbonyl product. Usually, the stable enolate ion is derived from a β-diketone, β-keto ester, malonic ester, or similar compound. The C–C bond formed in the conjugate addition step is the one between the α carbon of the acidic donor and the β carbon of the unsaturated acceptor.

Solution

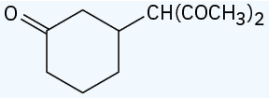


Exercise 12.11.1

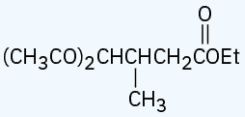
What product would you obtain from a base-catalyzed Michael reaction of 2,4-pentanedione with each of the following α,β-unsaturated acceptors?

a. 2-Cyclohexenone
b. Propenenitrile
c. Ethyl 2-butenoate

Answer

a. 

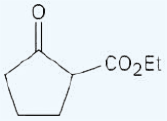
b. $(CH_3CO)_2CHCH_2CH_2CN$

c. 

Exercise 12.11.2

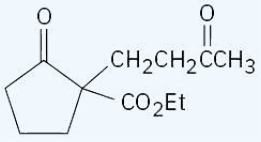
What product would you obtain from a base-catalyzed Michael reaction of 3-buten-2-one with each of the following nucleophilic donors?

a. $EtOCCH_2COEt$

b. 

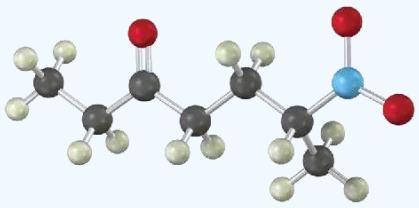
Answer

a. $(EtO_2C)_2CHCH_2CH_2CCH_3$

b. 

Exercise 12.11.3

How would you prepare the following compound using a Michael reaction (gray = H, black = C, red = O, blue = N)?



Answer

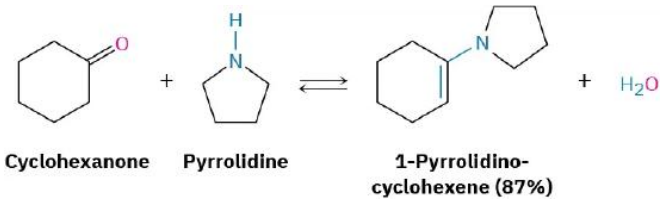
$CH_3CH_2COCH{=}CH_2 + CH_3CH_2NO_2$

This page titled 12.11: Conjugate Carbonyl Additions - The Michael Reaction is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

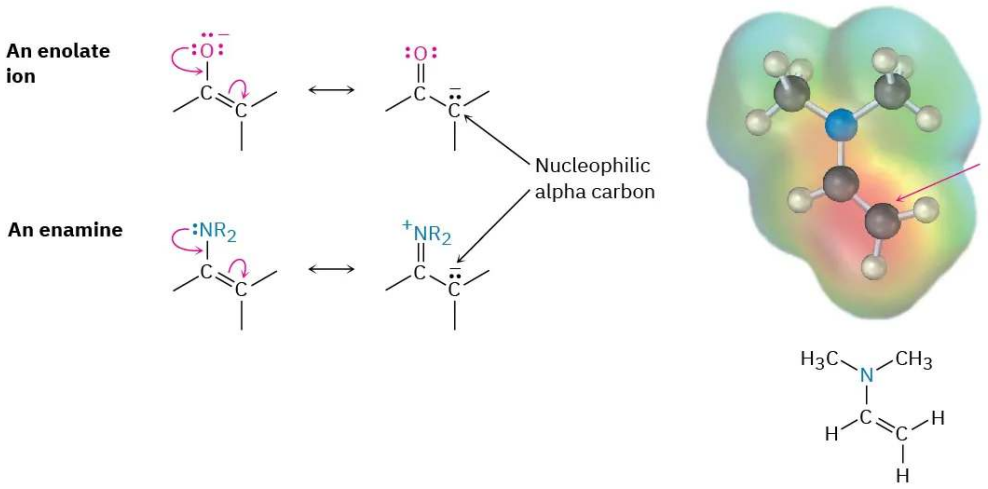
- **23.10: Conjugate Carbonyl Additions - The Michael Reaction** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

12.12: Carbonyl Condensations with Enamines - The Stork Enamine Reaction

In addition to enolate ions, other kinds of carbon nucleophiles also add to α,β-unsaturated acceptors in Michael-like reactions. Among the most important and useful of such nucleophiles, particularly in biological chemistry, are **enamines**, which are readily prepared by reaction between a ketone and a secondary amine (Section 19.8). For example:



As the following resonance structures indicate, enamines are electronically similar to enolate ions. Overlap of the nitrogen lone-pair orbital with the double-bond *p* orbitals leads to an increase in electron density on the α carbon atom, making that carbon nucleophilic. An electrostatic potential map of *N*,*N*-dimethylaminoethylene shows this shift of electron density (red) toward the α position.



Enamines behave in much the same way as enolate ions and enter into many of the same kinds of reactions. In the Stork enamine reaction, named for its discoverer, Gilbert Stork of Columbia University, for example, an enamine adds to an α,β-unsaturated carbonyl acceptor in a Michael-like process. The initial product is then hydrolyzed by aqueous acid to yield a 1,5-dicarbonyl compound. The overall reaction is thus a three-step sequence of:

a. enamine formation from a ketone,
b. Michael addition to an α,β-unsaturated carbonyl compound, and
c. enamine hydrolysis back to a ketone.

The net effect of the Stork enamine reaction is the Michael addition of a ketone to an α,β-unsaturated carbonyl compound. For example, cyclohexanone reacts with the cyclic amine pyrrolidine to yield an enamine; further reaction with an enone such as 3-buten-2-one yields a Michael adduct; and aqueous hydrolysis completes the sequence to give a 1,5-diketone (Figure 12.12.1).

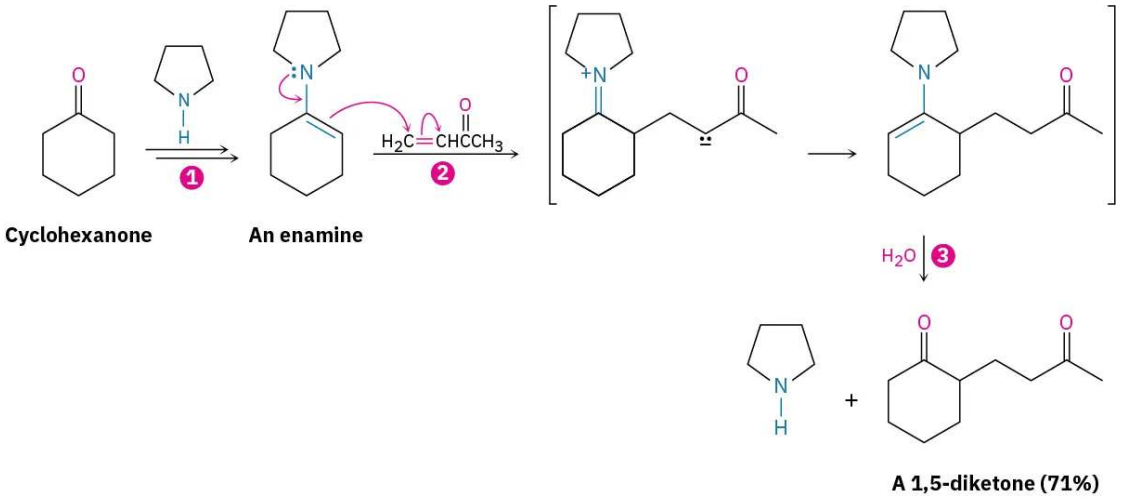
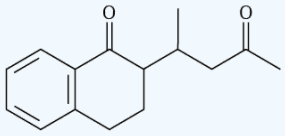


Figure 12.12.1: The Stork enamine reaction between cyclohexanone and 3-buten-2-one. (**1**) Cyclohexanone is first converted into an enamine, (**2**) the enamine adds to the *α*,*β*-unsaturated ketone in a Michael reaction, and (**3**) the conjugate addition product is hydrolyzed to yield a 1,5-diketone.

The enamine–Michael reaction has two advantages over the enolate-ion–Michael reaction that makes it particularly useful in biological pathways. First, an enamine is neutral, easily prepared, and easily handled, while an enolate ion is charged, sometimes difficult to prepare, and must be handled carefully. Second, an enamine from a *mono*ketone can be used in the Michael addition, whereas only enolate ions from *β*-dicarbonyl compounds can be used.

Worked Example 12.12.1: Using the Stork Enamine Reaction

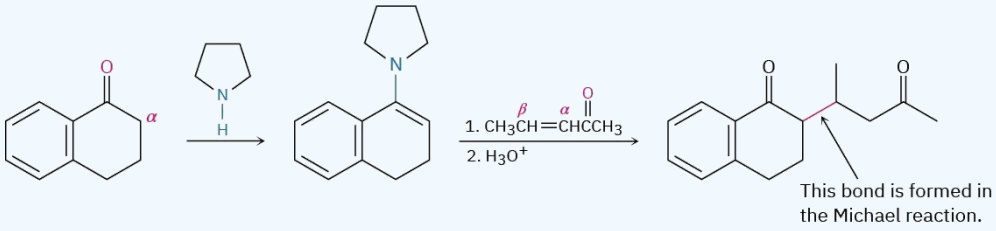
How might you use an enamine reaction to prepare the following compound?



Strategy

The overall result of an enamine reaction is the Michael addition of a ketone as donor to an *α*,*β*-unsaturated carbonyl compound as acceptor, yielding a 1,5-dicarbonyl product. The C–C bond formed in the Michael addition step is the one between the *α* carbon of the ketone donor and the *β* carbon of the unsaturated acceptor.

Solution



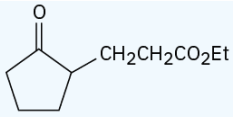
Exercise 12.12.1

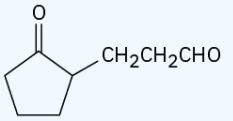
What products would result after hydrolysis from reaction of the enamine prepared from cyclopentanone and pyrrolidine with the following *α*,*β*-unsaturated acceptors?

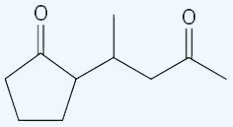
a. $H_2C{=}CHCO_2Et$
b. $H_2C{=}CHCHO$
c. $CH_3CH{=}CHCOCH_3$

Answer

https://chem.libretexts.org/@go/page/564336

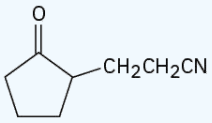
a. 

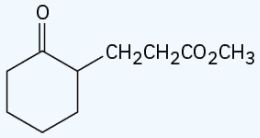
b. 

c. 

Exercise 12.12.2

Show how you might use an enamine reaction to prepare each of the following compounds:

a. 

b. 

Answer

a. Cyclopentanone enamine + propenenitrile

b. Cyclohexanone enamine + methyl propenoate

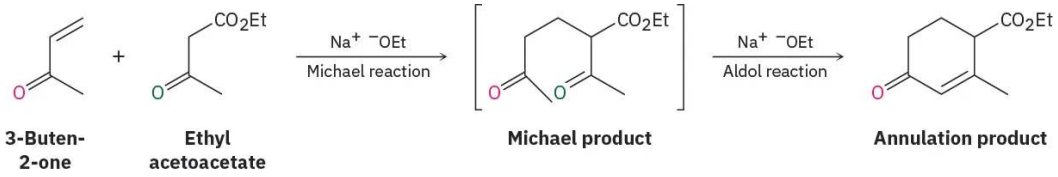
This page titled 12.12: Carbonyl Condensations with Enamines - The Stork Enamine Reaction is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **23.11: Carbonyl Condensations with Enamines - The Stork Enamine Reaction** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

12.13: The Robinson Annulation Reaction

Carbonyl condensation reactions are perhaps the most versatile methods available for synthesizing complex molecules. By putting a few fundamental reactions together in the proper sequence, some remarkably useful transformations can be carried out. One such example is the Robinson annulation reaction for the synthesis of polycyclic molecules. The word *annulation* derives from the Latin *annulus*, meaning "ring," so an annulation reaction is one that builds a new ring onto a molecule.

Named after Robert Robinson, a British chemist and 1947 Nobel Prize winner, the Robinson annulation is a two-step process that combines a Michael reaction with an intramolecular aldol reaction. It takes place between a nucleophilic donor, such as a β-keto ester; an enamine, or a β-diketone; and an α,β-unsaturated ketone acceptor, such as 3-buten-2-one. The product is a substituted 2-cyclohexenone.



The first step of the Robinson annulation is simply a Michael reaction. An enamine or an enolate ion from a β-keto ester or β-diketone effects a conjugate addition to an α,β-unsaturated ketone, yielding a 1,5-diketone. But as we saw in Section 23.6, 1,5-diketones undergo intramolecular aldol condensation to yield cyclohexenones when treated with base. Thus, the final product contains a six-membered ring, and an annulation has been accomplished. One example of this occurs during a synthesis of the steroid hormone estrone (Figure 12.13.1).

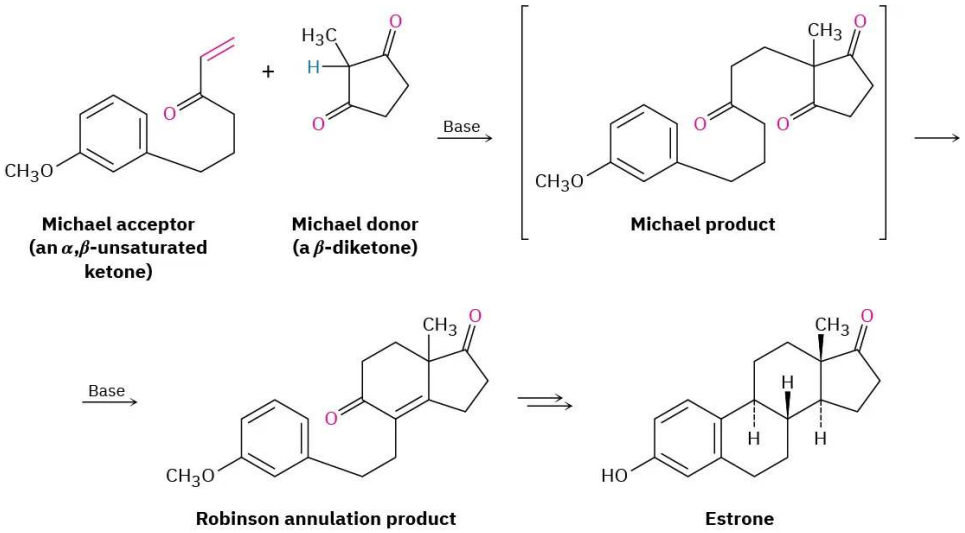
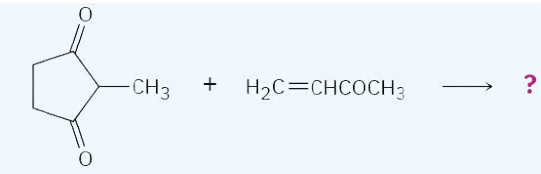


Figure 12.13.1: Synthesis of the steroid hormone estrone using a Robinson annulation reaction. The nucleophilic donor is a β-diketone.

In this example, the β-diketone 2-methyl-1,3-cyclopentanedione is used to generate the enolate ion required for Michael reaction and an aryl-substituted α,β-unsaturated ketone is used as the acceptor. Base-catalyzed Michael reaction between the two partners yields an intermediate triketone, which then cyclizes in an intramolecular aldol condensation to give a Robinson annulation product. Several further transformations are required to complete the synthesis of estrone.

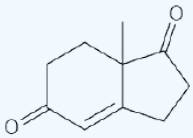
? Exercise 12.13.1

What product would you expect from a Robinson annulation reaction of 2-methyl-1,3-cyclopentanedione with 3-buten-2-one?



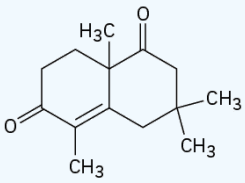
2-Methyl-1,3-cyclo-pentanedione | 3-Buten-2-one

Answer



Exercise 12.13.2

How would you prepare the following compound using a Robinson annulation reaction between a β-diketone and an α,β-unsaturated ketone? Draw the structures of both reactants and the intermediate Michael addition product.



Answer

2,5,5-Trimethyl-1,3-cyclohexanedione + 1-penten-3-one

This page titled 12.13: The Robinson Annulation Reaction is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **23.12: The Robinson Annulation Reaction** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

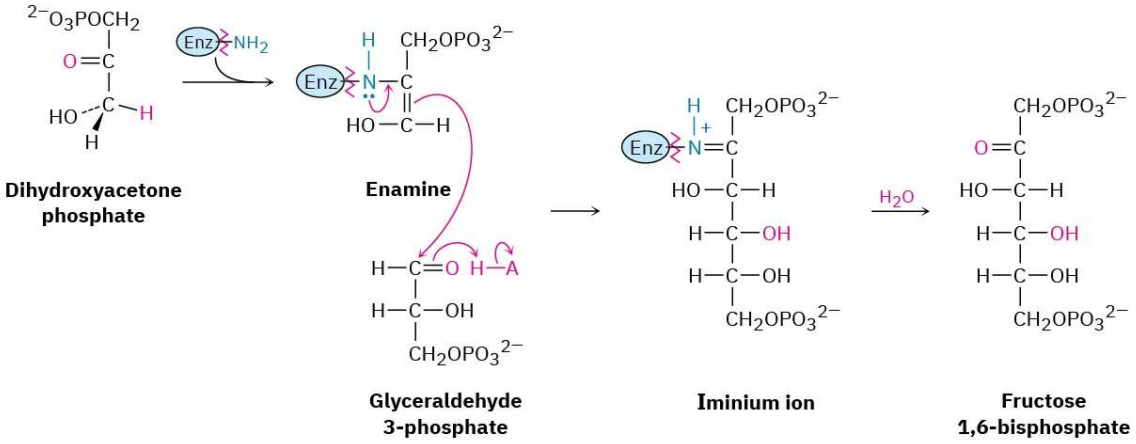
12.14: Some Biological Carbonyl Condensation Reactions

Biological Aldol Reactions

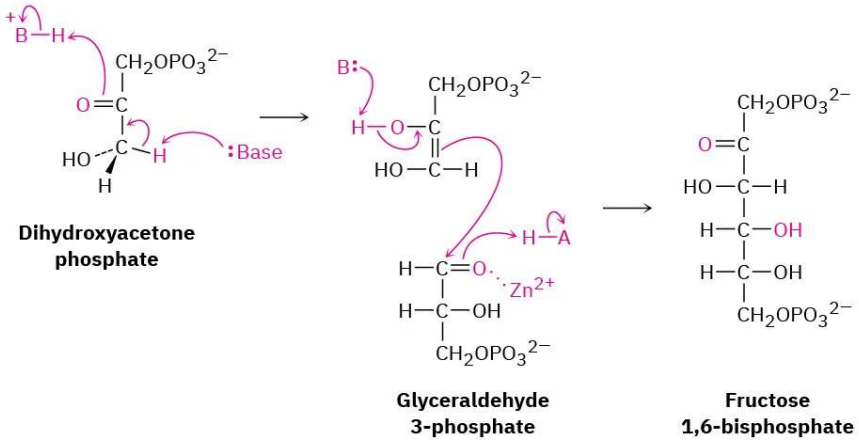
Aldol reactions occur in many biological pathways but are particularly common in carbohydrate metabolism, where enzymes called *aldolases* catalyze the addition of a ketone enolate ion to an aldehyde. Aldolases occur in all organisms and are of two types. Type I aldolases occur primarily in animals and higher plants; type II aldolases occur primarily in fungi and bacteria. Both types catalyze the same kind of reaction, but type I aldolases operate through an enamine while type II aldolases require a metal ion (usually Zn^{2+}) as a Lewis acid and operate through an enolate ion.

An example of an aldolase-catalyzed reaction occurs in glucose biosynthesis when dihydroxyacetone phosphate reacts with glyceraldehyde 3-phosphate to give fructose 1,6-bisphosphate. In animals and higher plants, dihydroxyacetone phosphate is first converted into an enamine by reaction with the $–NH_2$ group on a lysine amino acid in the enzyme. The enamine then adds to glyceraldehyde 3-phosphate, and the iminium ion that results is hydrolyzed. In bacteria and fungi, the aldol reaction occurs directly, with the ketone carbonyl group of glyceraldehyde 3-phosphate complexed to a Zn^{2+} ion to make it a better acceptor.

Type I aldolase



Type II aldolase

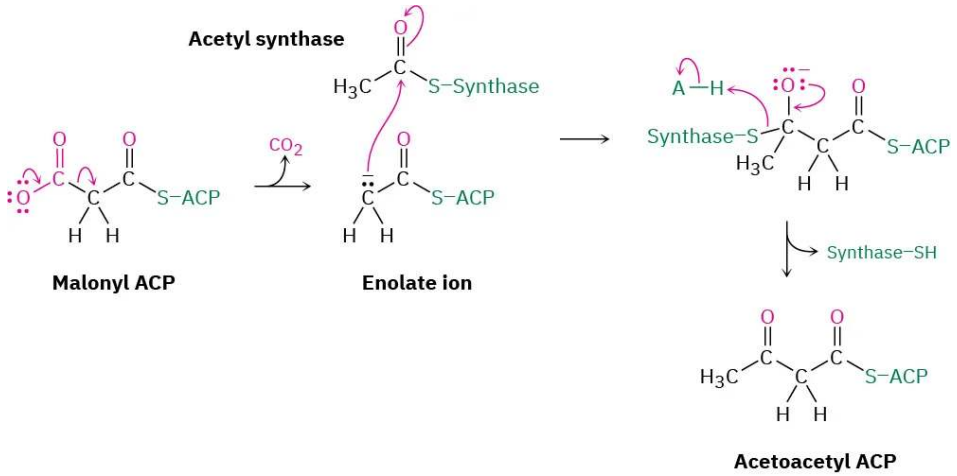


Note that the aldolase-catalyzed reactions are mixed aldol reactions, which take place between two different partners, as opposed to the symmetrical aldol reactions between identical partners usually carried out in the laboratory. Mixed aldol reactions often give mixtures of products in the laboratory but are successful in living systems because of the selectivity of the enzyme catalysts.

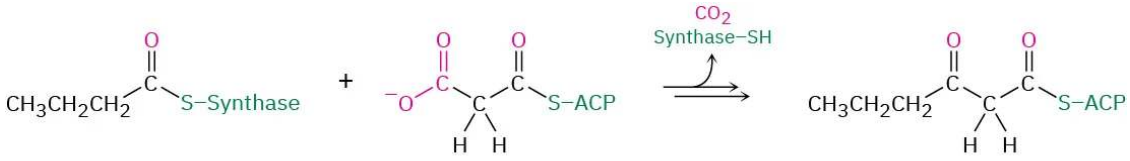
Biological Claisen Condensations

Claisen condensations, like aldol reactions, also occur in a large number of biological pathways. In fatty-acid biosynthesis, for instance, an enolate ion generated by decarboxylation (Section 22.7) of malonyl ACP adds to the carbonyl group of another acyl

group bonded through a thioester linkage to a synthase enzyme. The tetrahedral intermediate that results then expels the synthase, giving acetoacetyl ACP. (The abbreviation ACP stands for acyl carrier protein, which forms thioester bonds to acyl groups.)



Mixed Claisen condensations also occur frequently in living organisms, particularly in the pathway for fatty-acid biosynthesis that we'll discuss in **Section 29.4**. Butyryl synthase, for instance, reacts with malonyl ACP in a mixed Claisen condensation to give 3-ketohexanoyl ACP.



This page titled 12.14: Some Biological Carbonyl Condensation Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

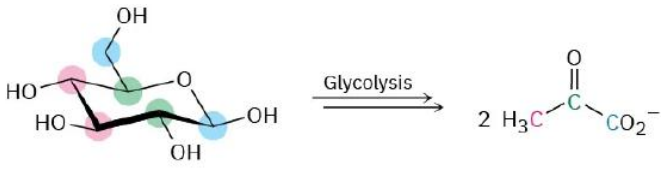
- **23.13: Some Biological Carbonyl Condensation Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

12.15: Chemistry Matters - A Prologue to Metabolism

Biochemistry is carbonyl chemistry. Almost all metabolic pathways used by living organisms involve one or more of the four fundamental carbonyl-group reactions we've seen in the chapters on Aldehydes and Ketones: Nucleophilic Addition Reactions through Carbonyl Condensation Reactions. The digestion and metabolic breakdown of all the major classes of food molecules—fats, carbohydrates, and proteins—take place by nucleophilic addition reactions, nucleophilic acyl substitutions, α substitutions, and carbonyl condensations. Similarly, hormones and other crucial biological molecules are built up from smaller precursors by these same carbonyl-group reactions.

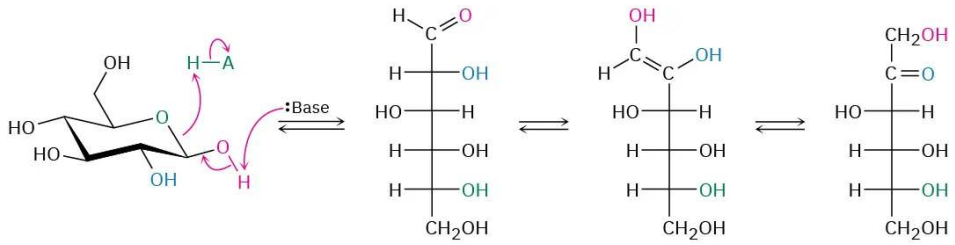
Figure 12.15.1: You are what you eat. Food molecules are metabolized by pathways that involve the four major carbonyl-group reactions. (credit: "Spring" by Giuseppe Arcimboldo, Louvre Museum/Wikimedia Commons, Public Domain)

Take *glycolysis*, for example, the metabolic pathway by which organisms convert glucose to pyruvate as the first step in extracting energy from carbohydrates.

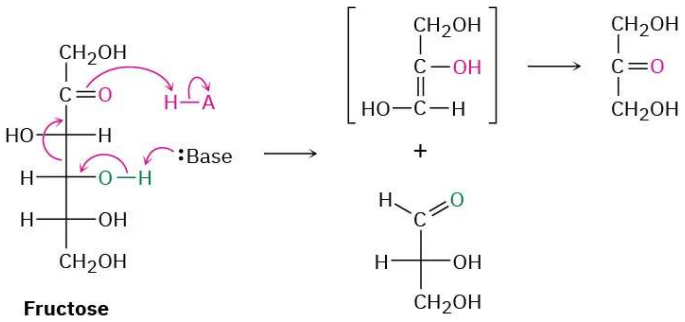


Glucose **Pyruvate**

Glycolysis is a ten-step process that begins with isomerization of glucose from its cyclic hemiacetal form to its open-chain aldehyde form—the reverse of a nucleophilic addition reaction. The aldehyde then undergoes tautomerization to yield an enol, which undergoes yet another tautomerization to give the ketone fructose.



Fructose, a β-hydroxy ketone, is then cleaved by a retro-aldol reaction into two three-carbon molecules—one ketone and one aldehyde. Further carbonyl-group reactions then occur until pyruvate is formed.



These few examples are only an introduction; we'll look at several of the major metabolic pathways in more detail in Chapter 29. The bottom line, however, is that you haven't seen the end of carbonyl-group chemistry if you have any interest in biological or medical fields. A solid grasp of carbonyl-group reactions is crucial to an understanding of biochemistry.

This page titled 12.15: Chemistry Matters - A Prologue to Metabolism is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **23.14: Chemistry Matters - A Prologue to Metabolism** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

12.16: Key Terms

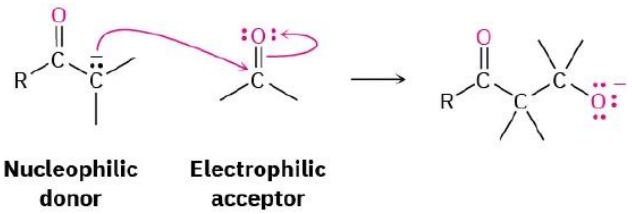
- aldol reaction
- carbonyl condensation reaction
- Claisen condensation reaction
- Dieckmann cyclization
- Michael reaction
- Robinson annulation reaction
- Stork enamine reaction

This page titled 12.16: Key Terms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **23.15: Key Terms** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

12.17: Summary

In this chapter, we've discussed the fourth and last of the common carbonyl-group reactions—the carbonyl condensation. A **carbonyl condensation reaction** takes place between two carbonyl partners and involves both nucleophilic addition and α-substitution processes. One carbonyl partner is converted by base into a nucleophilic enolate ion, which then adds to the electrophilic carbonyl group of the second partner. The first partner thus undergoes an α substitution, while the second undergoes a nucleophilic addition.



The **aldol reaction** is a carbonyl condensation that occurs between two aldehyde or ketone molecules. Aldol reactions are reversible, leading first to β-hydroxy aldehydes/ketones and then to α,β-unsaturated products after dehydration. Mixed aldol condensations between two different aldehydes or ketones generally give a mixture of all four possible products. A mixed reaction can be successful, however, if one of the two partners is an unusually good donor (ethyl acetoacetate, for instance) or if it can act only as an acceptor (formaldehyde and benzaldehyde, for instance). Intramolecular aldol condensations of 1,4- and 1,5-diketones are also successful and provide a good way to make five- and six-membered rings.

The **Claisen condensation reaction** is a carbonyl condensation that occurs between two ester components and gives a β-keto ester product. Mixed Claisen condensations between two different esters are successful only when one of the two partners has no acidic α hydrogens (ethyl benzoate and ethyl formate, for instance) and thus can function only as the acceptor partner. Intramolecular Claisen condensations, called **Dieckmann cyclization reactions**, yield five- and six-membered cyclic β-keto esters starting from 1,6- and 1,7-diesters.

The conjugate addition of a carbon nucleophile to an α,β-unsaturated acceptor is known as the **Michael reaction**. The best Michael reactions take place between relatively acidic donors (β-keto esters or β-diketones) and unhindered α,β-unsaturated acceptors. Enamines, prepared by reaction of a ketone with a disubstituted amine, are also good Michael donors in the Stork enamine reaction.

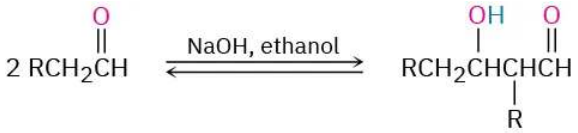
Carbonyl condensation reactions are widely used in synthesis. One example of their versatility is the **Robinson annulation reaction**, which leads to the formation of a substituted cyclohexenone. Treatment of a β-diketone or β-keto ester with an α,β-unsaturated ketone leads first to a Michael addition, which is followed by intramolecular aldol cyclization. Condensation reactions are also used widely in nature for the biosynthesis of such molecules as fats and steroids.

This page titled 12.17: Summary is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

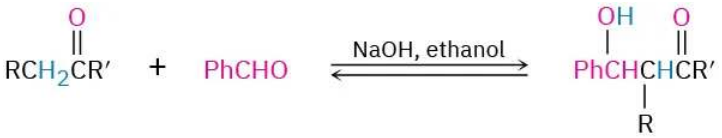
- **23.16: Summary** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

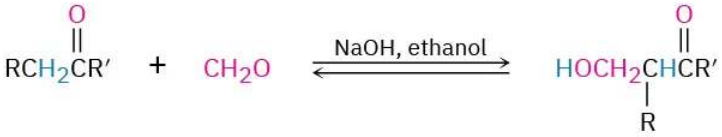
12.18: Summary of Reactions

1. Aldol reaction (Section 23.1)

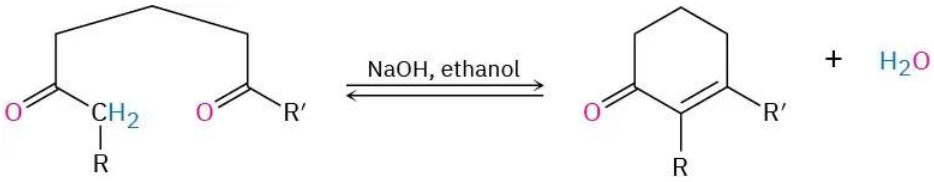


- Mixed aldol reaction (Section 23.5)

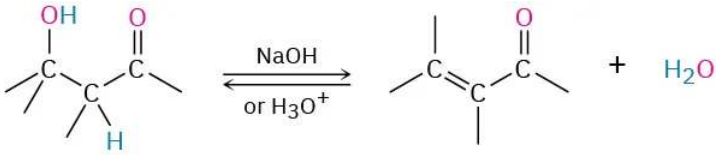




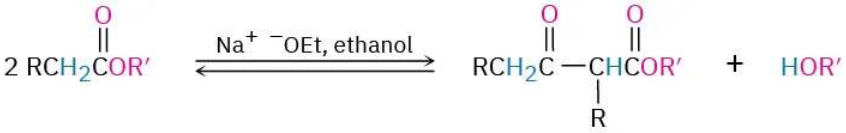
- Intramolecular aldol reaction (Section 23.6)



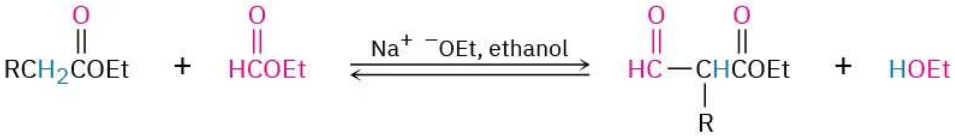
- Dehydration of aldol products (Section 23.3)



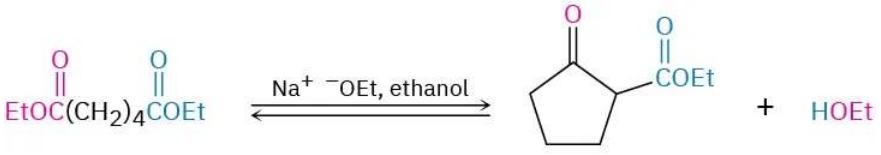
- Claisen condensation reaction (Section 23.7)

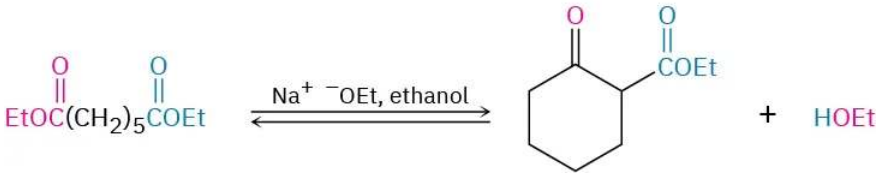


- Mixed Claisen condensation reaction (Section 23.8)

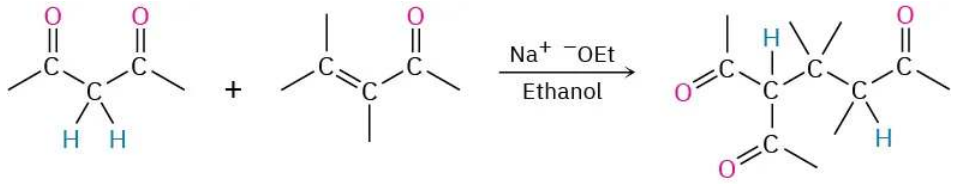


- Intramolecular Claisen condensation (Dieckmann cyclization; Section 23.9)

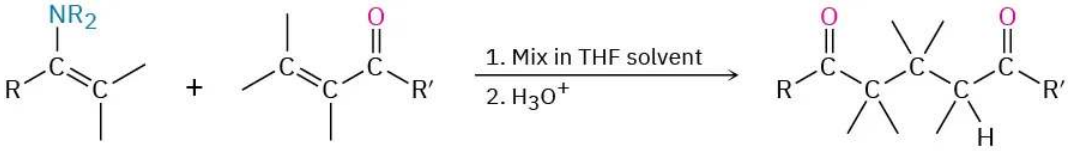




- Michael reaction (Section 23.10)



- Carbonyl condensations with enamines (Stork enamine reaction; Section 23.11)



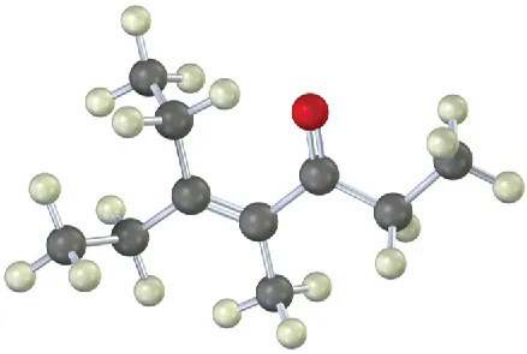
This page titled 12.18: Summary of Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **23.17: Summary of Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

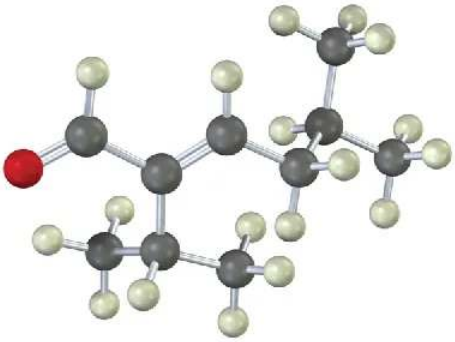
12.19: Additional Problems

Visualizing Chemistry

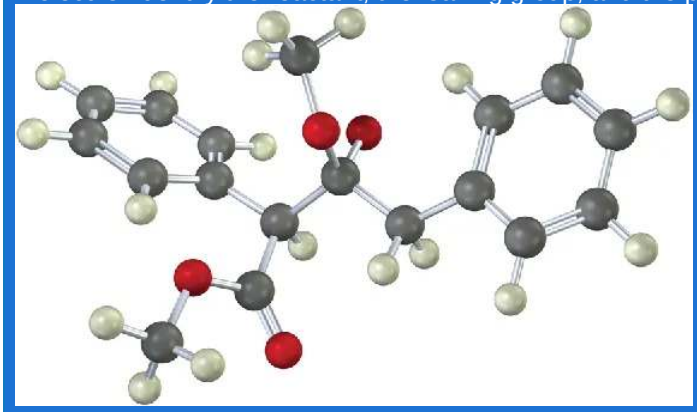
What ketones or aldehydes might the following enones have been prepared from by aldol reaction? (a)



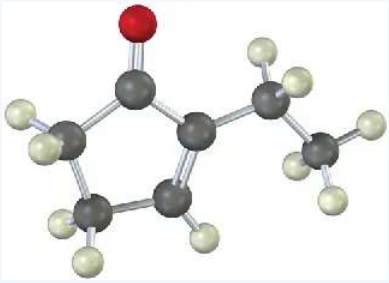
(b)



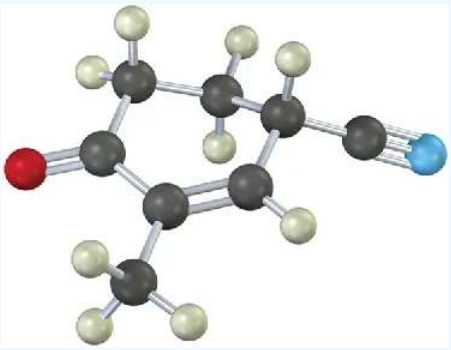
The following structure represents an intermediate formed by addition of an ester enolate ion to a second ester molecule. Identify the reactant, the leaving group, and the product.



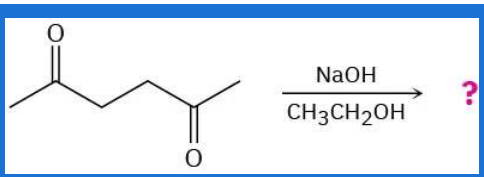
The following molecule was formed by an intramolecular aldol reaction. What dicarbonyl precursor was used for its preparation?

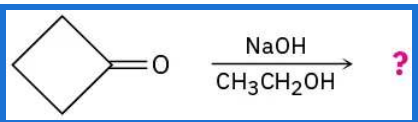


The following molecule was formed by a Robinson annulation reaction. What reactants were used?



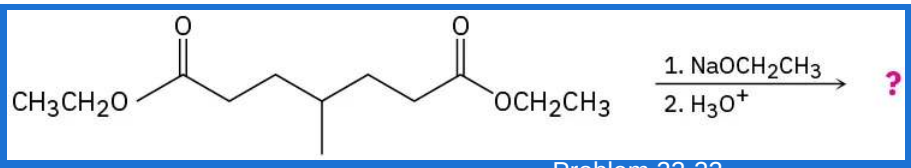
Mechanism Problems



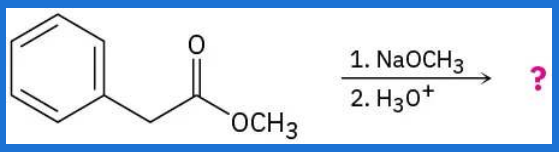


Problem 23-28 (b)

Based on your answers to Problem 23-27, predict the dehydration product for both reactions and write the mechanism.

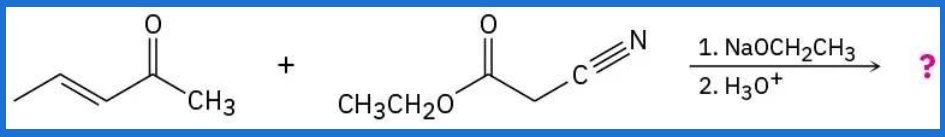


(b)

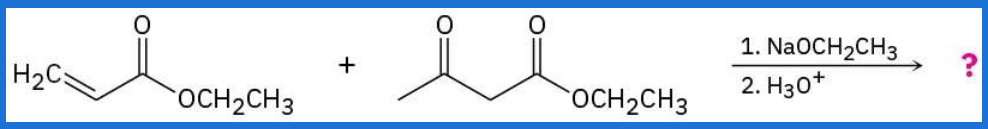


Problem 23-32

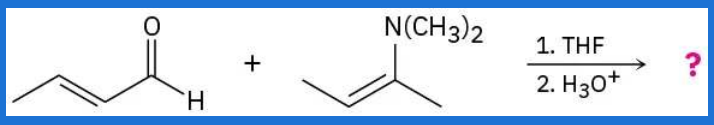
Problem 23-30 Predict the product(s) and provide the mechanisms for the following reactions. (a)



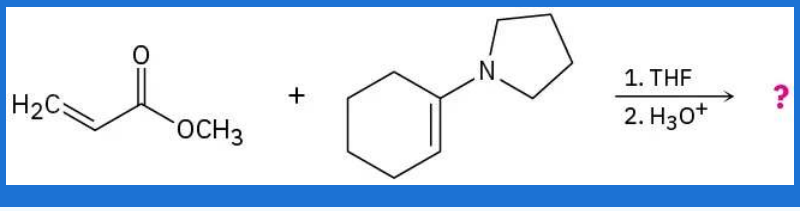
(b)



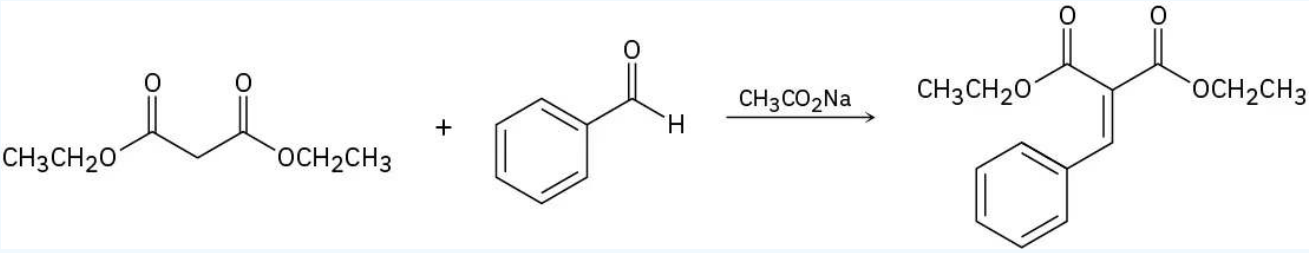
Problem 23-31 Predict the product(s) and provide the mechanisms for the following reactions. (a)



(b)

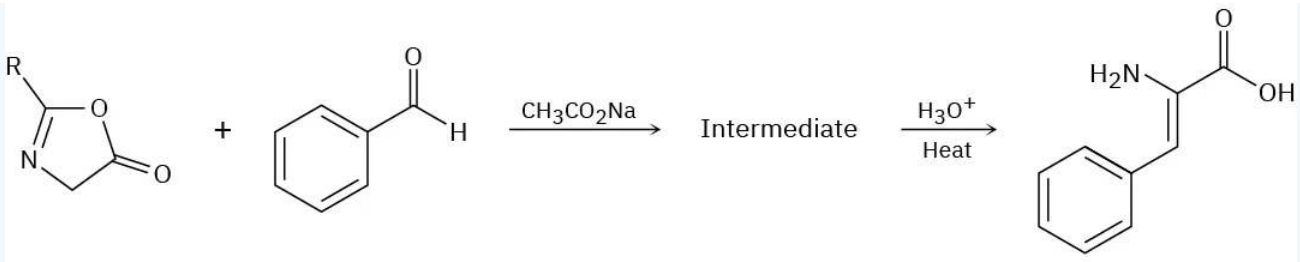


Knoevenagel condensation is a reaction involving an active methylene compound (a CH_2 flanked by two electron-withdrawing groups) and an aldehyde and ketone. Propose a mechanism for the reaction below.



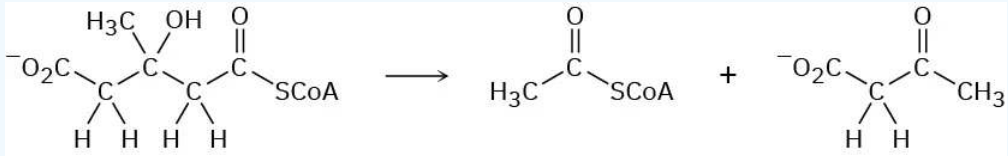
Azlactones are important starting materials used in the synthesis of dehydro α-aminoacids. They react with aldehydes to form an intermediate that is hydrolyzed under acidic conditions to give the final amino acid product. Provide the structure of the intermediate and propose a mechanism for its formation.

https://chem.libretexts.org/@go/page/564343



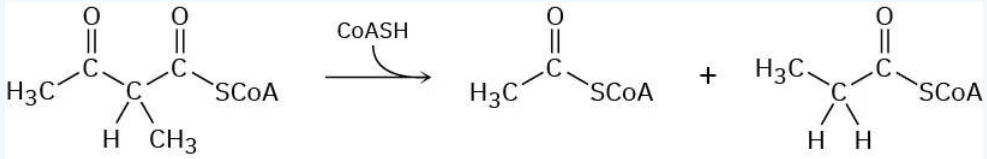
Azlactone **Deydro-α-amino acid**

Leucine, one of the twenty amino acids found in proteins, is metabolized by a pathway that includes the following step. Propose a mechanism.



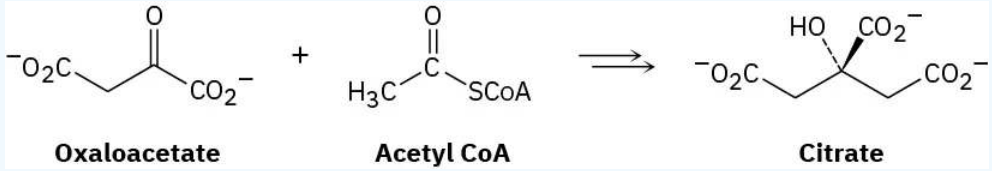
3-Hydroxy-3-methyl-glutaryl CoA **Acetyl CoA** **Acetoacetate**

Isoleucine, another of the twenty amino acids found in proteins, is metabolized by a pathway that includes the following step. Propose a mechanism.



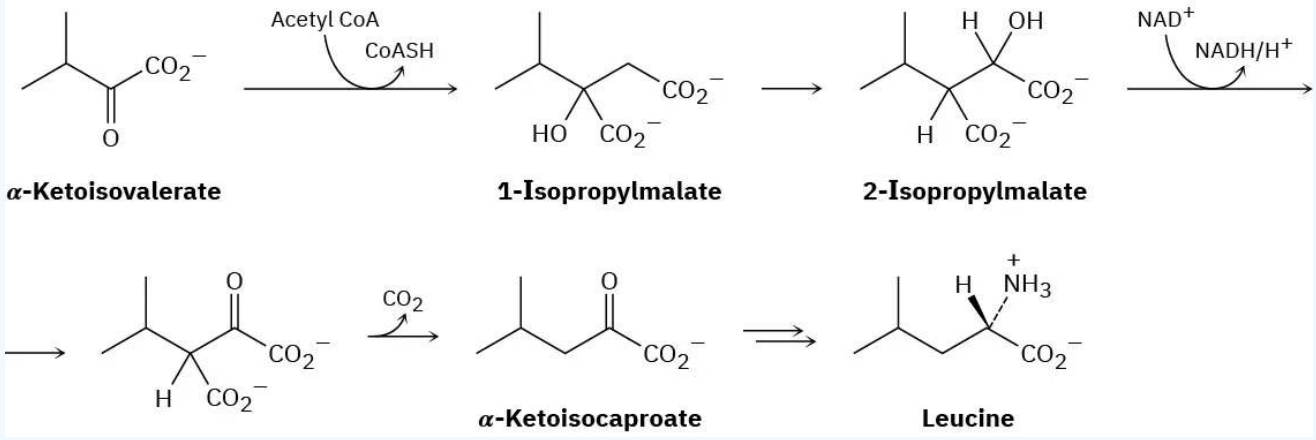
2-Methyl-3-keto-butyryl CoA **Acetyl CoA** **Propionyl CoA (propanoyl CoA)**

The first step in the citric acid cycle of food metabolism is reaction of oxaloacetate with acetyl CoA to give citrate. Propose a mechanism, using acid or base catalysis as needed.

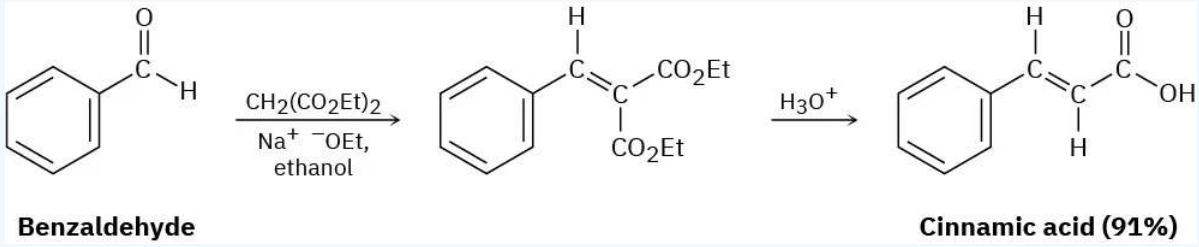


Oxaloacetate **Acetyl CoA** **Citrate**

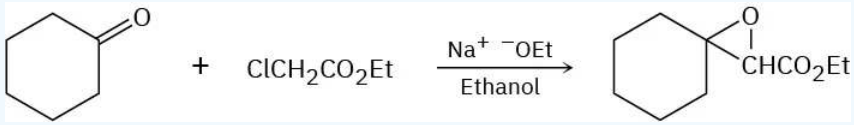
The amino acid leucine is biosynthesized from α-ketoisovalerate by the following sequence of steps. Show the mechanism of each.



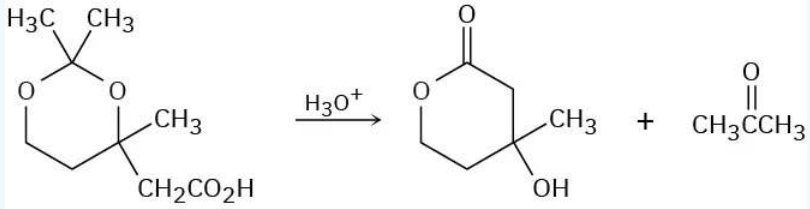
The Knoevenagel reaction was introduced in Problem 23-2. Show the mechanism for the Knoevenagel reaction of diethyl malonate with benzaldehyde.



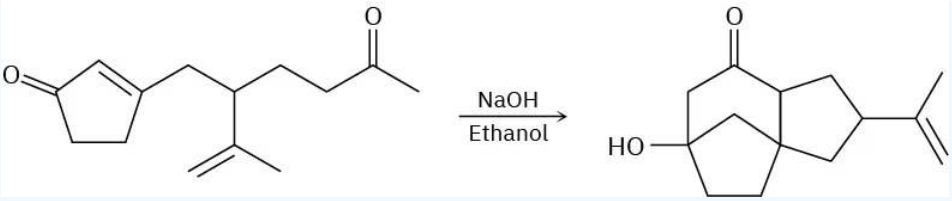
The Darzens reaction involves a two-step, base-catalyzed condensation of ethyl chloroacetate with a ketone to yield an epoxy ester. The first step is a carbonyl condensation reaction, and the second step is an S_N2 reaction. Write both steps, and show their mechanisms.



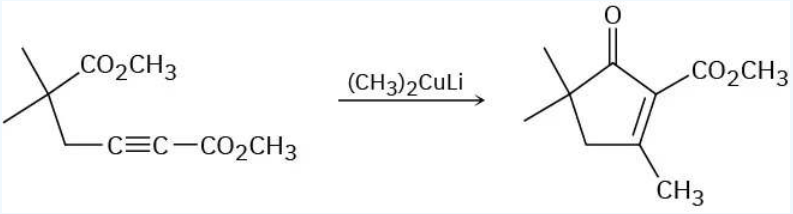
The following reaction involves a hydrolysis followed by an intramolecular nucleophilic acyl substitution reaction. Write both steps, and show their mechanisms.



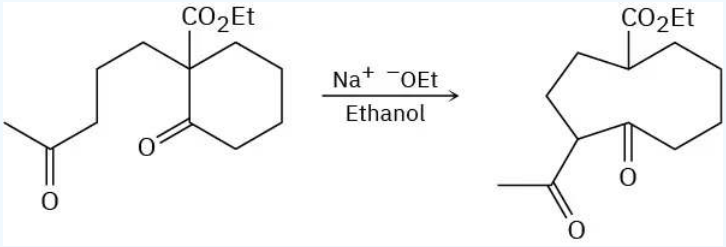
The following reaction involves an intramolecular Michael reaction followed by an intramolecular aldol reaction. Write both steps, and show their mechanisms.



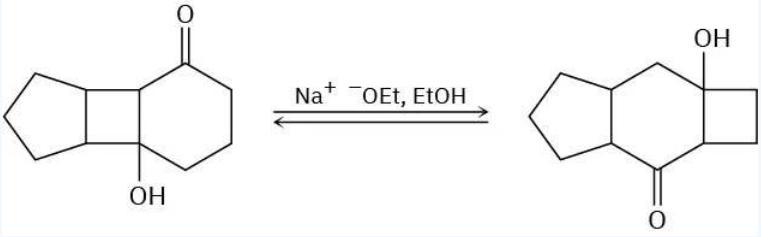
The following reaction involves a conjugate addition reaction followed by an intramolecular Claisen condensation. Write both steps, and show their mechanisms.



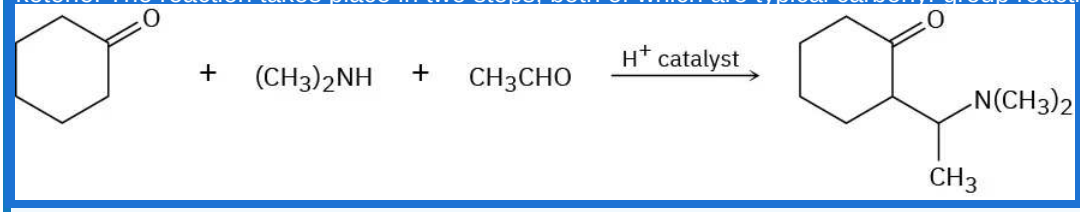
The following reaction involves an intramolecular aldol reaction followed by a *retro* aldol-like reaction. Write both steps, and show their mechanisms.



Propose a mechanism for the following base-catalyzed isomerization:



The Mannich reaction of a ketone, an amine, and an aldehyde is one of the few three-component reactions in organic chemistry. Cyclohexanone, for example, reacts with dimethylamine and acetaldehyde to yield an amino ketone. The reaction takes place in two steps, both of which are typical carbonyl-group reactions.

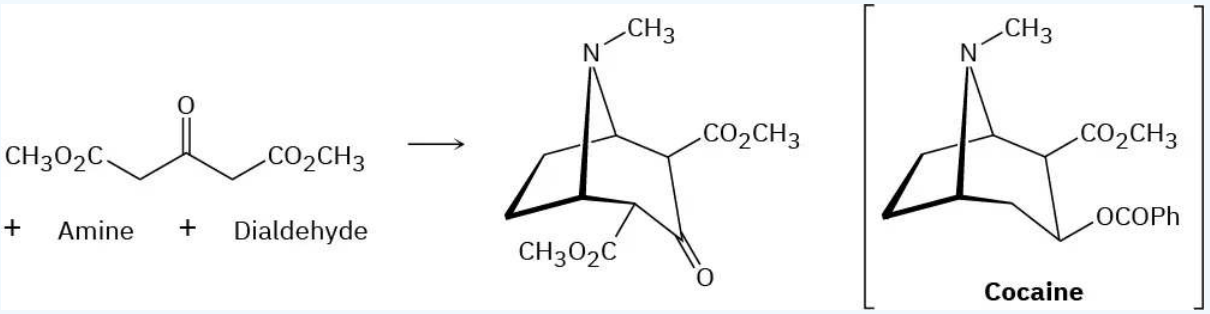


(a) The first step is reaction between the aldehyde and the amine to yield an intermediate iminium ion ($R_2C{=}NR_2^+$) plus water. Propose a mechanism, and show the structure of the intermediate iminium ion.

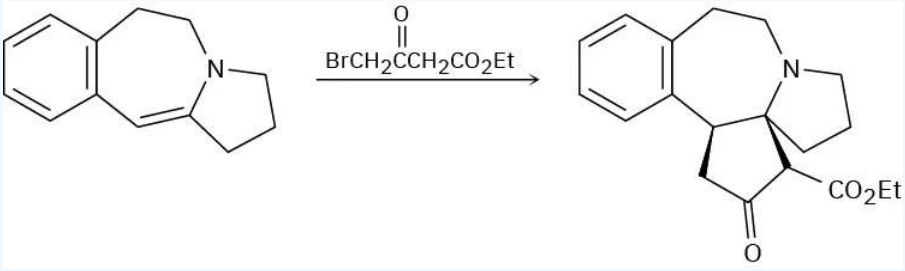
(b) The second step is reaction between the iminium ion intermediate and the ketone to yield the final product. Propose a mechanism.

https://chem.libretexts.org/@go/page/564343

Cocaine has been prepared by a sequence beginning with a Mannich reaction (Problem 23-45) between dimethyl acetonedicarboxylate, an amine, and a dialdehyde. Show the structures of the amine and dialdehyde.



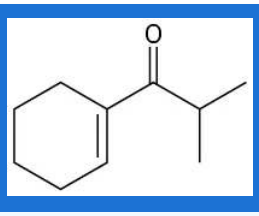
Propose a mechanism to account for the following reaction of an enamine with an alkyl halide:



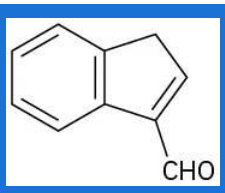
Aldol Reactions

Which of the following compounds would you expect to undergo aldol self-condensation? Show the product of each successful reaction.

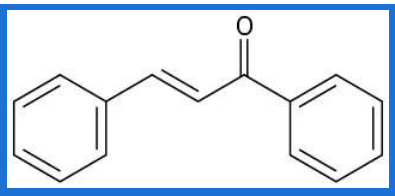
(a) Trimethylacetaldehyde **(b)** Cyclobutanone **(c)** Benzophenone (diphenyl ketone)
(d) 3-Pentanone **(e)** Decanal **(f)** 3-Phenyl-2-propenal



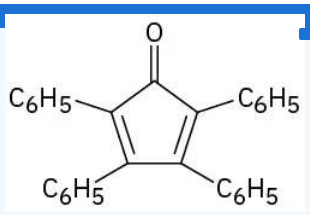
(c)



(d)



(b)



What product would you expect to obtain from aldol cyclization of hexanedial, OHCCH$_2$CH$_2$CH$_2$CH$_2$CHO ?

Intramolecular aldol cyclization of 2,5-heptanedione with aqueous NaOH yields a mixture of two enone products in the approximate ratio 9 : 1. Write their structures, and show how each is formed.

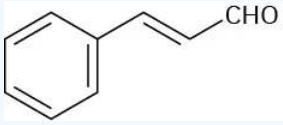
The major product formed by intramolecular aldol cyclization of 2,5-heptanedione (Problem 23-51) has two singlet absorptions in the ^{1}H NMR spectrum, at 1.65 δ and 1.90 δ, and has no absorptions in the range 3 to 10 δ. What is its structure?

Treatment of the minor product formed in the intramolecular aldol cyclization of 2,5-heptanedione (Problems 23-51 and 23-52) with aqueous NaOH converts it into the major product. Propose a mechanism to account for this base-catalyzed isomerization.

How can you account for the fact that 2,2,6-trimethylcyclohexanone yields no detectable aldol product even though it has an acidic α hydrogen?

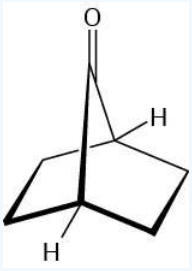
The aldol reaction is catalyzed by acid as well as base. What is the reactive nucleophile in the acid-catalyzed aldol reaction? Propose a mechanism.

Cinnamaldehyde, the aromatic constituent of cinnamon oil, can be synthesized by a mixed aldol condensation. Show the starting materials you would use, and write the reaction.



Cinnamaldehyde

The following bicyclic ketone does not undergo aldol self-condensation even though it has two α hydrogen atoms. Explain.



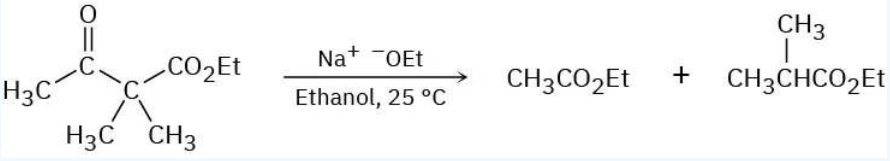
Claisen Condensations

$CH_3CO_2Et + CH_3CH_2CO_2Et$

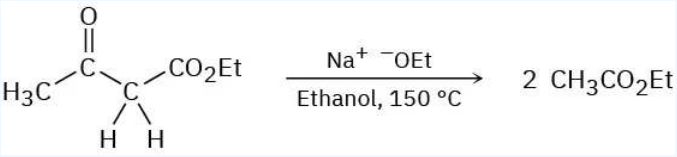
(b) $C_6H_5CO_2Et + C_6H_5CH_2CO_2Et$ (c) $EtOCO_2Et$ + cyclohexanone (d) $C_6H_5CHO + CH_3CO_2Et$

In the mixed Claisen reaction of cyclopentanone with ethyl formate, a much higher yield of the desired product is obtained by first mixing the two carbonyl components and then adding base, rather than by first mixing base with cyclopentanone and then adding ethyl formate. Explain.

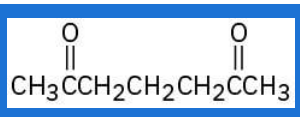
Ethyl dimethylacetoacetate reacts instantly at room temperature when treated with ethoxide ion to yield two products, ethyl acetate and ethyl 2-methylpropanoate. Propose a mechanism for this cleavage reaction.



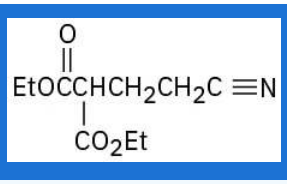
In contrast to the rapid reaction shown in Problem 23-60, ethyl acetoacetate requires a temperature over 150 °C to undergo the same kind of cleavage reaction. How can you explain the difference in reactivity?



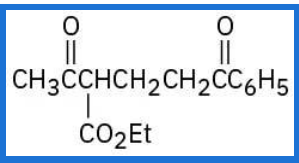
Michael and Enamine Reactions



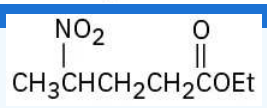
(c)



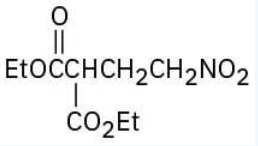
(d)



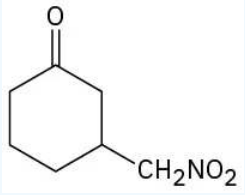
(b)

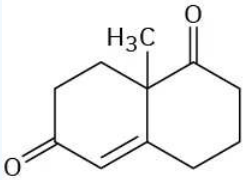


(e)



(f)

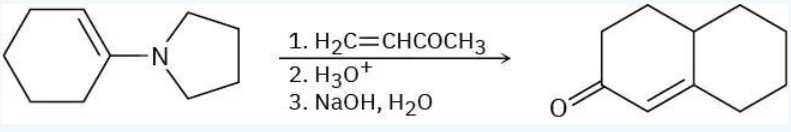




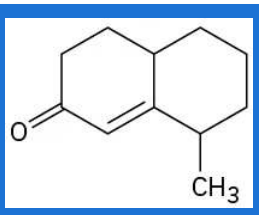
Wieland–Miescher ketone

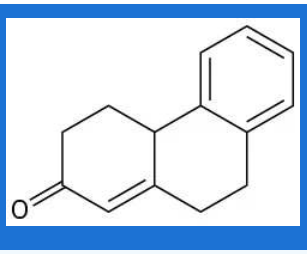
The so-called Wieland–Miescher ketone is a valuable starting material used in the synthesis of steroid hormones. How might you prepare it from 1,3-cyclohexanedione?

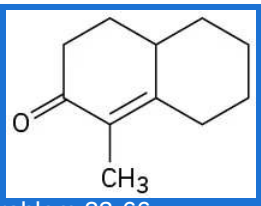
The Stork enamine reaction and the intramolecular aldol reaction can be carried out in sequence to allow the synthesis of cyclohexenones. For example, reaction of the pyrrolidine enamine of cyclohexanone with 3-buten-2-one, followed by enamine hydrolysis and base treatment, yields the product indicated. Write each step, and show the mechanism of each.



https://chem.libretexts.org/@go/page/564343

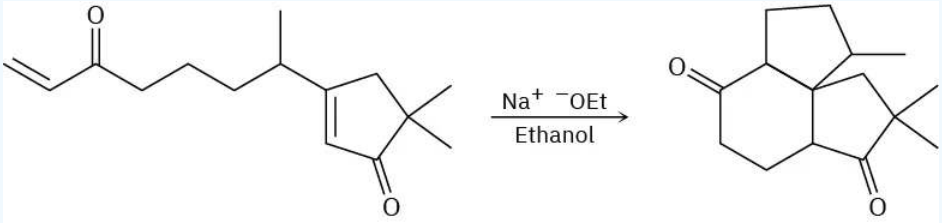

(c)




(b)

Problem 23-66

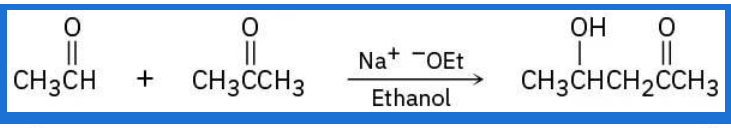
The following reaction involves two successive intramolecular Michael reactions. Write both steps, and show their mechanisms.



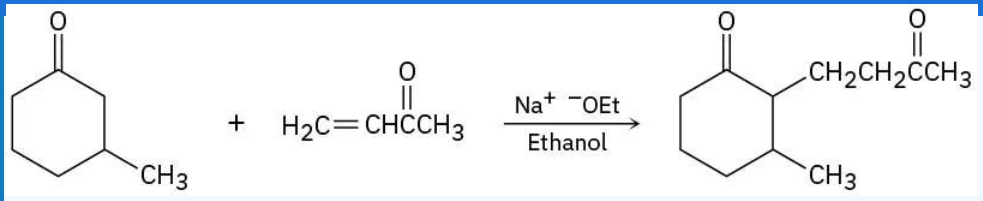
General Problems

Ethyl butanoate

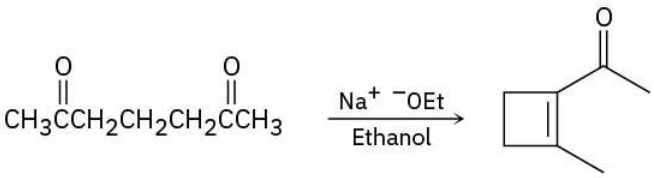
(b) Cycloheptanone (c) 3,7-Nonanedione (d) 3-Phenylpropanal



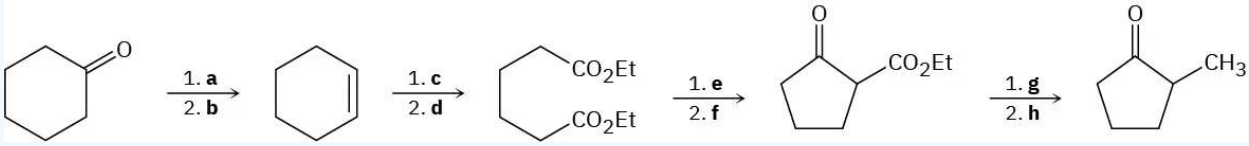
(b)



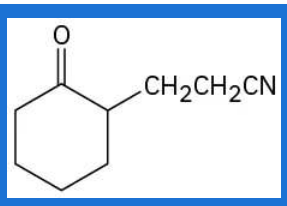
(c)



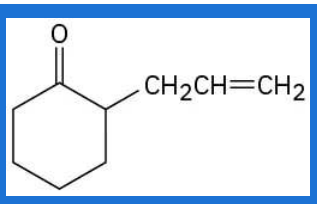
Fill in the missing reagents **a–h** in the following scheme:



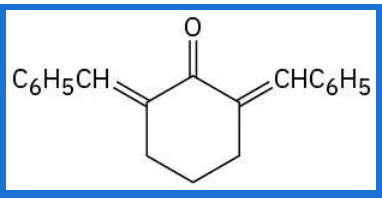
https://chem.libretexts.org/@go/page/564343



(c)

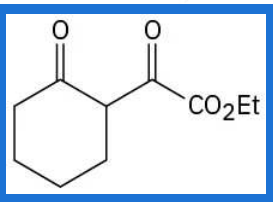


(d)

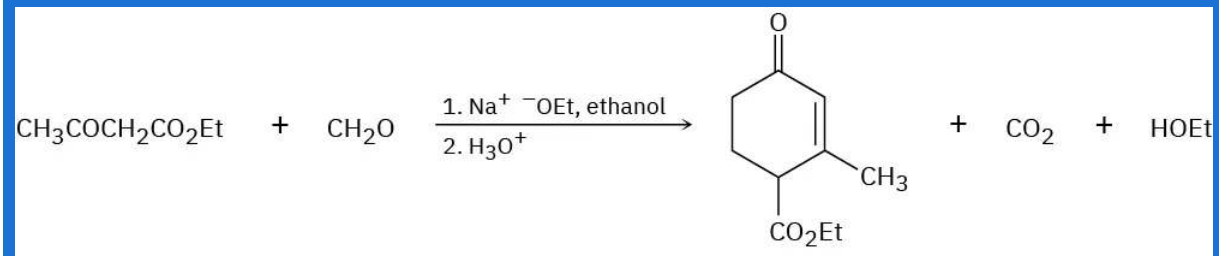


(b)

Problem 23-71



The compound known as Hagemann's ester is prepared by treatment of a mixture of formaldehyde and ethyl acetoacetate with base, followed by acid-catalyzed decarboxylation.



Hagemann's ester

(a)

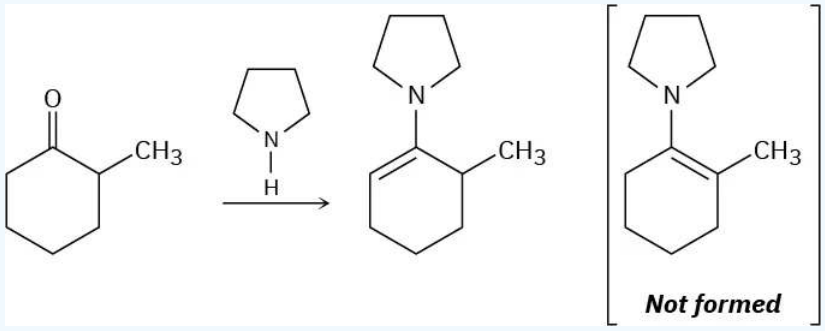
The first step is an aldol-like condensation between ethyl acetoacetate and formaldehyde to yield an α,β-unsaturated product. Write the reaction, and show the structure of the product.

(b)

The second step is a Michael reaction between ethyl acetoacetate and the unsaturated product of the first step. Show the structure of the product.

The third and fourth steps in the synthesis of Hagemann's ester from ethyl acetoacetate and formaldehyde (Problem 23-71) are an intramolecular aldol cyclization to yield a substituted cyclohexenone, and a decarboxylation reaction. Write both reactions, and show the products of each step.

When 2-methylcyclohexanone is converted into an enamine, only one product is formed despite the fact that the starting ketone is unsymmetrical. Build molecular models of the two possible products and explain the fact that the sole product is the one with the double bond opposite the methyl-substituted carbon.



This page titled 12.19: Additional Problems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **23.18: Additional Problems** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

CHAPTER OVERVIEW

13: Amines and Heterocycles

Learning Objectives

When you have completed Chapter 24, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design a multi-step synthesis that involves the use of any of the reactions described in this unit, and any of the reactions described in any previous unit.
3. solve road-map problems that require a knowledge of amine chemistry in addition to any of the chemistry discussed in previous units.
4. define, and use in context, the key terms introduced.

Amines are the first nitrogen-containing compounds that we study in detail in this course. We begin the chapter with an explanation of the differences in structure among primary, secondary and tertiary amines. We explain the nomenclature of aliphatic and arylamines, and examine the structure and bonding of these compounds, relating these features to their physical properties and basicity. We describe the use of amines to resolve racemic mixtures of chiral carboxylic acids.

Amines may be prepared by a number of different synthetic methods. We describe each of these methods and assess the relative merits of each. After a description of the reactions of aliphatic amines, we devote sections to a discussion of the use of tetraalkylammonium salts as phase-transfer agents. The chapter concludes with a summary of the spectroscopic properties of amines.

13.1: Why This Chapter?
13.2: Naming Amines
13.3: Structure and Properties of Amines
13.4: Basicity of Amines
13.5: Basicity of Arylamines
13.6: Biological Amines and the Henderson-Hasselbalch Equation
13.7: Synthesis of Amines
13.8: Reactions of Amines
13.9: Reactions of Arylamines
13.10: Heterocyclic Amines
13.11: Spectroscopy of Amines
13.12: Chemistry Matters - Green Chemistry II- Ionic Liquids
13.13: Key Terms
13.14: Summary
13.15: Summary of Reactions
13.16: Additional Problems

This page titled 13: Amines and Heterocycles is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

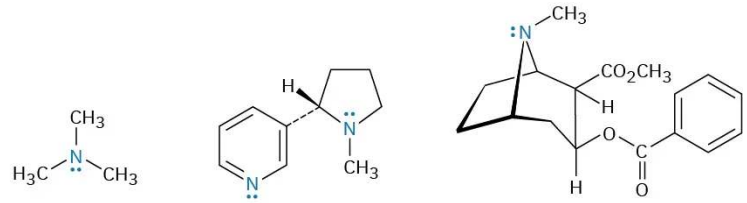
13.1: Why This Chapter?

By the end of this chapter, we will have seen all the common functional groups. Of those groups, carbonyl compounds and amines are the most abundant and have the richest chemistry. In addition to proteins and nucleic acids, the majority of pharmaceutical agents contain amine functional groups, and many of the common coenzymes necessary for biological catalysis are amines.

Figure 13.1.1: The characteristic and unmistakable odor of fish is due to a mixture of simple alkylamines. (credit: modification of work “Pike Place” by Sharat Ganapati/Flickr, CC BY 2.0)

Amines are organic derivatives of ammonia in the same way that alcohols and ethers are organic derivatives of water. Like ammonia, amines contain a nitrogen atom with a lone pair of electrons, making amines both basic and nucleophilic. We’ll soon see, in fact, that most of the chemistry of amines depends on the presence of this lone pair of electrons.

Amines occur widely in all living organisms. Trimethylamine, for instance, occurs in animal tissues and is partially responsible for the distinctive odor of fish; nicotine is found in tobacco; and cocaine is a stimulant found in the leaves of the South American coca bush. In addition, amino acids are the building blocks from which all proteins are made, and cyclic amine bases are constituents of nucleic acids.



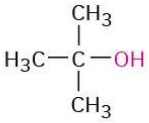
Trimethylamine **Nicotine** **Cocaine**

This page titled 13.1: Why This Chapter? is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

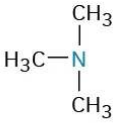
- **24.0: Why This Chapter?** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

13.2: Naming Amines

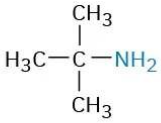
Amines can be either alkyl-substituted (alkylamines) or aryl-substituted (arylamines). Although much of the chemistry of the two classes is similar, there are also substantial differences. Amines are classified as primary (RNH_2), secondary (R_2NH), or tertiary (R_3N), depending on the number of organic substituents attached to nitrogen. Thus, methylamine (CH_3NH_2) is a primary amine, dimethylamine [$(CH_3)_2NH$] is a secondary amine, and trimethylamine [$(CH_3)_3N$] is a tertiary amine. Note that this usage of the terms *primary*, *secondary*, and *tertiary* differs from our previous usage. When we speak of a tertiary alcohol or alkyl halide, we refer to the degree of substitution at the alkyl carbon atom, but when we speak of a tertiary amine, we refer to the degree of substitution at the nitrogen atom.



***tert*-Butyl alcohol**
(a tertiary alcohol)

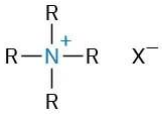


Trimethylamine
(a tertiary amine)



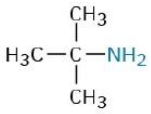
***tert*-Butylamine**
(a primary amine)

Compounds containing a nitrogen atom with four attached groups also exist, but the nitrogen atom must carry a formal positive charge. Such compounds are called quaternary ammonium salts.

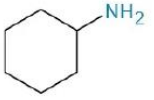


A quaternary ammonium salt

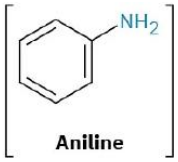
Primary amines are named in the IUPAC system in several ways. For simple amines, the suffix *-amine* is added to the name of the alkyl substituent. You might also recall from the chapter on Benzene and Aromaticity that the aromatic phenylamine, $H_2N–C_6H_5$, has the common name *aniline*.



***tert*-Butylamine**

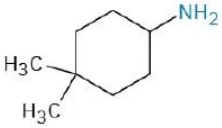


Cyclohexylamine

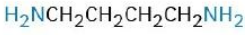


Aniline

Alternatively, the suffix *-amine* can be used in place of the final *-e* in the name of the parent compound.

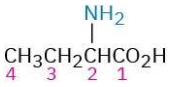


4,4-Dimethylcyclohexanamine

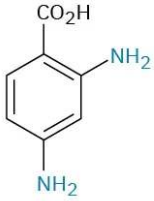


1,4-Butanediamine

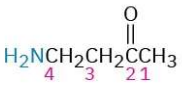
Amines with more than one functional group are named by considering the $-NH_2$ as an *amino* substituent on the parent molecule.



2-Aminobutanoic acid

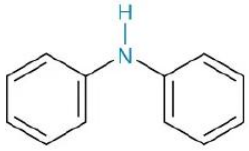


2,4-Diaminobenzoic acid

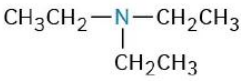


4-Amino-2-butanone

Symmetrical secondary and tertiary amines are named by adding the prefix *di-* or *tri-* to the alkyl group.

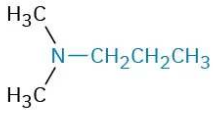


Diphenylamine

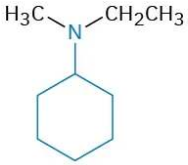


Triethylamine

Unsymmetrically substituted secondary and tertiary amines are referred to as *N*-substituted primary amines. The largest alkyl group takes the parent name, and the other alkyl groups are considered *N*-substituents on the parent (*N* because they're attached to nitrogen).



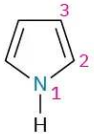
***N,N*-Dimethylpropylamine**



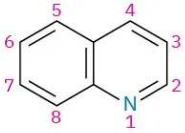
***N*-Ethyl-*N*-methylcyclohexylamine**

Heterocyclic amines—compounds in which the nitrogen atom occurs as part of a ring—are also common, and each different heterocyclic ring system has its own parent name. The heterocyclic nitrogen atom is always numbered as position 1.

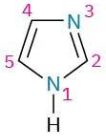
Pyridine



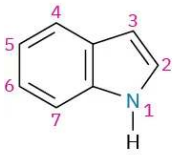
Pyrrole



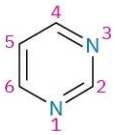
Quinoline



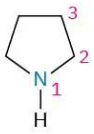
Imidazole



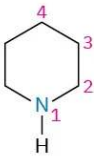
Indole



Pyrimidine



Pyrrolidine

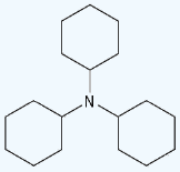


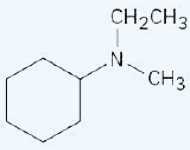
Piperidine

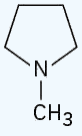
? Exercise 13.2.1

Name the following compounds:

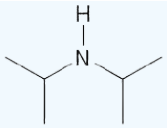
a. $CH_3NHCH_2CH_3$

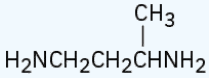
b. 

c. 

d. 

https://chem.libretexts.org/@go/page/564346

e. 

f. 

Answer

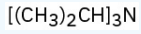
a. N-Methylethylamine
b. Tricyclohexylamine
c. N-Ethyl-N-methylcyclohexylamine
d. N-Methylpyrrolidine
e. Diisopropylamine
f. 1,3-Butanediamine

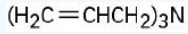
Exercise 13.2.2

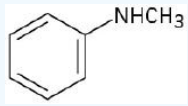
Draw structures corresponding to the following IUPAC names:

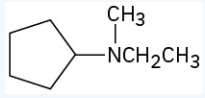
a. Triisopropylamine
b. Triallylamine
c. N-Methylaniline
d. N-Ethyl-N-methylcyclopentylamine
e. N-Isopropylcyclohexylamine
f. N-Ethylpyrrole

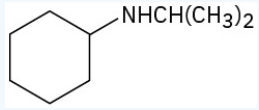
Answer

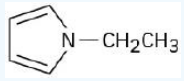
a. 

b. 

c. 

d. 

e. 

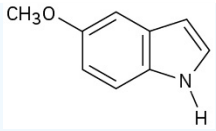
f. 

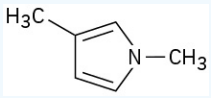
Exercise 13.2.3

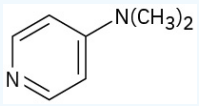
Draw structures for the following heterocyclic amines:

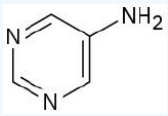
a. 5-Methoxyindole
b. 1,3-Dimethylpyrrole
c. 4-(N,N-Dimethylamino)pyridine
d. 5-aminopyrimidine

Answer

a. 

b. 

c. 

d. 

This page titled 13.2: Naming Amines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

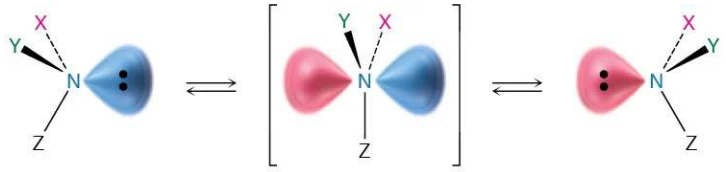
- **24.1: Naming Amines** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

13.3: Structure and Properties of Amines

The bonding in alkylamines is similar to the bonding in ammonia. The nitrogen atom is sp^3-hybridized, with its three substituents occupying three corners of a regular tetrahedron and the lone pair of electrons occupying the fourth corner. As you might expect, the C–N–C bond angles are close to the 109° tetrahedral value. For trimethylamine, the C–N–C bond angle is 108° and the C–N bond length is 147 pm.

Trimethylamine

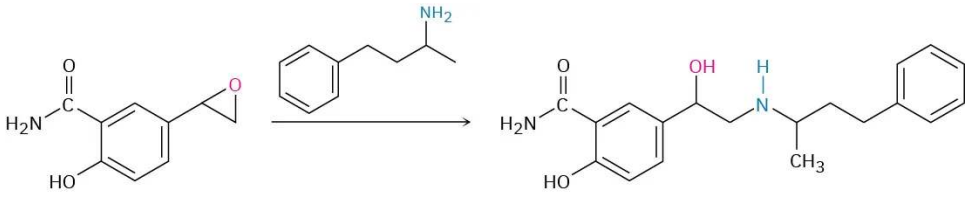
One consequence of tetrahedral geometry is that an amine with three different substituents on nitrogen is chiral, as we saw in Section 5.10. Unlike chiral carbon compounds, however, chiral amines can't usually be resolved because the two enantiomeric forms rapidly interconvert by a *pyramidal inversion*, much as an alkyl halide inverts in an S_N2 reaction. Pyramidal inversion occurs by a momentary rehybridization of the nitrogen atom to planar, sp^2 geometry, followed by rehybridization of the planar intermediate to tetrahedral, sp^3 geometry (Figure 24.2). The barrier to inversion is about 25 kJ/mol (6 kcal/mol), an amount only twice as large as the barrier to rotation about a C–C single bond.



sp^3-hybridized (tetrahedral) **sp^2-hybridized (planar)** **sp^3-hybridized (tetrahedral)**

Figure 24.2: Pyramidal inversion rapidly interconverts the two mirror-image (enantiomeric) forms of an amine.

Alkylamines have a variety of applications in the chemical industry as starting materials for the preparation of insecticides and pharmaceuticals. Labetalol, for instance, a so-called β-blocker used for the treatment of high blood pressure, is prepared by S_N2 reaction of an epoxide with a primary amine. The substance marketed for drug use is a mixture of all four possible stereoisomers, but the biological activity results primarily from the (*R*,*R*) isomer.



Labetalol

Like alcohols, amines with fewer than five carbon atoms are generally water-soluble. Also like alcohols, primary and secondary amines form hydrogen bonds and are highly associated. As a result, amines have higher boiling points than alkanes of similar molecular weight. Diethylamine (MW = 73 amu) boils at 56.3 °C, for instance, while pentane (MW = 72 amu) boils at 36.1 °C.

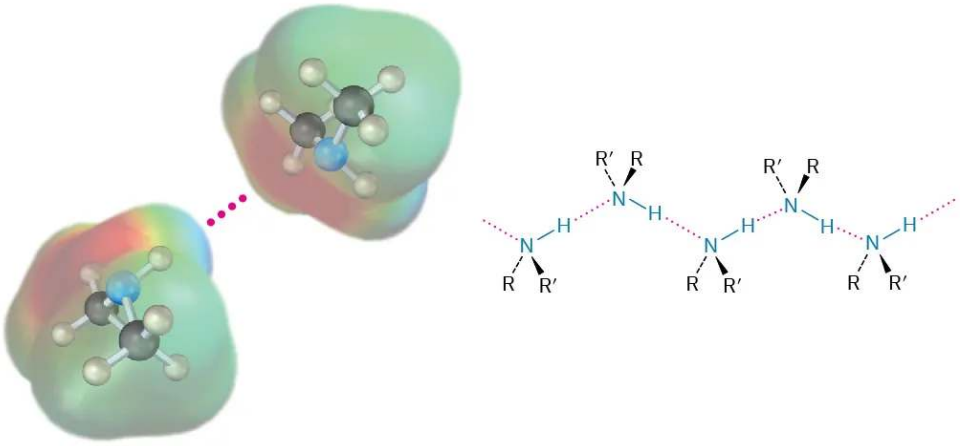


Figure 13.3.1: Hydrogen bonding in amines.

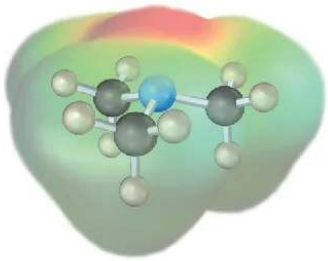
One other characteristic of amines is their odor. Low-molecular-weight amines such as trimethylamine have a distinctive fishlike aroma, while diamines such as cadaverine (1,5-pentanediamine) and putrescine (1,4-butanediamine) have the appalling odors you might expect from their common names. Both of these diamines arise from the decomposition of decaying tissue.

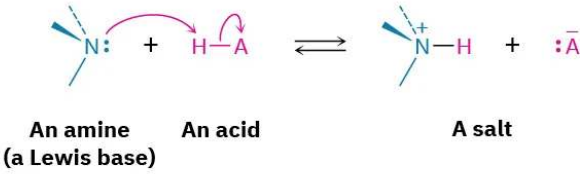
This page titled 13.3: Structure and Properties of Amines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.2: Structure and Properties of Amines** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

13.4: Basicity of Amines

The chemistry of amines is dominated by the lone pair of electrons on nitrogen, which makes amines both basic and nucleophilic. They react with acids to form acid–base salts, and they react with electrophiles in many of the polar reactions seen in past chapters. Note in the following electrostatic potential map of trimethylamine how the negative (red) region corresponds to the lone pair of electrons on nitrogen.





Amines are much stronger bases than alcohols and ethers, their oxygen-containing analogs. When an amine is dissolved in water, an equilibrium is established in which water acts as an acid and transfers a proton to the amine. Just as the acid strength of a carboxylic acid can be measured by defining an acidity constant K_a (Section 2.8), the base strength of an amine can be measured by defining an analogous *basicity constant* K_b. The larger the value of K_b and the smaller the value of pK_b, the more favorable the proton-transfer equilibrium and the stronger the base.

For the reaction

msub

RNH2 + H2O ⇄ RNH3+ + OH–Kb = [RNH3+] [OH–][RNH2]pKb = –log KbRNH2 + H2O ⇄ RNH3+ + OH–Kb = [RNH3+] [OH–][RNH2]pKb = –log Kb

In practice, K_b values are not often used. Instead, the most convenient way to measure the *basicity* of an amine (RNH_2) is to look at the *acidity* of the corresponding ammonium ion (RNH_3^+).

For the reaction

msub

RNH3+ + H2O ⇄ RNH2 + H3O+Ka = [RNH2] [H3O+][RNH3+]RNH3+ + H2O ⇄ RNH2 + H3O+Ka = [RNH2] [H3O+] [RNH3+]

so

$$K_a \cdot K_b = [\text{mfrac}]$$

RNH2] [H3O+][RNH3+][RNH3+] [OH–][RNH2]= [H3O+] [OH–] = Kw = 1.00 × 10–14Ka · Kb = [RNH2] [H3O+][RNH3+] [RNH3+] [OH–][RNH2]= [H3O+] [OH–] = Kw = 1.00 × 10–14

Thus

$$K_a = \text{mfrac}$$

KwKb and Kb = KwKaKa = KwKb and Kb = KwKa

and

pKa+ pKb = 14pKa+ pKb = 14

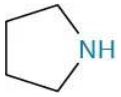
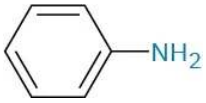
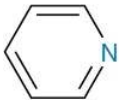
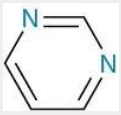
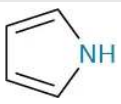
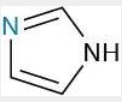
These equations say that the K_b of an amine multiplied by the K_a of the corresponding ammonium ion is equal to K_w, the ion-product constant for water (1.00×10^{-14}). Thus, if we know K_a for an ammonium ion, we also know K_b for the corresponding

amine base because $K_b = K_w/K_a$. The more acidic the ammonium ion, the less tightly the proton is held and the weaker the corresponding base. That is, a weaker base has an ammonium ion with a smaller pK_a and a stronger base has an ammonium ion with a larger pK_a.

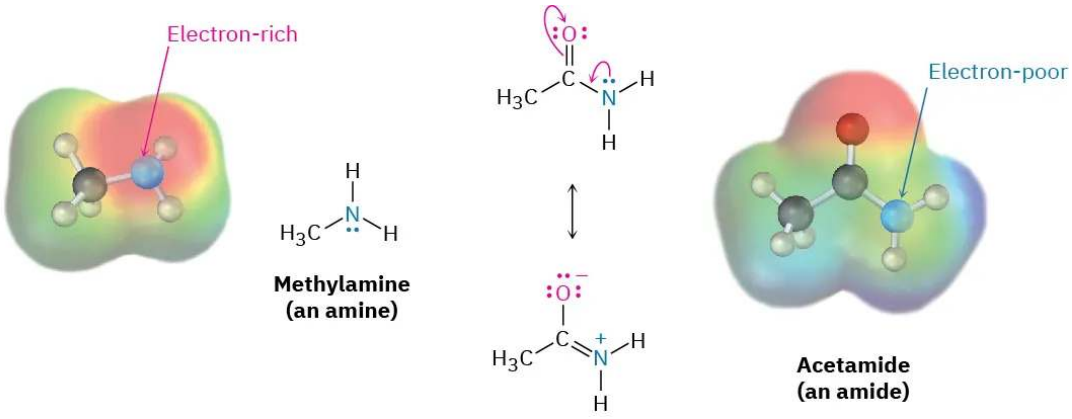
Weaker base	Smaller pK_a for ammonium ion
Stronger base	Larger pK_a for ammonium ion

Table 13.4.1 lists pK_a values of the ammonium ions from a variety of amines and indicates that there is a substantial range of amine basicities. Most simple alkylamines are similar in their base strength, with pK_a's for their ammonium ions in the narrow range 10 to 11. Arylamines, however, are considerably less basic than alkylamines, as are the heterocyclic amines pyridine and pyrrole.

Table 13.4.1 Basicity of Some Common Amines

Name	Structure	pK_a of ammonium ion
Ammonia	NH_3	9.26
	Primary alkylamine	
Methylamine	CH_3NH_2	10.64
Ethylamine	$CH_3CH_2NH_2$	10.75
	Secondary alkylamine	
Diethylamine	$(CH_3CH_2)_2NH$	10.98
Pyrrolidine		11.27
	Tertiary alkylamine	
Triethylamine	$(CH_3CH_2)_3N$	10.76
	Arylamine	
Aniline		4.63
	Heterocyclic amine	
Pyridine		5.25
Pyrimidine		1.3
Pyrrole		0.4
Imidazole		6.95

In contrast with amines, amides ($RCONH_2$) are nonbasic. Amides aren't protonated by aqueous acids, and they are poor nucleophiles. The main reason for this difference in basicity between amines and amides is that an amide is stabilized by delocalization of the nitrogen lone-pair electrons through orbital overlap with the carbonyl group. In resonance terms, amides are more stable and less reactive than amines because they are hybrids of two resonance forms. This amide resonance stabilization is lost when the nitrogen atom is protonated, so protonation is disfavored. The following electrostatic potential maps clearly show a reduced electron density on the amide nitrogen.



To purify amines, it's often possible to take advantage of their basicity. For example, if a mixture of a basic amine and a neutral compound such as a ketone or alcohol is dissolved in an organic solvent and aqueous acid is added, the basic amine dissolves in the water layer as its protonated salt, while the neutral compound remains in the organic solvent layer. Separation of the water layer and neutralization of the ammonium ion by addition of NaOH then provides the pure amine (Figure 13.4.1).

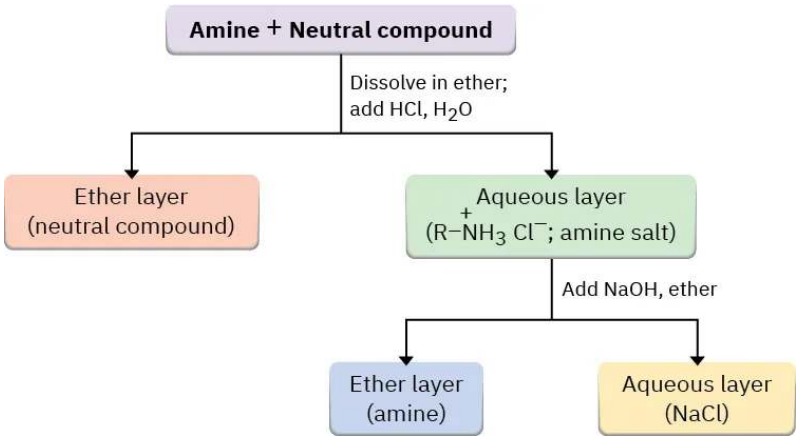
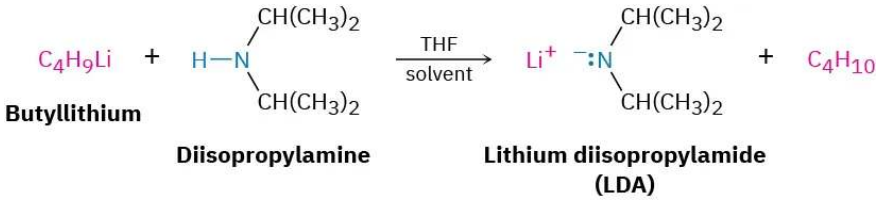


Figure 13.4.1: Separation and purification of an amine component from a mixture by extraction of its ammonium salt into water.

In addition to their behavior as bases, primary and secondary amines can also act as very weak acids because an N–H proton can be removed by a sufficiently strong base. We've seen, for example, how diisopropylamine ($pK_a \approx 36$) reacts with butyllithium to yield lithium diisopropylamide (LDA; Section 22.5). Dialkylamine anions like LDA are very strong bases that are often used in laboratory organic chemistry for the generation of enolate ions from carbonyl compounds (Section 22.7). They are not, however, encountered in biological chemistry.



Exercise 13.4.1

Select the more basic amine from each of the following pairs of compounds.

a. CH3CH2NH2 or CH3CH2CONH2
b. NaOH or CH3NH2
c. CH3NHCH3 or pyridine

Answer

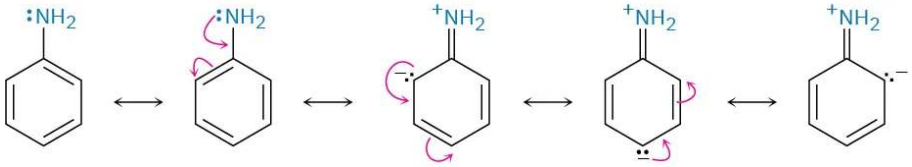
(a) $CH_3CH_2NH_2$
(b) NaOH
(c) CH_3NHCH_3

This page titled 13.4: Basicity of Amines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.3: Basicity of Amines** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.
- **24.3: Basicity of Amines** by Dietmar Kennepohl, Layne Morsch, Steven Farmer, Tim Soderberg, William Reusch is licensed CC BY-SA 4.0.

13.5: Basicity of Arylamines

As noted previously, arylamines are generally less basic than alkylamines. Anilinium ion has pK_a = 4.63, for instance, whereas methylammonium ion has pK_a = 10.64. Arylamines are less basic than alkylamines because the nitrogen lone-pair electrons are delocalized by interaction with the aromatic ring's π electron system and are less available for bonding to H^+. In resonance terms, arylamines are stabilized relative to alkylamines because of their five resonance forms.



Much of the resonance stabilization is lost on protonation, however, so the energy difference between protonated and nonprotonated forms is higher for arylamines than it is for alkylamines. As a result, arylamines are less basic. Figure 13.5.1 illustrates this difference.

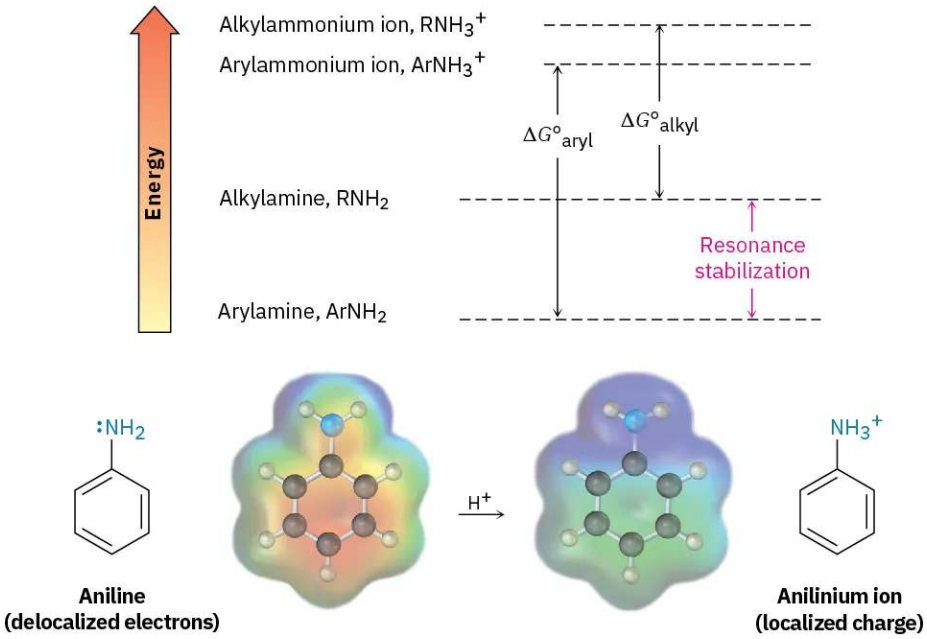


Figure 13.5.1: Arylamines have a larger positive $\Delta G°$ for protonation and are therefore less basic than alkylamines, primarily because of resonance stabilization of the ground state. Electrostatic potential maps show that lone-pair electron density is delocalized in the amine but the charge is localized in the corresponding ammonium ion.

Substituted arylamines can be either more basic or less basic than aniline, depending on the substituent. Electron-donating substituents, such as $–CH_3$, $–NH_2$, and $–OCH_3$, which increase the reactivity of an aromatic ring toward electrophilic substitution (Section 16.4), also increase the basicity of the corresponding arylamine. Electron-withdrawing substituents, such as –Cl, $–NO_2$, and –CN, which decrease ring reactivity toward electrophilic substitution, also decrease arylamine basicity. Table 13.5.2 considers only *p*-substituted anilines, but similar trends are observed for ortho and meta derivatives.

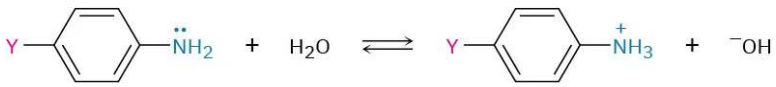
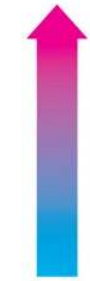


Table 13.5.2 Base Strength of Some *p*-Substituted Anilines

https://chem.libretexts.org/@go/page/564349

	Substituent, Y	pK_a	
Stronger base  Weaker base	$-NH_2$	6.15	Activating groups
	$-OCH_3$	5.34	
	$-CH_3$	5.08	
	–H	4.63	
	–Cl	3.98	Deactivating groups
	–Br	3.86	
	–CN	1.74	
	$-NO_2$	1.00	

? Exercise 13.5.1

Add exercises text here.

Answer

Add texts here. Do not delete this text first.

This page titled 13.5: Basicity of Arylamines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.4: Basicity of Arylamines** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

13.6: Biological Amines and the Henderson-Hasselbalch Equation

We saw in Section 20.3 that the extent of dissociation of a carboxylic acid HA in an aqueous solution buffered to a given pH can be calculated with the Henderson–Hasselbalch equation. Furthermore, we concluded that at the physiological pH of 7.3 inside living cells, carboxylic acids are almost entirely dissociated into their carboxylate anions, RCO_2^-.

Henderson–Hasselbalch equation:

$$\text{pH} = \text{p}K\text{a} + \log\frac{[\text{A}^-]}{[\text{HA}]} \quad \text{so} \quad \log\frac{[\text{A}^-]}{[\text{HA}]} = \text{pH} -$$

What about amine bases? In what form do they exist at physiological pH? As the amine (A^- = RNH_2), or as the ammonium ion (HA = RNH_3^+)? Let's take a 0.0010 M solution of methylamine at pH = 7.3, for example. According to Table 24.1, the pK_a of methylammonium ion is 10.64, so from the Henderson–Hasselbalch equation, we have

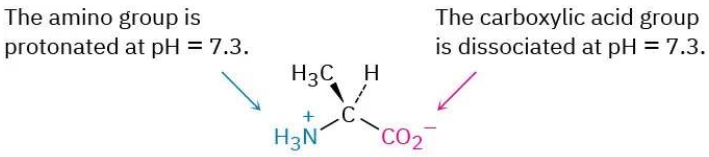
$$\log\frac{\text{msub}]}{\text{msub}^+]} = \text{pH} - \text{p}K_\text{a} = 7.3 - 10.64 = -3.34$$

$$\frac{\text{msub}]}{\text{msub}^+]} = \text{antilog}(-3.34) = 4.6 \times 10^{-4} \quad \text{so} \quad \text{msub}] = (4.6 \times 10^{-4}\text{msub}^+]$$

In addition, we know that

$$\text{msubmsub}^+] = 0.0010 \text{ M}$$

Solving the two simultaneous equations gives [RNH_3^+] = 0.0010 M and [RNH_2] = 5×10^{-7} M. In other words, at a physiological pH of 7.3, essentially 100% of the methylamine in a 0.0010 M solution exists in its protonated form as methylammonium ion. The same is true of other amine bases, so we always write cellular amines in their protonated form and amino acids in their ammonium carboxylate form to reflect their structures at physiological pH.



Alanine
(an amino acid)

Exercise 13.6.1

Add exercises text here.

Answer

Add texts here. Do not delete this text first.

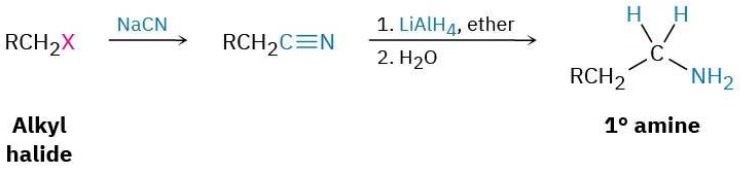
This page titled 13.6: Biological Amines and the Henderson-Hasselbalch Equation is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.5: Biological Amines and the Henderson-Hasselbalch Equation** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

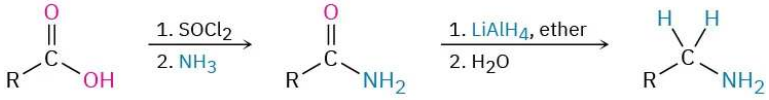
13.7: Synthesis of Amines

Reduction of Nitriles, Amides, and Nitro Compounds

We've already seen in Section 20.7 and Section 21.7 how amines can be prepared by reduction of nitriles and amides with $LiAlH_4$. The two-step sequence of S_N2 displacement with CN^- followed by reduction thus converts an alkyl halide into a primary alkylamine having an additional carbon atom. Amide reduction converts carboxylic acids and their derivatives into amines with the same number of carbon atoms.

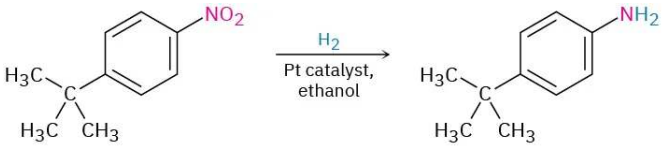


Alkyl halide **1° amine**

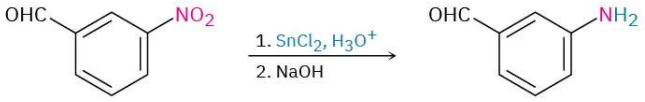


Carboxylic acid **1° amine**

Arylamines are usually prepared by nitration of an aromatic starting material, followed by reduction of the nitro group (Section 16.2). The reduction step can be carried out in many different ways, depending on the circumstances. Catalytic hydrogenation over platinum works well but is often incompatible with the presence elsewhere in the molecule of other reducible groups, such as C=C bonds or carbonyl groups. Iron, zinc, tin, and tin(II) chloride ($SnCl_2$) are also effective when used in acidic aqueous solution. Tin(II) chloride is particularly mild and is often used when other reducible functional groups are present.



***p-tert*-Butylnitrobenzene** ***p-tert*-Butylaniline (100%)**



***m*-Nitrobenzaldehyde** ***m*-Aminobenzaldehyde (90%)**

? Exercise 13.7.1

Propose structures for either a nitrile or an amide that might be a precursor of each of the following amines:

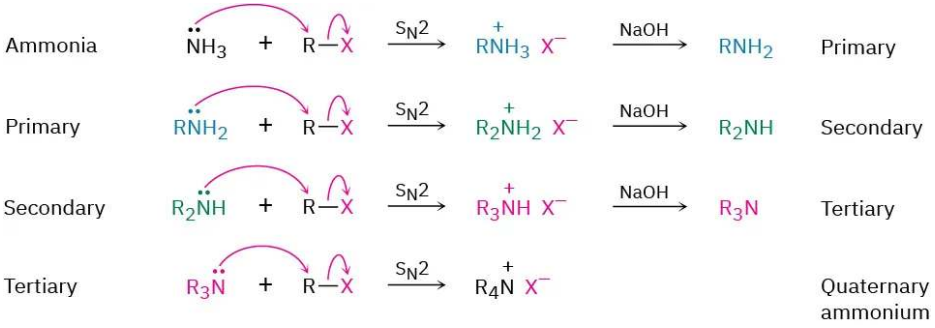
a. $CH_3CH_2CH_2NH_2$
b. $(CH_3CH_2CH_2)_2NH$
c. Benzylamine, $C_6H_5CH_2NH_2$
d. *N*-Ethylaniline

Answer

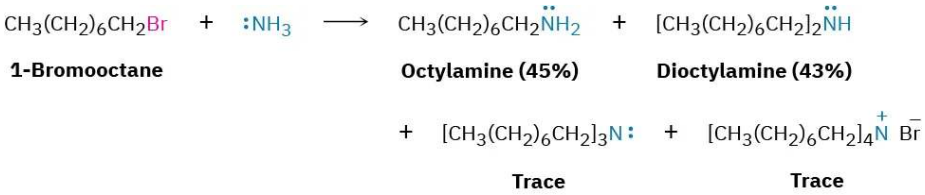
a. Propanenitrile or propanamide
b. *N*-Propylpropanamide
c. Benzonitrile or benzamide
d. *N*-Phenylacetamide

S_N2 Reactions of Alkyl Halides

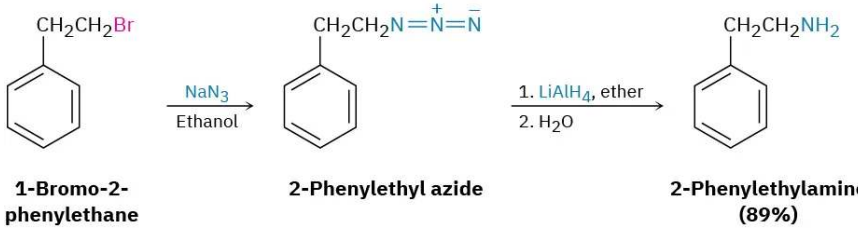
Ammonia and other amines are good nucleophiles in S_N2 reactions. As a result, the simplest method of alkylamine synthesis is by S_N2 alkylation of ammonia or an alkylamine with an alkyl halide. If ammonia is used, a primary amine results; if a primary amine is used, a secondary amine results; and so on. Even tertiary amines react rapidly with alkyl halides to yield quaternary ammonium salts, $R_4N^+ X^-$.



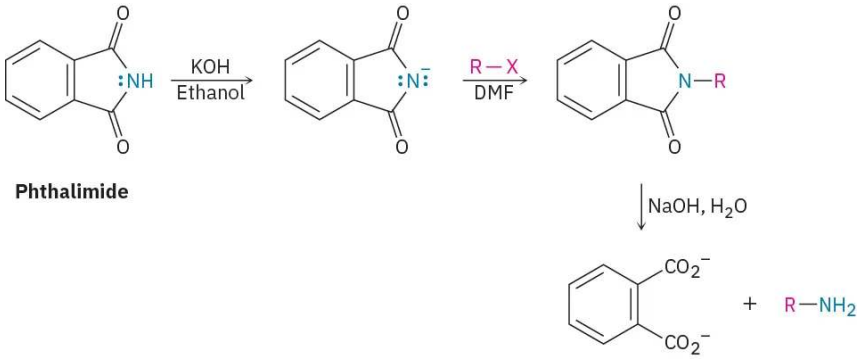
Unfortunately, these reactions don't stop cleanly after a single alkylation has occurred. Because ammonia and primary amines have similar reactivity, the initially formed monoalkylated substance often undergoes further reaction to yield a mixture of products. Even secondary and tertiary amines undergo further alkylation, although to a lesser extent. For example, treatment of 1-bromooctane with a twofold excess of ammonia leads to a mixture containing only 45% octylamine. A nearly equal amount of dioctylamine is produced by double alkylation, along with smaller amounts of trioctylamine and tetraoctylammonium bromide.



A better method for preparing primary amines is to use azide ion, N_3^-, rather than ammonia, as the nucleophile for S_N2 reaction with a primary or secondary alkyl halide. The product is an alkyl azide, which is not nucleophilic, so overalkylation can't occur. Subsequent reduction of the alkyl azide with $LiAlH_4$ then leads to the desired primary amine. Although this method works well, low-molecular-weight alkyl azides are explosive and must be handled carefully.



Another alternative for preparing a primary amine from an alkyl halide is the Gabriel amine synthesis, which uses a *phthalimide* alkylation. An imide (O=C–N–C=OSection 22.7). Basic hydrolysis of the *N*-alkylated imide then yields a primary amine product. The imide hydrolysis step is analogous to the hydrolysis of an amide (Section 21.7).



Phthalimide

? Exercise 13.7.2

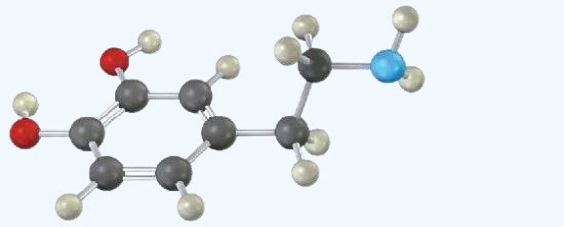
Write the mechanism of the last step in Gabriel amine synthesis, the base-promoted hydrolysis of a phthalimide to yield an amine plus phthalate ion.

Answer

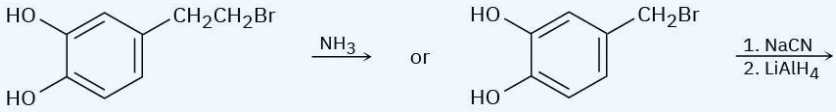
The reaction takes place by two nucleophilic acyl substitution reactions.

? Exercise 13.7.3

Show two methods for the synthesis of dopamine, a neurotransmitter involved in regulation of the central nervous system. Use any alkyl halide needed.

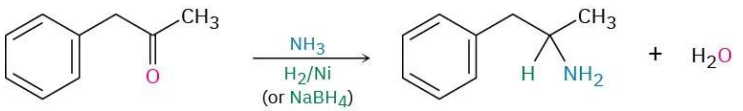


Answer



Reductive Amination of Aldehydes and Ketones

Amines can be synthesized in a single step by treatment of an aldehyde or ketone with ammonia or an amine in the presence of a reducing agent, a process called reductive amination. For example, amphetamine, a central nervous system stimulant, is prepared commercially by reductive amination of phenyl-2-propanone with ammonia using hydrogen gas over a nickel catalyst as the reducing agent. In the laboratory, either $NaBH_4$ or the related $NaBH(OAc)_3$ is commonly used (OAc = acetate).



Phenyl-2-propanone **Amphetamine**

Reductive amination takes place by the pathway shown in Figure 13.7.1. An imine intermediate is first formed by a nucleophilic addition reaction (Section 19.8), and the C═N bond of the imine is then reduced to the amine, much as the C═O bond of a ketone can be reduced to an alcohol.

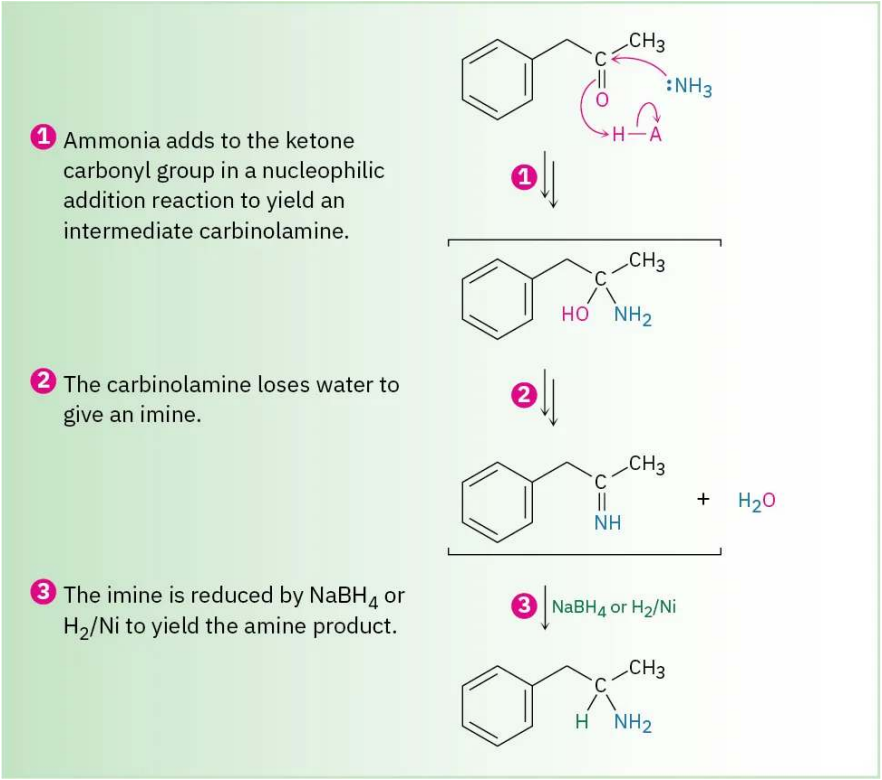
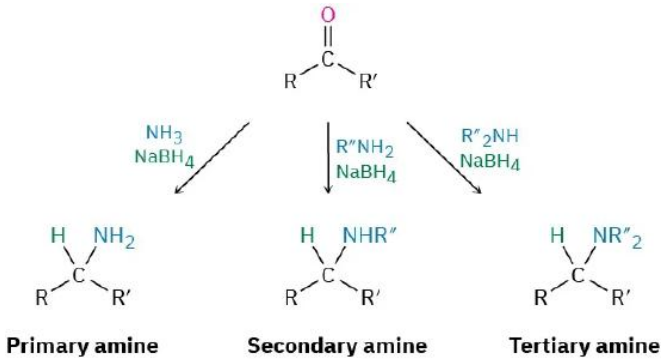
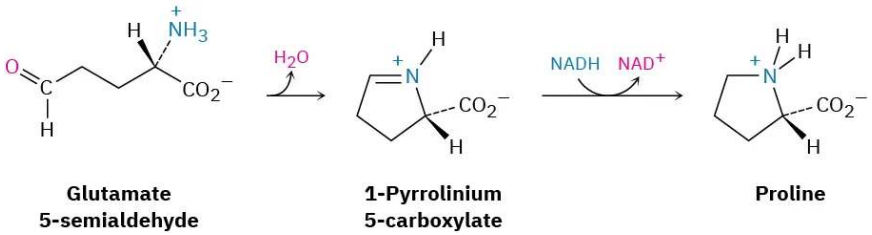


Figure 13.7.1: Mechanism for reductive amination of a ketone to yield an amine.

Ammonia, primary amines, and secondary amines can all be used in the reductive amination reaction, yielding primary, secondary, and tertiary amines, respectively.

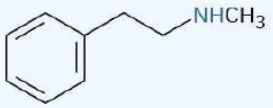


Reductive aminations also occur in various biological pathways. In the biosynthesis of the amino acid proline, for instance, glutamate 5-semialdehyde undergoes internal imine formation to give 1-pyrrolinium 5-carboxylate, which is then reduced by nucleophilic addition of hydride ion to the C=N bond. Reduced nicotinamide adenine dinucleotide, NADH, acts as the biological reducing agent.



Worked Example 13.7.1: Using a Reductive Amination Reaction

How might you prepare *N*-methyl-2-phenylethylamine using a reductive amination reaction?

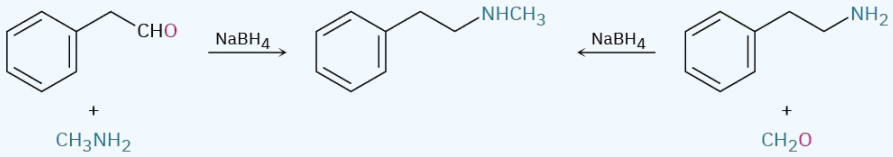


***N*-Methyl-2-phenylethylamine**

Strategy

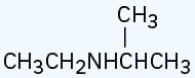
Look at the target molecule, and identify the groups attached to nitrogen. One of the groups must be derived from the aldehyde or ketone component, and the other must be derived from the amine component. In the case of *N*-methyl-2-phenylethylamine, two combinations can lead to the product: phenylacetaldehyde plus methylamine or formaldehyde plus 2-phenylethylamine. It's usually better to choose the combination with the simpler amine component—methylamine in this case—and to use an excess of that amine as reactant.

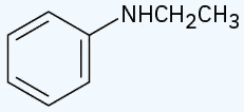
Solution

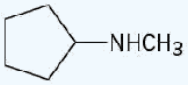


Exercise 13.7.4

How might the following amines be prepared using reductive amination reactions? Show all precursors if more than one is possible.

a. 

b. 

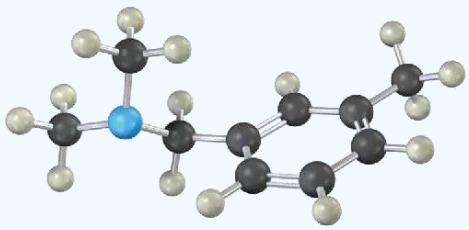
c. 

Answer

a. Ethylamine + acetone, or isopropylamine + acetaldehyde
b. Aniline + acetaldehyde
c. Cyclopentylamine + formaldehyde, or methylamine + cyclopentanone

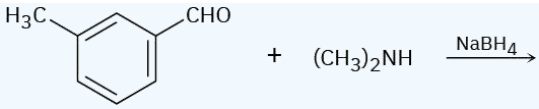
Exercise 13.7.5

How could you prepare the following amine using a reductive amination reaction?



Answer

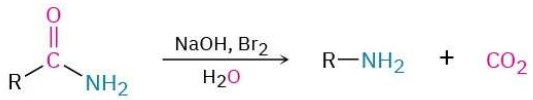
https://chem.libretexts.org/@go/page/564351



Hofmann and Curtius Rearrangements

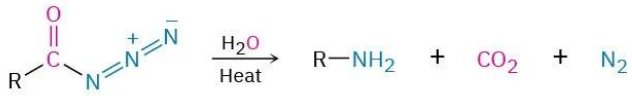
Carboxylic acid derivatives can be converted into primary amines with loss of one carbon atom by both the Hofmann rearrangement and the Curtius rearrangement. Although the Hofmann rearrangement involves a primary amide and the Curtius rearrangement involves an acyl azide, both proceed through similar mechanisms.

Hofmann rearrangement



An amide

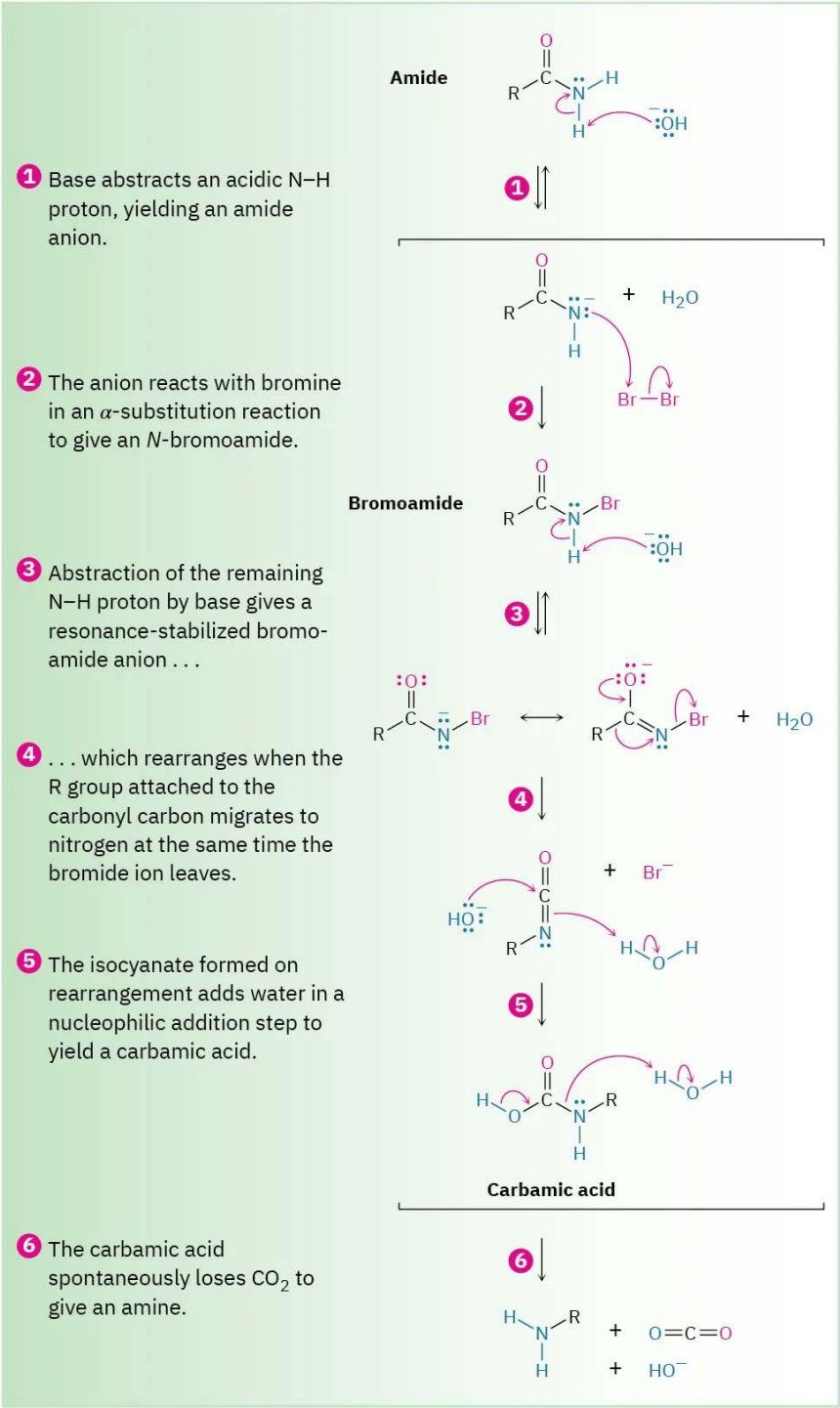
Curtius rearrangement



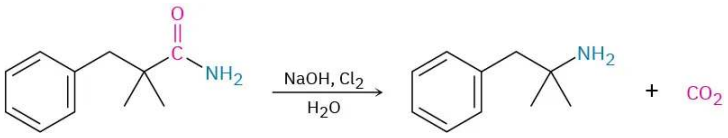
An acyl azide

Hofmann rearrangement occurs when a primary amide, $RCONH_2$, is treated with Br_2 and base (Figure 24.7). The overall mechanism is lengthy, but most of the individual steps have been encountered before. Thus, the bromination of an amide in steps **1** and **2** is analogous to the base-promoted bromination of a ketone enolate ion (Section 22.6), and the rearrangement of the bromoamide anion in step **4** is analogous to a carbocation rearrangement (Section 7.11). Nucleophilic addition of water to the isocyanate carbonyl group in step **5** is a typical carbonyl-group process (Section 19.4), as is the final decarboxylation step **6** (Section 22.7).

Figure 13.7.2: Mechanism of the Hofmann rearrangement of an amide to an amine. Each step is analogous to a reaction studied previously.

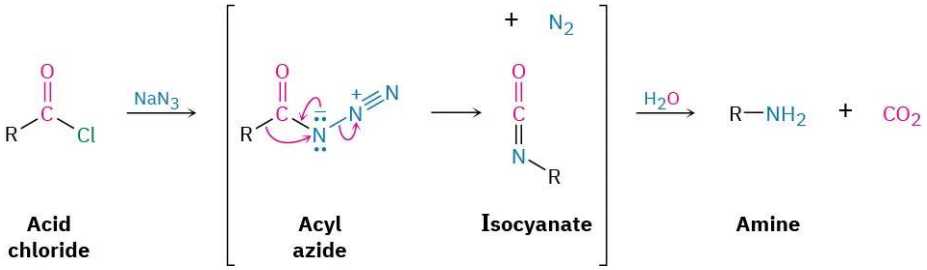


Despite its mechanistic complexity, the Hofmann rearrangement often gives high yields of both arylamines and alkylamines. For example, the appetite-suppressant drug phentermine is prepared commercially by Hofmann rearrangement of a primary amide. Commonly known by the name Fen-Phen, the combination of phentermine with another appetite-suppressant, fenfluramine, is suspected of causing heart damage.



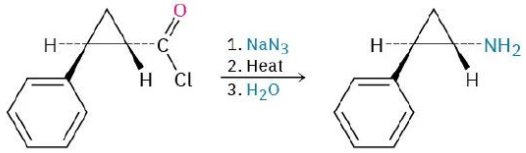
2,2-Dimethyl-3-phenyl-propanamide **Phentermine**

The **Curtius rearrangement**, like the Hofmann rearrangement, involves migration of an –R group from the C═O carbon atom to the neighboring nitrogen with simultaneous loss of a leaving group. The reaction takes place on heating an acyl azide that is itself prepared by nucleophilic acyl substitution of an acid chloride.



Acid chloride **Acyl azide** **Isocyanate** **Amine**

Also like the Hofmann rearrangement, the Curtius rearrangement is often used commercially. The antidepressant drug tranylcypromine, for instance, is made by Curtius rearrangement of 2-phenylcyclopropanecarbonyl chloride.



***trans*-2-Phenylcyclo-propanecarbonyl chloride** **Tranylcypromine**

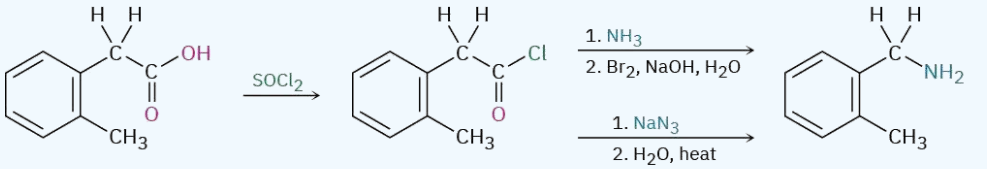
Worked Example 13.7.2: Using the Hofmann and Curtius Rearrangements

How would you prepare *o*-methylbenzylamine from a carboxylic acid, using both Hofmann and Curtius rearrangements?

Strategy

Both Hofmann and Curtius rearrangements convert a carboxylic acid derivative—either an amide (Hofmann) or an acid chloride (Curtius)—into a primary amine with loss of one carbon, RCOY → RNH_2. Both reactions begin with the same carboxylic acid, which can be identified by replacing the $–NH_2$ group of the amine product by a $–CO_2H$ group. In the present instance, *o*-methylphenylacetic acid is needed.

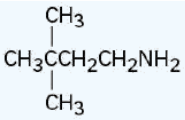
Solution

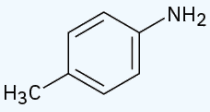


***o*-Methylphenyl-acetic acid** ***o*-Methylbenzylamine**

Exercise 13.7.6

How would you prepare the following amines, using both Hofmann and Curtius rearrangements on a carboxylic acid derivative?

a. 

b. 

Answer

a. 4,4-Dimethylpentanamide or 4,4-dimethylpentanoyl azide

b. *p*-Methylbenzamide or *p*-methylbenzoyl azide

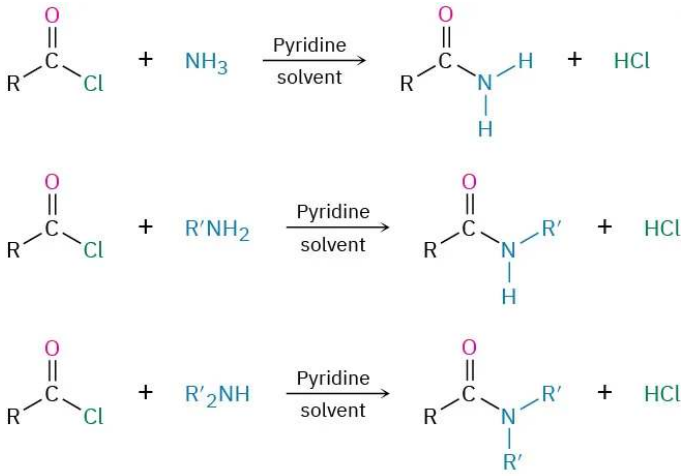
This page titled 13.7: Synthesis of Amines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.6: Synthesis of Amines** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

13.8: Reactions of Amines

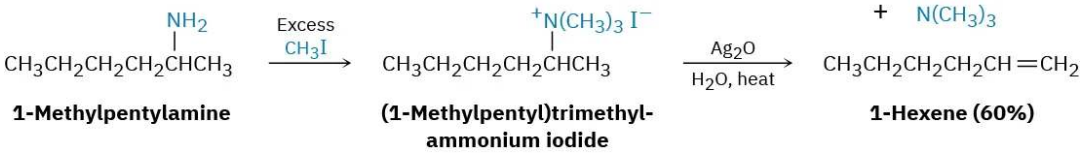
Alkylation and Acylation

We've already studied the two most general reactions of amines—alkylation and acylation. As we saw earlier in this chapter, primary, secondary, and tertiary amines can be alkylated by reaction with a primary alkyl halide. Alkylations of primary and secondary amines are difficult to control and often give mixtures of products, but tertiary amines are cleanly alkylated to give quaternary ammonium salts. Primary and secondary (but not tertiary) amines can also be acylated by nucleophilic acyl substitution reaction with an acid chloride or an acid anhydride to yield an amide (Section 21.4 and Section 21.5). Note that overacylation of the nitrogen does not occur because the amide product is much less nucleophilic and less reactive than the starting amine.



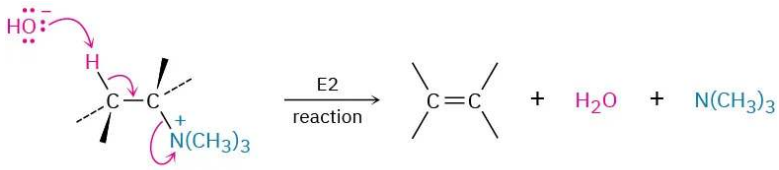
Hofmann Elimination Reaction

Like alcohols, amines can be converted into alkenes by an elimination reaction. But because an amide ion, NH_2^-, is such a poor leaving group, it must first be converted into a better leaving group. In the Hofmann elimination reaction, an amine is completely methylated by reaction with an excess amount of iodomethane to produce the corresponding quaternary ammonium salt. This salt then undergoes elimination to give an alkene on heating with a base, typically silver oxide, Ag_2O. For example, 1-methylpentylamine is converted into 1-hexene.



1-Methylpentylamine | **(1-Methylpentyl)trimethylammonium iodide** | **1-Hexene (60%)**

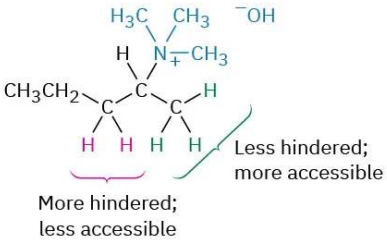
Silver oxide acts by exchanging iodide ion for hydroxide ion in the quaternary salt, thus providing the base necessary for elimination. The actual elimination step is an E2 reaction (Section 11.8) in which hydroxide ion removes a proton while the positively charged nitrogen atom leaves.

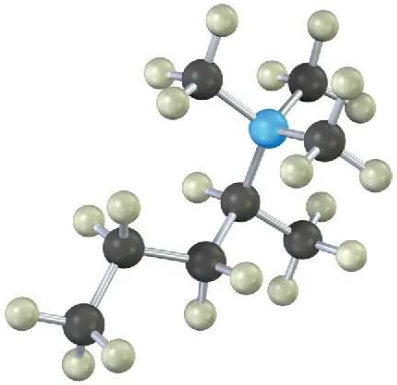


Quaternary ammonium salt | **Alkene**

Unlike what happens in other E2 reactions, the major product of Hofmann elimination is the less highly substituted alkene rather than the more highly substituted one, as shown by the reaction of (1-methylbutyl)trimethylammonium hydroxide to give 1-pentene

rather than the alternative 2-pentene. The reason for this non-Zaitsev result is probably steric. Because of the large size of the trialkylamine leaving group, the base must abstract a hydrogen from the more accessible, least hindered position.



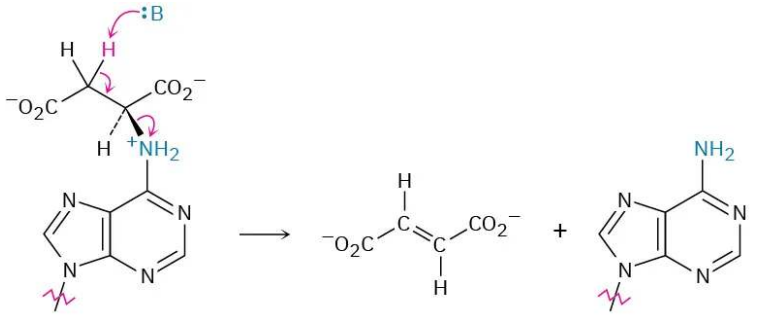


(1-Methylbutyl)trimethylammonium hydroxide

$CH_3CH_2CH_2CH{=}CH_2$ + $CH_3CH_2CH{=}CHCH_3$

1-Pentene (94%) **2-Pentene (6%)**

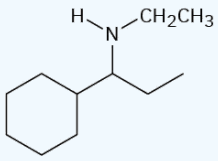
The Hofmann elimination reaction is not often currently used in the laboratory, but analogous biological eliminations occur frequently, although usually with protonated ammonium ions rather than quaternary ammonium salts. In the biosynthesis of nucleic acids, for instance, a substance called adenylosuccinate undergoes an elimination of a positively charged nitrogen to give fumarate plus adenosine monophosphate.



Adenylosuccinate **Fumarate** **Adenosine monophosphate**

Worked Example 13.8.1: Predicting the Product of a Hofmann Elimination

What product would you expect from Hofmann elimination of the following amine?

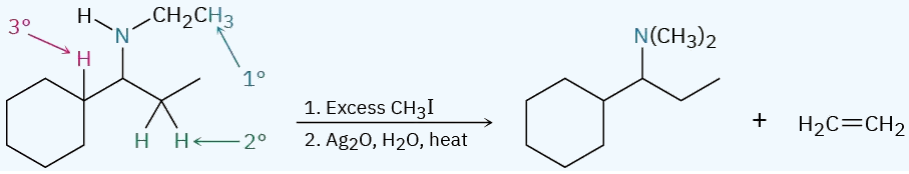


Strategy

The Hofmann elimination is an E2 reaction that converts an amine into an alkene and occurs with non-Zaitsev regiochemistry to form the less highly substituted double bond. To predict the product, look at the reactant and identify the positions from which elimination might occur (the positions two carbons away from nitrogen). Then, carry out an elimination using the most accessible hydrogen. In the present instance, there are three possible positions from which elimination might occur—one

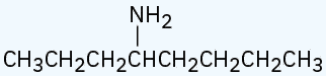
primary, one secondary, and one tertiary. The primary position is the most accessible and leads to the least highly substituted alkene, ethylene.

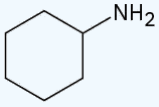
Solution

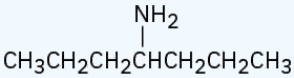


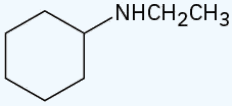
Exercise 13.8.1

What products would you expect from Hofmann elimination of the following amines? If more than one product is formed, indicate which is major.

a. 

b. 

c. 

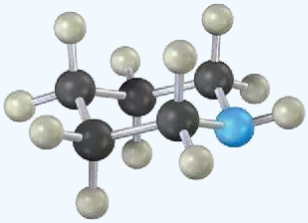
d. 

Answer

a. 3-Octene and 4-octene
b. Cyclohexene
c. 3-Heptene
d. Ethylene and cyclohexene

Exercise 13.8.2

What product would you expect from Hofmann elimination of a heterocyclic amine such as piperidine? Write all the steps.



Piperidine

Answer

$H_2C{=}\ CHCH_2CH_2CH_2N(CH_3)_2$

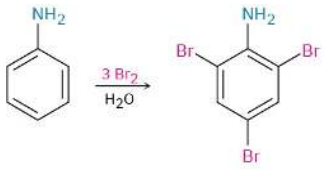
This page titled 13.8: Reactions of Amines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.7: Reactions of Amines** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

13.9: Reactions of Arylamines

Electrophilic Aromatic Substitutions

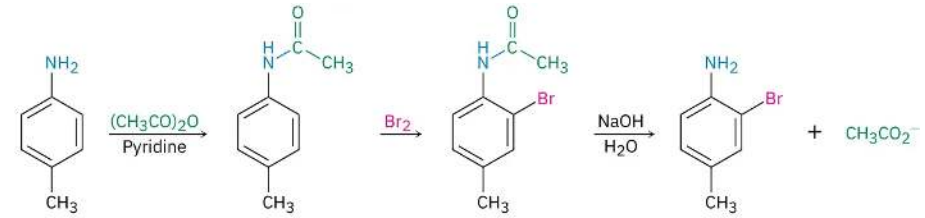
An amino group is strongly activating and ortho- and para-directing in electrophilic aromatic substitution reactions (Section 16.4). This high reactivity of amino-substituted benzenes can be a drawback at times because it's often difficult to prevent polysubstitution. Reaction of aniline with Br_2, for instance, takes place rapidly and yields the 2,4,6-tribrominated product. The amino group is so strongly activating that it's not possible to stop at the monobromo stage.



Aniline **2,4,6-Tribromoaniline (100%)**

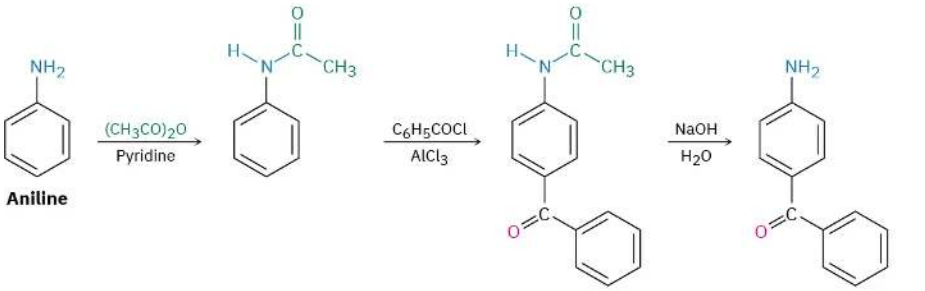
Another drawback to the use of amino-substituted benzenes in electrophilic aromatic substitution reactions is that Friedel–Crafts reactions are not successful (Section 16.3). The amino group forms an acid–base complex with the $AlCl_3$ catalyst, which prevents further reaction. Both drawbacks can be overcome, however, by carrying out electrophilic aromatic substitution reactions on the corresponding amide rather than on the free amine.

As we saw in Section 21.5, treatment of an amine with acetic anhydride yields the corresponding acetyl amide, or acetamide. Although still activating and ortho-, para-directing, amido substituents (R–N–C=O) are less strongly activating and less basic than amino groups because their nitrogen lone-pair electrons are delocalized by the neighboring carbonyl group. As a result, bromination of an *N*-arylamide occurs cleanly to give a monobromo product, and hydrolysis of the amide with aqueous base then gives the free amine. For example, *p*-toluidine (4-methylaniline) can be acetylated, brominated, and hydrolyzed to yield 2-bromo-4-methylaniline. None of the 2,6-dibrominated product is obtained.



***p*-Toluidine** **2-Bromo-4-methylaniline (79%)**

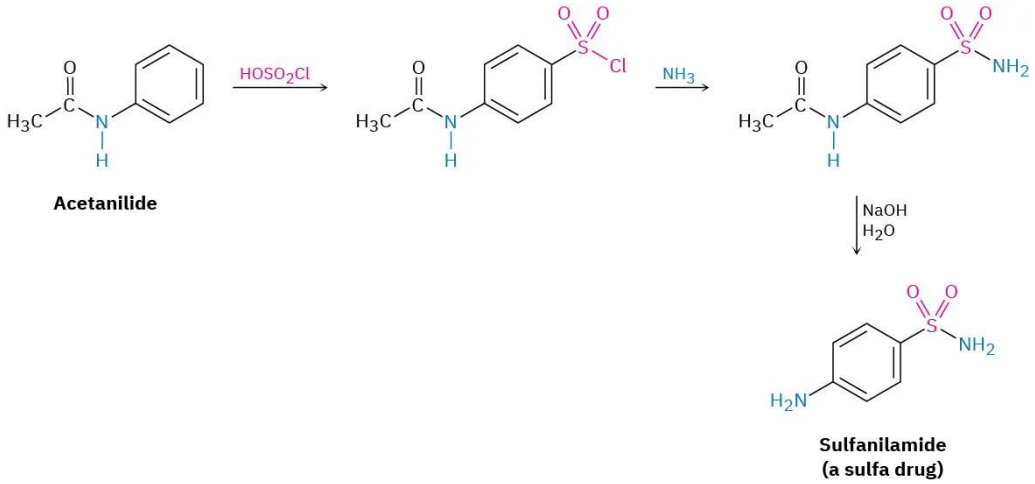
Friedel–Crafts alkylations and acylations of *N*-arylamides also proceed normally. For example, benzoylation of acetanilide (*N*-acetylaniline) under Friedel–Crafts conditions gives 4-aminobenzophenone in 80% yield after hydrolysis.



Aniline **4-Aminobenzophenone (80%)**

Moderating the reactivity of an amino-substituted benzene by forming an amide is a useful trick that allows many kinds of electrophilic aromatic substitutions to be carried out that would otherwise be impossible. One example is the preparation of the sulfa drugs, such as sulfanilamide.

Sulfa drugs were among the first pharmaceutical agents to be used clinically against bacterial infection. Although they have largely been replaced today by safer and more powerful antibiotics, sulfa drugs are credited with saving the lives of thousands of wounded during World War II and are still prescribed for urinary tract infections. They are prepared by chlorosulfonation of acetanilide, followed by reaction of *p*-(*N*-acetylamino)benzenesulfonyl chloride with ammonia or some other amine to give a sulfonamide. Hydrolysis of the amide then yields the sulfa drug. Note that hydrolysis of the amide can be carried out in the presence of the sulfonamide group because sulfonamides hydrolyze very slowly.

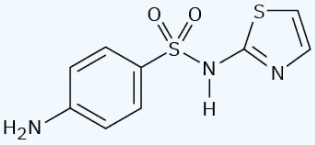


Acetanilide

Sulfanilamide (a sulfa drug)

Exercise 13.9.1

Propose a synthesis of the drug sulfathiazole from benzene and any necessary amine.



Sulfathiazole

Answer

1. HNO_3, H_2SO_4; 2. H_2/PtO_2; 3. $(CH_3CO)_2O$; 4. $HOSO_2Cl$; 5. aminothiazole; 6. H_2O, NaOH

Exercise 13.9.2

Propose syntheses of the following compounds from benzene:

a. *N*,*N*-Dimethylaniline
b. *p*-Chloroaniline
c. *m*-Chloroaniline
d. 2,4-Dimethylaniline

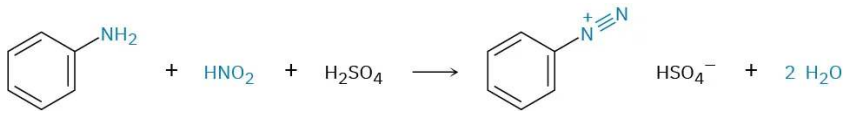
Answer

a. 1. HNO_3, H_2SO_4; 2. H_2/PtO_2; 3. 2 CH_3Br
b. 1. HNO_3, H_2SO_4; 2. H_2/PtO_2; 3. $(CH_3CO)_2O$; 4. Cl_2; 5. H_2O, NaOH
c. 1. HNO_3, H_2SO_4; 2. Cl_2, $FeCl_3$; 3. $SnCl_2$
d. 1. HNO_3, H_2SO_4; 2. H_2/PtO_2; 3. $(CH_3CO)_2O$; 4. 2 CH_3Cl, $AlCl_3$; 5. H_2O, NaOH

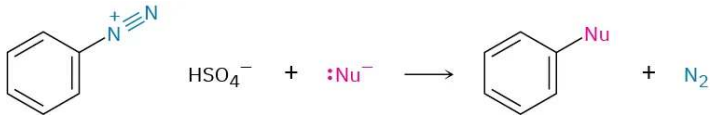
Diazonium Salts: The Sandmeyer Reaction

Primary arylamines react with nitrous acid, HNO_2, to yield stable arenediazonium salts, $Ar-\overset{+}{N}\equiv NX^-$ a process called a **diazotization reaction**. Alkylamines also react with nitrous acid, but the corresponding alkanediazonium products are so reactive

they can't be isolated. Instead, they lose nitrogen instantly to yield carbocations. The analogous loss of N_2 from an arenediazonium ion to yield an aryl cation is disfavored by the instability of the cation.

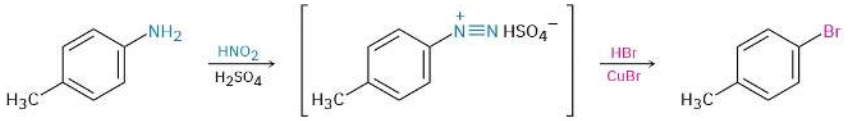


Arenediazonium salts are useful because the diazonio group (–N≡N) can be replaced by a nucleophile in a substitution reaction.

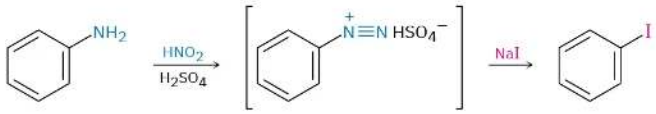


Many different nucleophiles—halide, hydride, cyanide, and hydroxide among others—react with arenediazonium salts, yielding many different kinds of substituted benzenes. The overall sequence of (**1**) nitration, (**2**) reduction, (**3**) diazotization, and (**4**) nucleophilic substitution is perhaps the single most versatile method of aromatic substitution.

Aryl chlorides and bromides are prepared by reaction of an arenediazonium salt with the corresponding copper(I) halide, CuX, a process called the **Sandmeyer reaction**. Aryl iodides can be prepared by direct reaction with NaI without using a copper(I) salt. Yields generally fall between 60% and 80%.

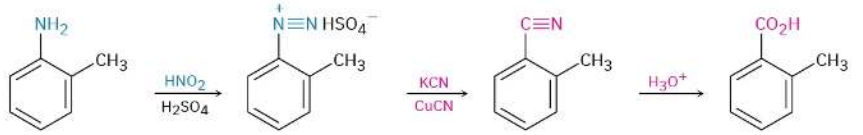


***p*-Methylaniline** **p-Bromotoluene (73%)**



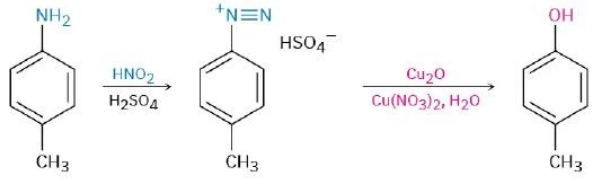
Aniline **Iodobenzene (67%)**

Similar treatment of an arenediazonium salt with CuCN yields the nitrile ArCN, which can then be further converted into other functional groups such as carboxyl. For example, Sandmeyer reaction of o-methylbenzenediazonium bisulfate with CuCN yields o-methylbenzonitrile, which can be hydrolyzed to give o-methylbenzoic acid. This product can't be prepared from o-xylene by the usual side-chain oxidation route because both methyl groups would be oxidized.



***o*-Methylaniline** ***o*-Methylbenzene-diazonium bisulfate** ***o*-Methylbenzonitrile** ***o*-Methylbenzoic acid**

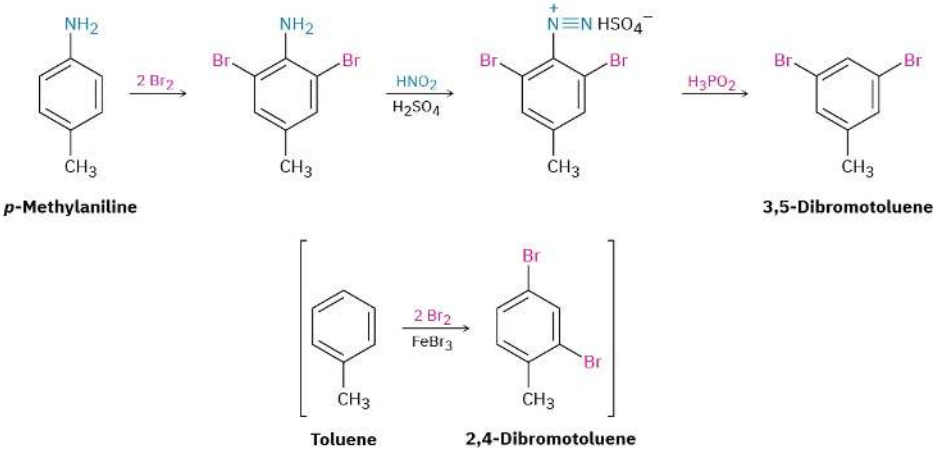
The diazonio group can also be replaced by –OH to yield a phenol and by –H to yield an arene. A phenol is prepared by reaction of the arenediazonium salt with copper(I) oxide in an aqueous solution of copper(II) nitrate, a reaction that is especially useful because few other general methods exist for introducing an –OH group onto an aromatic ring.



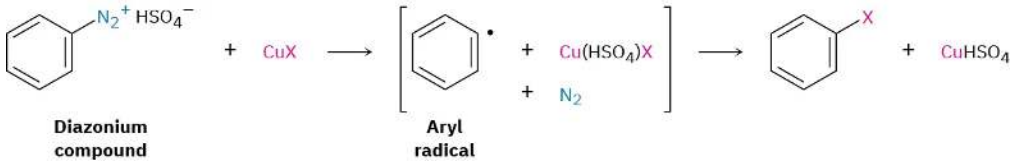
***p*-Methylaniline (*p*-Toluidine)** ***p*-Cresol (93%)**

Reduction of a diazonium salt to give an arene occurs on treatment with hypophosphorous acid, H_3PO_2. This reaction is used primarily when there is a need for temporarily introducing an amino substituent onto a ring to take advantage of its directing effect.

Suppose, for instance, that you needed to make 3,5-dibromotoluene. This product can't be made by direct bromination of toluene because reaction would occur at positions 2 and 4. Starting with p-methylaniline (p-toluidine), however, dibromination occurs ortho to the strongly directing amino substituent, and diazotization followed by treatment with H_3PO_2 to remove the amino group yields the desired product.

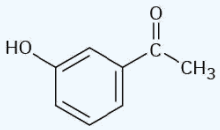


Mechanistically, these diazonio replacement reactions occur through radical rather than polar pathways. In the presence of a copper(I) compound, for instance, it's thought that the arenediazonium ion is first converted to an aryl radical plus copper(II), followed by subsequent reaction to give product plus regenerated copper(I) catalyst.



Worked Example 13.9.1: Using Diazonium Replacement Reactions

How would you prepare m-hydroxyacetophenone from benzene, using a diazonium replacement reaction in your scheme?



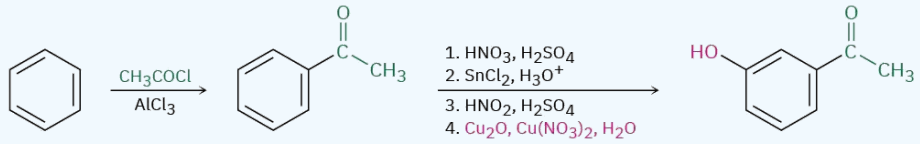
***m*-Hydroxyacetophenone**

Strategy

As always, organic syntheses are planned by working retrosynthetically from the final product, one step at a time. First, identify the functional groups in the product and recall how those groups can be synthesized. m-Hydroxyacetophenone has an –OH group and a $–COCH_3$ group in a meta relationship on a benzene ring. A hydroxyl group is generally introduced onto an aromatic ring by a four-step sequence of nitration, reduction, diazotization, and diazonio replacement. An acetyl group is introduced by a Friedel–Crafts acylation reaction.

Next, ask yourself what an immediate precursor of the target might be. Since an acetyl group is a meta director while a hydroxyl group is an ortho and para director, acetophenone might be a precursor of m-hydroxyacetophenone. Benzene, in turn, is a precursor of acetophenone.

Solution



https://chem.libretexts.org/@go/page/564353

? Exercise 13.9.3

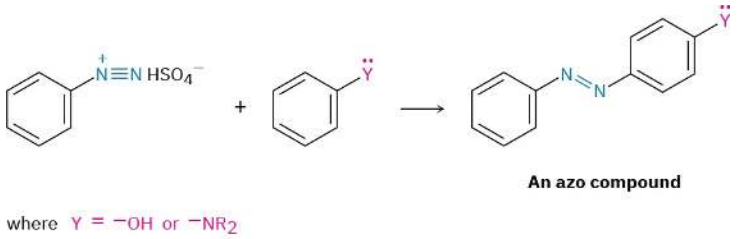
a. p-Bromobenzoic acid
b. m-Bromobenzoic acid
c. m-Bromochlorobenzene
d. p-Methylbenzoic acid
e. 1,2,4-Tribromobenzene

Answer

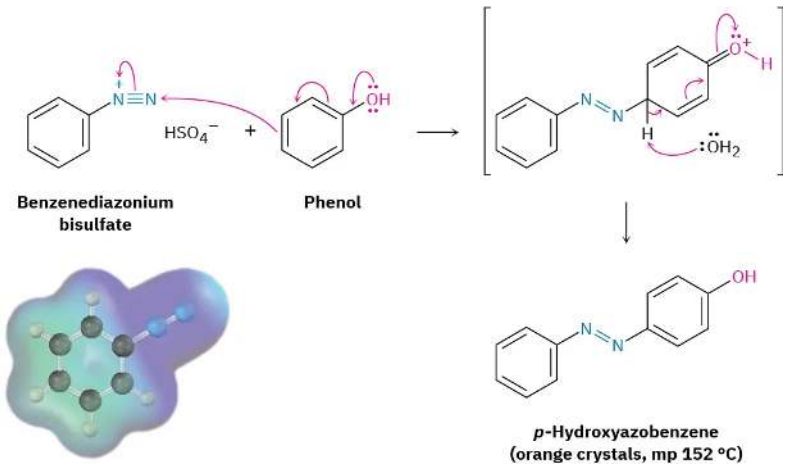
a. 1. CH_3Cl, $AlCl_3$; 2. HNO_3, H_2SO_4; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuBr; 6. $KMnO_4$, H_2O
b. 1. HNO_3, H_2SO_4; 2. Br_2, $FeBr_3$; 3. $SnCl_2$, H_3O^+; 4. $NaNO_2$, H_2SO_4; 5. CuCN; 6. H_3O^+
c. 1. HNO_3, H_2SO_4; 2. Cl_2, $FeCl_3$; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuBr
d. 1. CH_3Cl, $AlCl_3$; 2. HNO_3, H_2SO_4; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuCN; 6. H_3O^+
e. 1. HNO_3, H_2SO_4; 2. H_2/PtO_2; 3. $(CH_3CO)_2O$; 4. 2 Br_2; 5. H_2O, NaOH; 6. $NaNO_2$, H_2SO_4; 7. CuBr

Diazonium Coupling Reactions

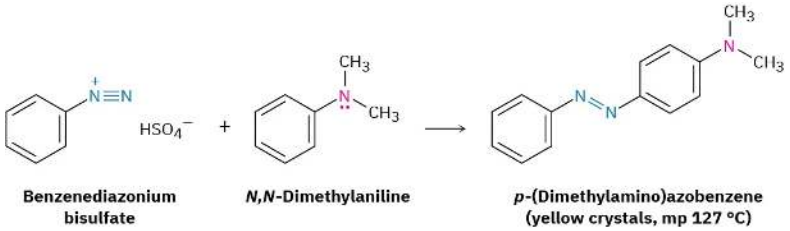
Arenediazonium salts undergo a coupling reaction with activated aromatic rings such as phenols and arylamines to yield brightly colored azo compounds, $\mathbf{Ar{-}N{=}N{-}Ar'}$.



Diazonium coupling reactions are typical electrophilic aromatic substitutions in which the positively charged diazonium ion is the electrophile that reacts with the electron-rich ring of a phenol or arylamine. Reaction usually occurs at the para position.



Azo-coupled products are widely used as dyes for textiles because their extended conjugated π electron system causes them to absorb in the visible region of the electromagnetic spectrum (Section 14.9). p-(Dimethylamino)-azobenzene, for instance, is a bright yellow compound that was at one time used as a coloring agent in margarine.



Exercise 13.9.4

Propose a synthesis of *p*-(dimethylamino)azobenzene with benzene as your only organic starting material.

Answer

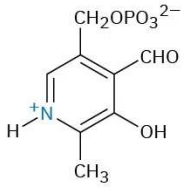
1. HNO_3, H_2SO_4; 2. $SnCl_2$; 3a. 2 equiv. CH_3I; 3b. $NaNO_2$, H_2SO_4; 4. product of 3a + product of 3b

This page titled 13.9: Reactions of Arylamines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

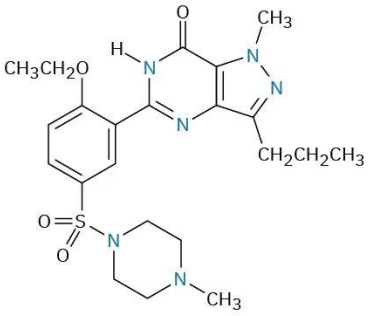
- **24.8: Reactions of Arylamines** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

13.10: Heterocyclic Amines

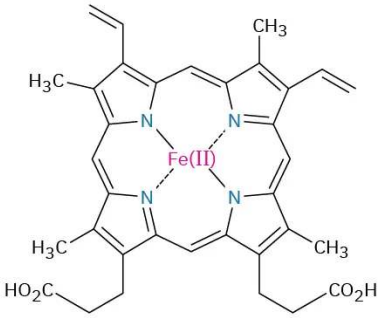
As noted in Section 15.5 in connection with a discussion of aromaticity, a cyclic organic compound that contains atoms of two or more elements in its ring is a called a *heterocycle*. Heterocyclic amines are particularly common, and many have important biological properties. Pyridoxal phosphate, a coenzyme; sildenafil (Viagra), a well-known pharmaceutical; and heme, the oxygen carrier in blood, are a few examples.



Pyridoxal phosphate (a coenzyme)



Sildenafil (Viagra)

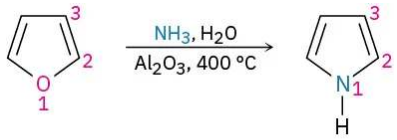


Heme

Most heterocycles have the same chemistry as their open-chain counterparts. Lactones and acyclic esters behave similarly, lactams and acyclic amides behave similarly, and cyclic and acyclic ethers behave similarly. In certain cases, however, particularly when the ring is unsaturated, heterocycles have unique and interesting properties.

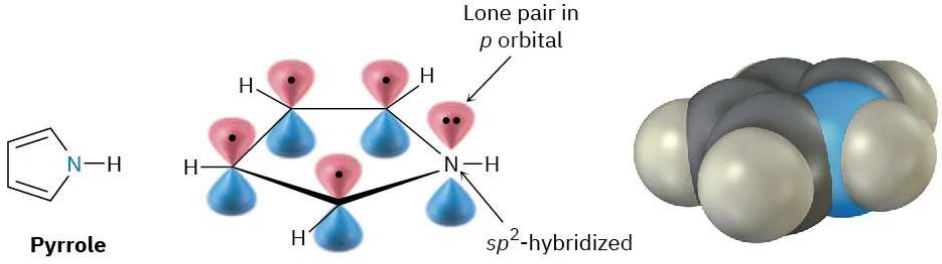
Pyrrole and Imidazole

Pyrrole, the simplest five-membered unsaturated heterocyclic amine, is obtained commercially by treatment of furan with ammonia over an alumina catalyst at 400 °C. Furan, the oxygen-containing analog of pyrrole, is obtained by acid-catalyzed dehydration of the five-carbon sugars found in oat hulls and corncobs.



Furan **Pyrrole**

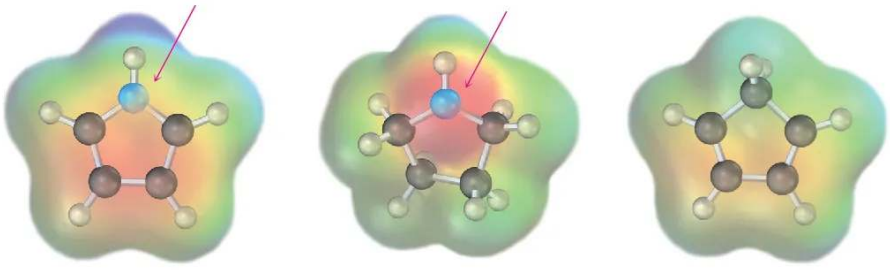
Although pyrrole appears to be both an amine and a conjugated diene, its chemical properties are not consistent with either of these structural features. Unlike most other amines, pyrrole is not basic—the pK_a of the pyrrolinium ion is 0.4; unlike most other conjugated dienes, pyrrole undergoes electrophilic substitution reactions rather than additions. The reason for both of these properties, as noted in Section 15.5, is that pyrrole has six π electrons and is aromatic. Each of the four carbons contributes one π electron, and the sp^2-hybridized nitrogen contributes two more from its lone pair.



Pyrrole **Six π electrons**

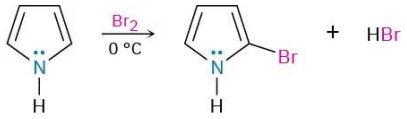
Because the nitrogen lone pair is a part of the aromatic sextet, protonation on nitrogen would destroy the aromaticity of the ring. The nitrogen atom in pyrrole is therefore less electron-rich, less basic, and less nucleophilic than the nitrogen in an aliphatic amine. By the same token, the carbon atoms of pyrrole are more electron-rich and more nucleophilic than typical double-bond carbons.

The pyrrole ring is therefore reactive toward electrophiles in the same way as enamines (Section 23.11). Electrostatic potential maps show how the pyrrole nitrogen is electron-poor (less red) compared with the nitrogen in its saturated counterpart pyrrolidine, while the pyrrole carbon atoms are electron-rich (more red) compared with the carbons in 1,3-cyclopentadiene.



Pyrrole **Pyrrolidine** **1,3-Cyclopentadiene**

The chemistry of pyrrole is similar to that of activated benzene rings. In general, however, the heterocycles are more reactive toward electrophiles than benzene rings, and low temperatures are often necessary to control the reactions. Halogenation, nitration, sulfonation, and Friedel–Crafts acylation can all be accomplished. For example:



Pyrrole **2-Bromopyrrole (92%)**

Electrophilic substitutions normally occur at C2, the position next to the nitrogen, because reaction at this position leads to a more stable intermediate cation having three resonance forms, whereas reaction at C3 gives a less stable cation with only two resonance forms (Figure 13.10.1).

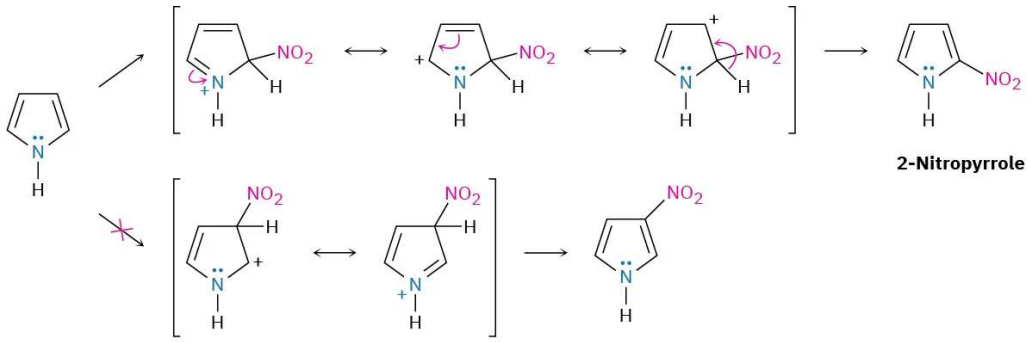
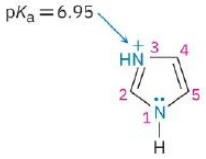
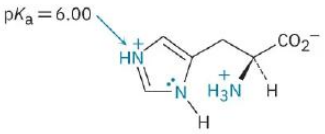


Figure 13.10.1: Electrophilic nitration of pyrrole. The intermediate produced by reaction at C2 is more stable than that produced by reaction at C3.

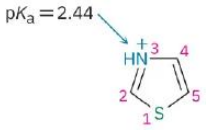
Other common five-membered heterocyclic amines include imidazole and thiazole. Imidazole, a constituent of the amino acid histidine, has two nitrogens, only one of which is basic. Thiazole, the five-membered ring system on which the structure of thiamin (vitamin B_1) is based, also contains a basic nitrogen that is alkylated in thiamin to form a quaternary ammonium ion.



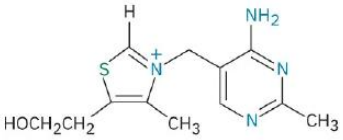
Imidazole



Histidine



Thiazole

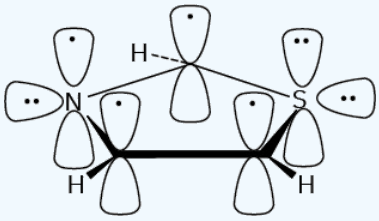


Thiamin (vitamin B_1)

? Exercise 13.10.1

Draw an orbital picture of thiazole. Assume that both the nitrogen and sulfur atoms are sp^2-hybridized, and show the orbitals that the lone pairs occupy.

Answer



? Exercise 13.10.2

What is the percent protonation of the imidazole nitrogen atom in histidine at a physiological pH of 7.3 **(Section 24.5)**?

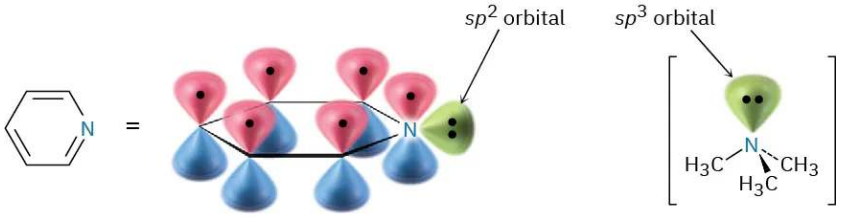
Answer

4.1% protonated

Pyridine and Pyrimidine

Pyridine is the nitrogen-containing heterocyclic analog of benzene. Like benzene, pyridine is a flat, aromatic molecule, with bond angles of 120° and C–C bond lengths of 139 pm, intermediate between typical single and double bonds. The five carbon atoms and the sp^2-hybridized nitrogen atom each contribute one π electron to the aromatic sextet, and the lone-pair electrons occupy an sp^2 orbital in the plane of the ring (Section 15.5).

As shown previously in Table 24.1, pyridine (pK_a = 5.25) is a stronger base than pyrrole but a weaker base than the alkylamines. The diminished basicity of pyridine compared with that of alkylamines is due to the fact that the lone-pair electrons on the pyridine nitrogen are in an sp^2 orbital, while those on an alkylamine nitrogen are in an sp^3 orbital. Because s orbitals have their maximum electron density at the nucleus but p orbitals have a node at the nucleus, electrons in an orbital with more s character are held more closely to the positively charged nucleus and are less available for bonding. As a result, the sp^2-hybridized nitrogen atom (33% s character) in pyridine is less basic than the sp^3-hybridized nitrogen in an alkylamine (25% s character).

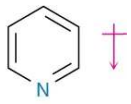


Pyridine

Unlike benzene, pyridine undergoes electrophilic aromatic substitution reactions with difficulty. Halogenation can be carried out under drastic conditions, but nitration occurs in very low yield, and Friedel–Crafts reactions are not successful. Reactions usually give the 3-substituted product.

Pyridine **3-Bromopyridine (30%)**

The low reactivity of pyridine toward electrophilic aromatic substitution is caused by a combination of factors. One is that acid–base complexation between the basic ring's nitrogen atom and the incoming electrophile places a positive charge on the ring, thereby deactivating it. Equally important is that the electron density of the ring is decreased by the electron-withdrawing inductive effect of the electronegative nitrogen atom. Thus, pyridine has a substantial dipole moment (μ = 2.26 D), with the ring carbons acting as the positive end of the dipole. Reaction of an electrophile with the positively polarized carbon atoms is therefore difficult.



μ = 2.26 D

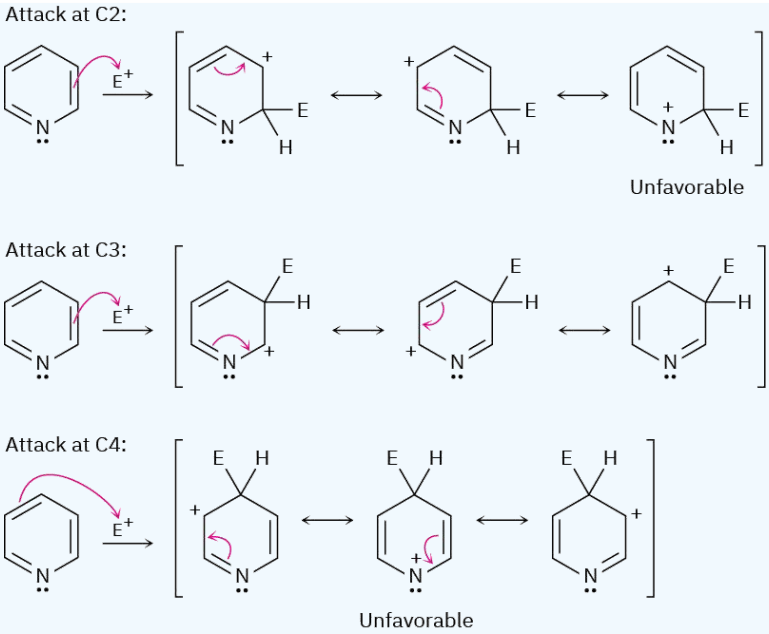
In addition to pyridine, the six-membered diamine pyrimidine is also found commonly in biological molecules, particularly as a constituent of nucleic acids. With a pK_a of 1.3, pyrimidine is substantially less basic than pyridine because of the inductive effect of the second nitrogen.

Pyrimidine
$pK_a = 1.3$

? Exercise 13.10.3

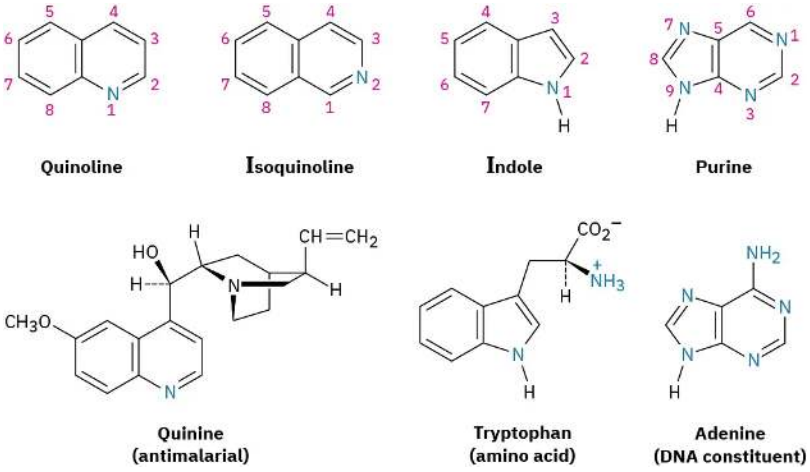
Electrophilic aromatic substitution reactions of pyridine normally occur at C3. Draw the carbocation intermediates resulting from reaction of an electrophile at C2, C3, and C4, and explain the observed result.

Answer

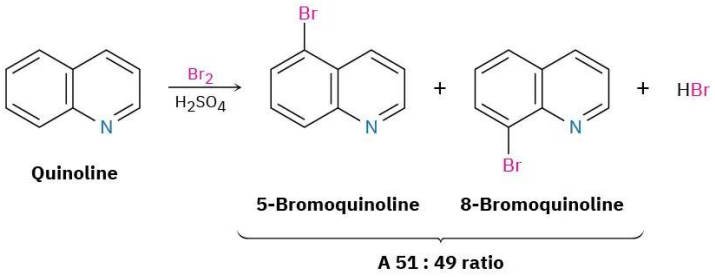


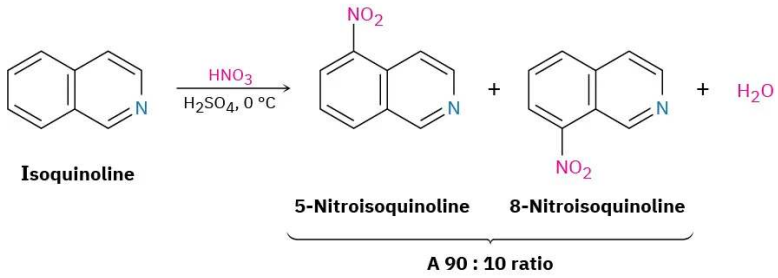
Polycyclic Heterocycles

As we saw in Section 15.6, quinoline, isoquinoline, indole, and purine are common polycyclic heterocycles. The first three contain both a benzene ring and a heterocyclic aromatic ring, while purine contains two heterocyclic rings joined together. All four ring systems occur commonly in nature, and many compounds with these rings have pronounced physiological activity. The quinoline alkaloid quinine, for instance, is widely used as an antimalarial drug; tryptophan is a common amino acid; and the purine adenine is a constituent of nucleic acids.



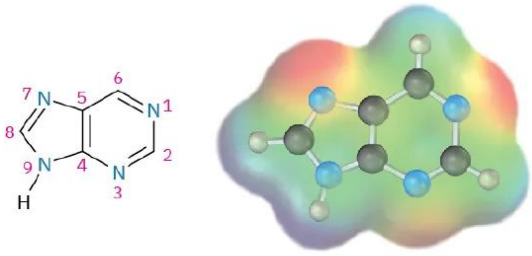
The chemistry of these polycyclic heterocycles is just what you might expect from a knowledge of the simpler heterocycles pyridine and pyrrole. Quinoline and isoquinoline both have basic, pyridine-like nitrogen atoms, and both undergo electrophilic substitutions. As with pyridine, both quinoline and isoquinoline are less reactive toward electrophilic substitution than benzene because of the electronegative nitrogen atom that withdraws electrons from the ring. Reaction occurs on the benzene ring rather than on the nitrogen-containing pyridine ring, and a mixture of substitution products is obtained.





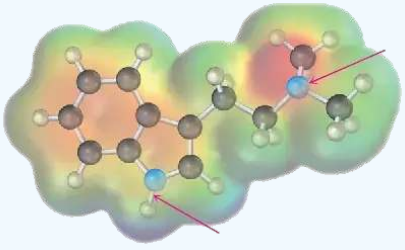
Indole has a nonbasic, pyrrole-like nitrogen and undergoes electrophilic substitution more easily than benzene. Substitution occurs at C3 of the electron-rich pyrrole ring rather than on the benzene ring.

Purine has three basic, pyridine-like nitrogens with lone-pair electrons in sp^2 orbitals in the plane of the ring. The remaining purine nitrogen is nonbasic and pyrrole-like, with its lone-pair electrons as part of the aromatic π electron system.



? Exercise 13.10.4

Which nitrogen atom in the hallucinogenic indole alkaloid N,N-dimethyltryptamine is more basic? Explain.



***N,N*-Dimethyltryptamine**

Answer

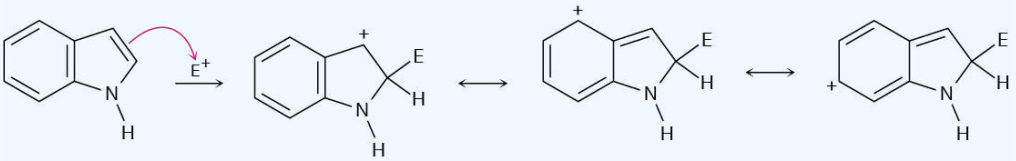
The side-chain nitrogen is more basic than the ring nitrogen.

? Exercise 13.10.1

Indole reacts with electrophiles at C3 rather than at C2. Draw resonance forms of the intermediate cations resulting from reaction at C2 and C3, and explain the observed results.

Answer

Reaction at C2 is disfavored because the aromaticity of the benzene ring is lost.



This page titled 13.10: Heterocyclic Amines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.9: Heterocyclic Amines** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

13.11: Spectroscopy of Amines

Infrared Spectroscopy

Primary and secondary amines can be identified by a characteristic N–H stretching absorption in the 3300 to 3500 cm^{-1} range of the IR spectrum. Alcohols also absorb in this range (Section 17.11), but amine absorption bands are generally sharper and less intense than hydroxyl bands. Primary amines show a pair of bands at about 3350 and 3450 cm^{-1} from the symmetric and asymmetric stretching modes, and secondary amines show a single band at 3350 cm^{-1}. Tertiary amines have no absorption in this region because they have no N–H bonds. Figure 24.9 recalls the IR spectrum of cyclohexylamine from Section 12.8.

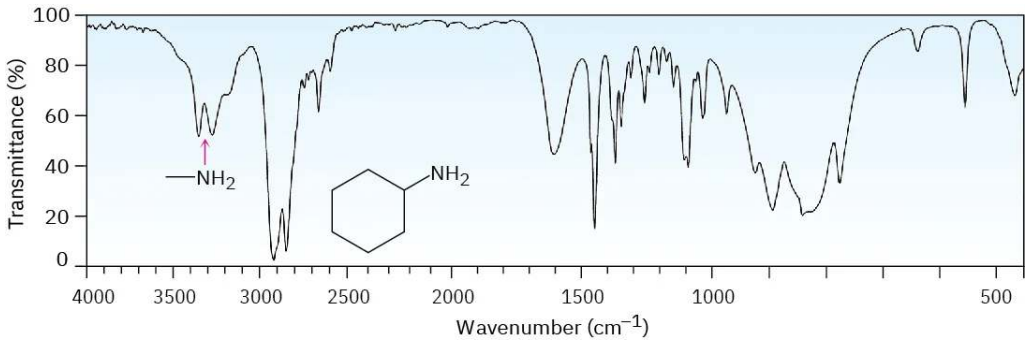
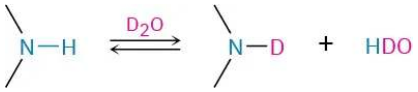


Figure 24.9: IR spectrum of cyclohexylamine.

Nuclear Magnetic Resonance Spectroscopy

Amines are difficult to identify solely by ^1H NMR spectroscopy because N–H hydrogens tend to appear as broad signals without clear-cut coupling to neighboring C–H hydrogens. As with O–H absorptions (Section 17.11), amine N–H absorptions can appear over a wide range and are best identified by adding a small amount of D_2O to the sample. Exchange of N–D for N–H occurs, and the N–H signal disappears from the NMR spectrum.



Hydrogens on the carbon next to nitrogen are deshielded because of the electron-withdrawing effect of the nitrogen, and they therefore absorb further downfield than alkane hydrogens. *N*-Methyl groups are particularly distinctive because they absorb as a sharp three-proton singlet at 2.2 to 2.6 δ. This *N*-methyl resonance at 2.42 δ is easily seen in the ^1H NMR spectrum of *N*-methylcyclohexylamine (Figure 13.11.1).

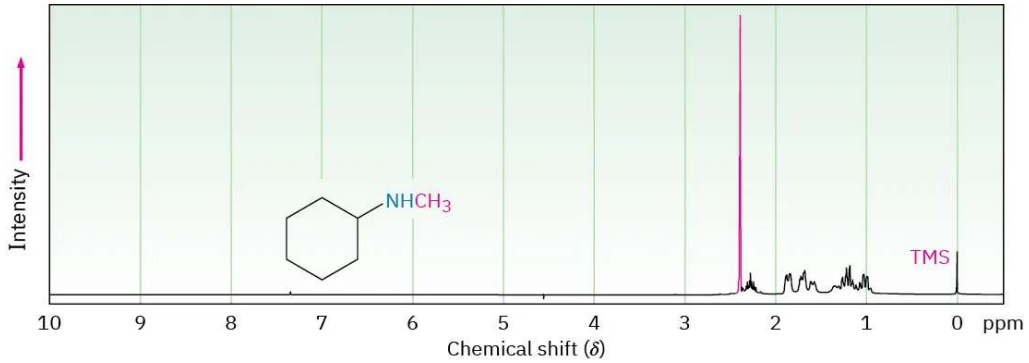
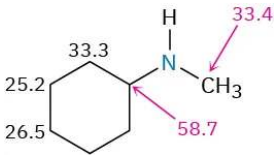


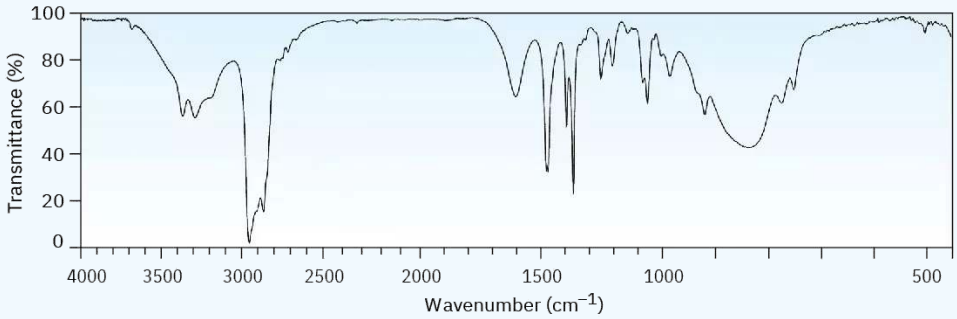
Figure 13.11.1: Proton NMR spectrum of *N*-methylcyclohexylamine.

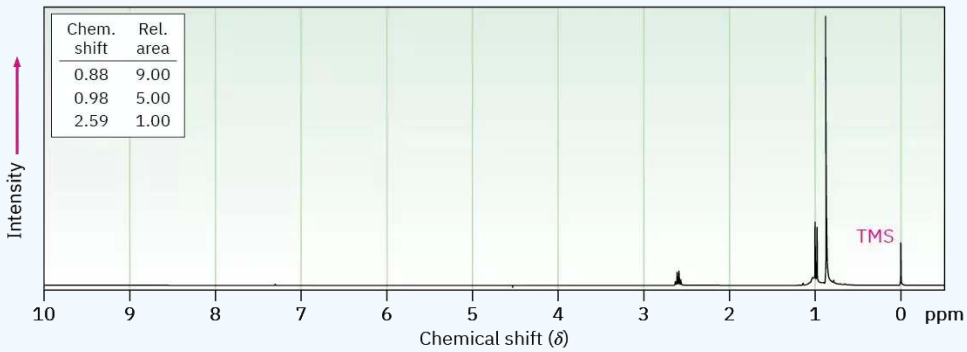
Carbons next to amine nitrogens are slightly deshielded in the ^{13}C NMR spectrum and absorb about 20 ppm downfield from where they would absorb in an alkane of similar structure. In *N*-methylcyclohexylamine, for example, the ring carbon to which nitrogen is attached absorbs at a position 24 ppm downfield from any other ring carbon.



? Exercise 13.11.1

Compound **A**, $C_6H_{12}O$, has an IR absorption at 1715 cm^{-1} and gives compound **B**, $C_6H_{15}N$, when treated with ammonia and $NaBH_4$. The IR and ^1H NMR spectra of **B** are shown. What are the structures of **A** and **B**?





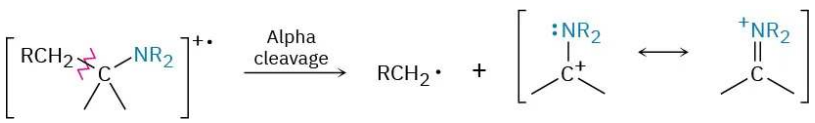
Answer

$(CH_3)_3CCOCH_3 \longrightarrow (CH_3)_3CCH(NH_2)CH_3$

Mass Spectrometry

The *nitrogen rule* of mass spectrometry says that a compound with an odd number of nitrogen atoms has an odd-numbered molecular weight. Thus, the presence of nitrogen in a molecule is detected simply by observing its mass spectrum. An odd-numbered molecular ion usually means that the unknown compound has one or three nitrogen atoms, and an even-numbered molecular ion usually means that a compound has either zero or two nitrogen atoms. The logic behind the rule derives from the fact that nitrogen is trivalent, thus requiring an odd number of hydrogen atoms. For example, morphine has the formula $C_{17}H_{19}NO_3$ and a molecular weight of 285 amu.

Alkylamines undergo a characteristic α cleavage in the mass spectrometer, similar to the cleavage observed for alcohols (Section 17.11). C–C bond nearest the nitrogen atom is broken, yielding an alkyl radical and a resonance-stabilized, nitrogen-containing cation.



As an example, the mass spectrum of *N*-ethylpropylamine shown in Figure 13.11.2 has peaks at m/z = 58 and m/z = 72, corresponding to the two possible modes of α cleavage.

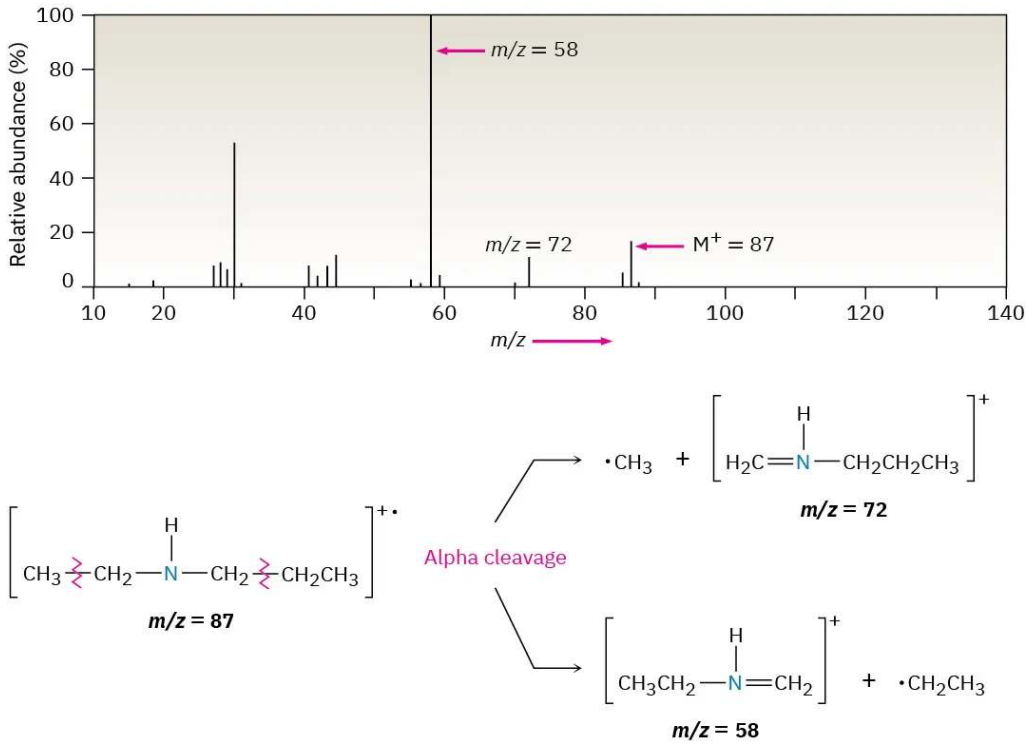


Figure 13.11.2: Mass spectrum of *N*-ethylpropylamine. The two possible modes of α cleavage lead to the observed fragment ions at m/z = 58 and m/z = 72.

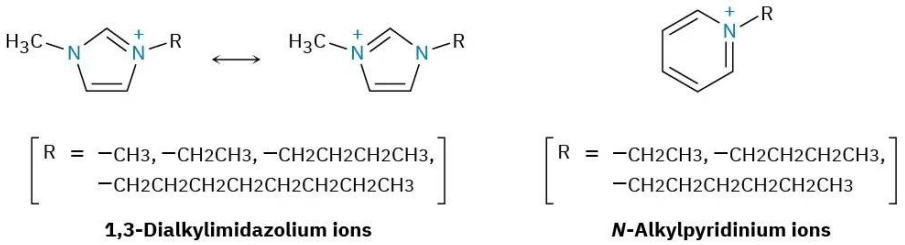
This page titled 13.11: Spectroscopy of Amines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.10: Spectroscopy of Amines** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

13.12: Chemistry Matters - Green Chemistry II- Ionic Liquids

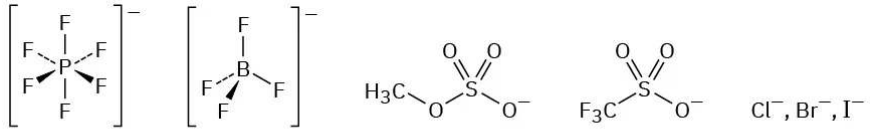
Liquids made of ions? Usually when we think of ionic compounds, we think of high-melting solids: sodium chloride, magnesium sulfate, lithium carbonate, and so forth. But yes, there are also ionic compounds that are liquid at room temperature, and they are gaining importance as reaction solvents, particularly for use in green chemistry processes (see the Chapter 11 *Chemistry Matters*). More than 1500 ionic liquids are known, and about 500 are available commercially.

Ionic liquids have been studied for nearly a century; the first to be discovered was ethylammonium nitrate, $CH_3CH_2NH_3^+$ NO_3^-, with a melting point of 12 °C. More generally, however, the ionic liquids in use today are salts in which the cation is unsymmetrical and in which one or both of the ions are bulky so that the charges are dispersed over a large volume. Both factors minimize the crystal lattice energy and disfavor formation of the solid. Typical cations are quaternary ammonium ions from heterocyclic amines, either 1,3-dialkylimidazolium ions, *N*-alkylpyridinium ions, or ring-substituted *N*-alkylpyridinium ions.



1,3-Dialkylimidazolium ions **N-Alkylpyridinium ions**

Anions are just as varied as the cations. Hexafluorophosphate, tetrafluoroborate, alkyl sulfates, trifluoromethanesulfonates (triflates), and halides are some anion possibilities.

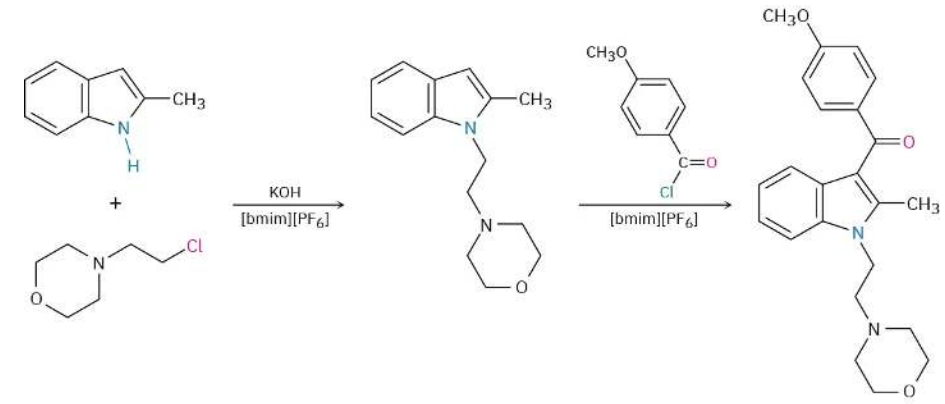


Hexafluoro-phosphate **Tetrafluoro-borate** **Methyl sulfate** **Trifluoromethane-sulfonate** **Halide**

Ionic liquids have several important features that make them attractive for use, both as solvents in green chemistry and as specialty chemicals in such applications as paint additives and refrigerants:

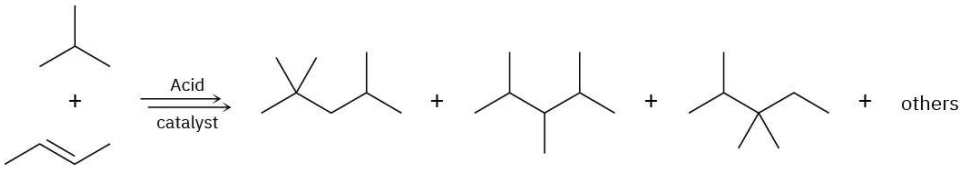
- They dissolve both polar and nonpolar organic compounds, giving high solute concentrations and thereby minimizing the amount of solvent needed.
- They can be optimized for specific reactions by varying cation and anion structures.
- They are nonflammable.
- They are thermally stable.
- They have negligible vapor pressures and do not evaporate.
- They are generally recoverable and can be reused many times.

As an example of their use in organic chemistry, the analgesic drug pravadoline has been synthesized in two steps using 1-butyl-3-methylimidazolium hexafluorophosphate, abbreviated [bmim][PF_6], as the solvent for both steps. The first step is a base-induced S_N2 reaction of 2-methylindole with a primary alkyl halide, and the second is a Friedel–Crafts acylation. Both steps take place with 95% yield, and the ionic solvent is recovered simply by washing the reaction mixture, first with toluene and then with water.



Pravadoline

The first commercial process using an ionic liquid catalyst was introduced by PetroChina in 2008, when they opened a plant producing 65,000 tons per year of alkylate gasoline from isobutane. The aluminum-based ionic liquid catalyst replaced the sulfuric acid and hydrofluoric acid catalysts that had previously been used.



52% **20%** **18%**

This page titled 13.12: Chemistry Matters - Green Chemistry II- Ionic Liquids is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.11: Chemistry Matters - Green Chemistry II- Ionic Liquids** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

13.13: Key Terms

- alkylamine
- amine
- arylamine
- azo compound ($\mathrm{R–N=N–R'}$)
- Curtius rearrangement
- Gabriel amine synthesis
- heterocyclic amine
- Hofmann elimination reaction
- Hofmann rearrangement
- imide ($\mathrm{O=C–N–C=O}$)
- primary amine ($\mathrm{RNH_2}$)
- quaternary ammonium salt
- reductive amination
- Sandmeyer reaction
- secondary amine ($\mathrm{R_2NH}$)
- tertiary amine ($\mathrm{R_3N}$)

This page titled 13.13: Key Terms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.12: Key Terms** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

13.14: Summary

We've now seen all the common functional groups that occur in organic and biological chemistry. Of those groups, amines are among the most abundant and have among the richest chemistry. In addition to proteins and nucleic acids, the majority of pharmaceutical agents contain amine functional groups and many of the common coenzymes necessary for biological reactions are amines.

Amines are organic derivatives of ammonia. They are named in the IUPAC system either by adding the suffix *-amine* to the name of the alkyl substituent or by considering the amino group as a substituent on a more complex parent molecule.

The chemistry of amines is dominated by the lone-pair electrons on nitrogen, which makes amines both basic and nucleophilic. The basicity of **arylamines** is generally lower than that of **alkylamines** because the nitrogen lone-pair electrons are delocalized by interaction with the aromatic π system. Electron-withdrawing substituents on the aromatic ring further weaken the basicity of a substituted aniline, while electron-donating substituents increase basicity. Alkylamines are sufficiently basic that they exist almost entirely in their protonated form at the physiological pH of 7.3.

Heterocyclic amines are compounds that contain one or more nitrogen atoms as part of a ring. Saturated heterocyclic amines usually have the same chemistry as their open-chain analogs, but unsaturated heterocycles such as pyrrole, imidazole, pyridine, and pyrimidine are aromatic. All four are unusually stable, and all undergo aromatic substitution on reaction with electrophiles. Pyrrole is nonbasic because its nitrogen lone-pair electrons are part of the aromatic π system. Fused-ring heterocycles such as quinoline, isoquinoline, indole, and purine are also commonly found in biological molecules.

Arylamines are prepared by nitration of an aromatic ring followed by reduction. Alkylamines are prepared by S_N2 reaction of ammonia or an amine with an alkyl halide or by the **Gabriel amine synthesis**. Amines can also be prepared by a number of reductive methods, including $LiAlH_4$ reduction of amides, nitriles, and azides. Also important is the **reductive amination** reaction in which a ketone or an aldehyde is treated with an amine in the presence of a reducing agent such as $NaBH_4$. In addition, amines result from **Hofmann** and **Curtius rearrangements** of carboxylic acid derivatives. Both methods involve migration of the –R group bonded to the carbonyl carbon and yield a product that has one less carbon atom than the starting material.

Many of the reactions of amines are familiar from past chapters. Thus, amines react with alkyl halides in S_N2 reactions and with acid chlorides in nucleophilic acyl substitution reactions. Amines also undergo E2 elimination to yield alkenes if they are first quaternized by treatment with iodomethane and then heated with silver oxide, a process called the **Hofmann elimination**.

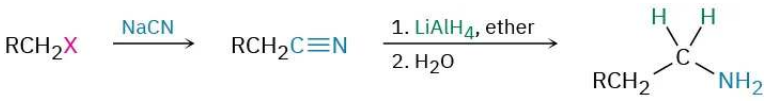
Arylamines are converted by diazotization with nitrous acid into **arenediazonium salts**, $ArN_2^+ X^-$. The diazonio group can then be replaced by many other substituents by the **Sandmeyer reaction** to give a wide variety of substituted aromatic compounds. Aryl chlorides, bromides, iodides, and nitriles can be prepared from arenediazonium salts, as can arenes and phenols. In addition to their reactivity toward substitution reactions, diazonium salts undergo coupling with phenols and arylamines to give brightly colored **azo compounds**.

This page titled 13.14: Summary is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

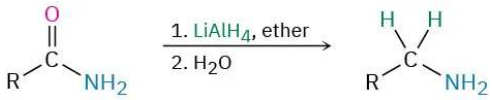
- **24.13: Summary** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

13.15: Summary of Reactions

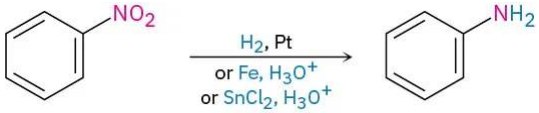
1. Synthesis of amines (Section 24.6)
   a. Reduction of nitriles



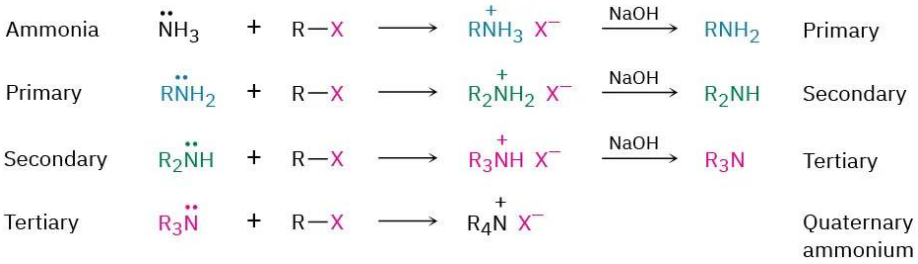
- Reduction of amides



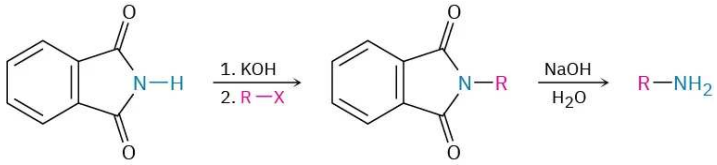
- Reduction of nitrobenzenes



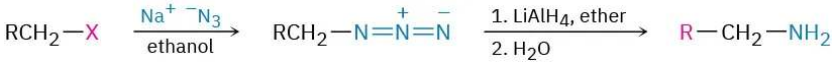
- S_N2 Alkylation of alkyl halides



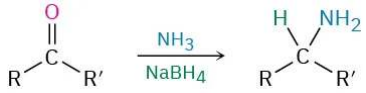
- Gabriel amine synthesis



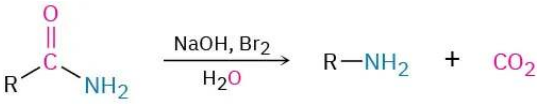
- Reduction of azides



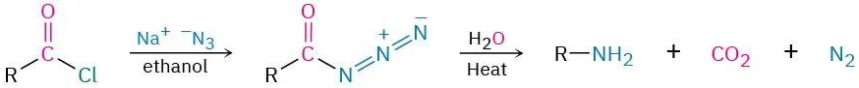
- Reductive amination of aldehydes/ketones



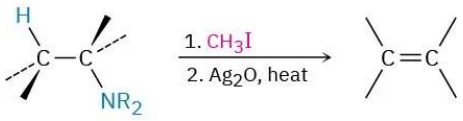
- Hofmann rearrangement of amides



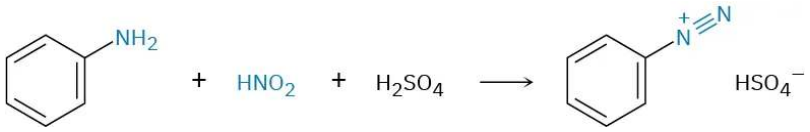
- Curtius rearrangement of acyl azides



- Reactions of amines
   a. Alkylation with alkyl halides; see reaction 1(d)
   b. Hofmann elimination (Section 24.7)

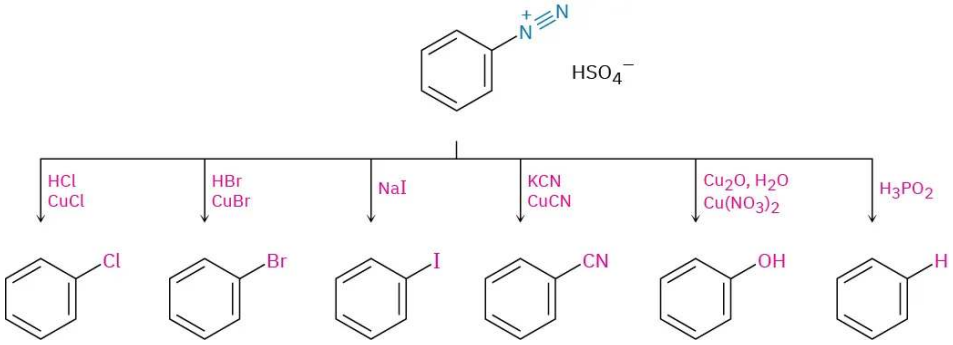


c. Diazotization (Section 24.8)

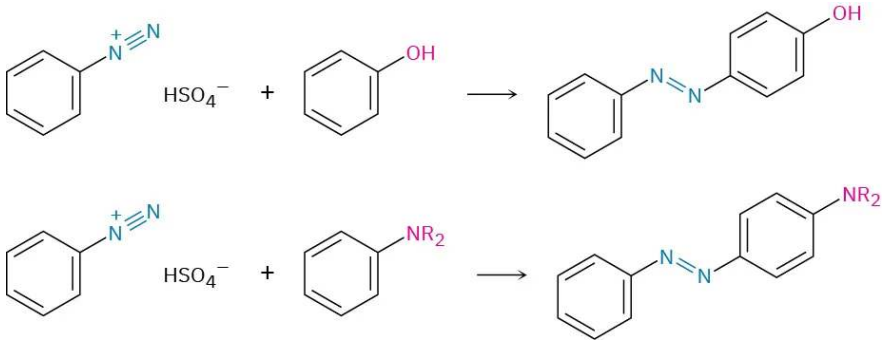


- Reactions of arenediazonium salts (Section 24.8)

a. Nucleophilic substitutions



b. Diazonium coupling



This page titled 13.15: Summary of Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

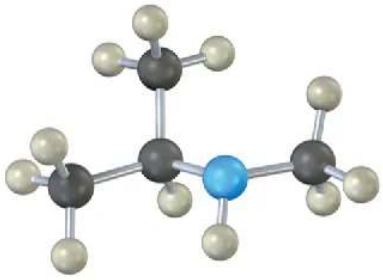
- **24.14: Summary of Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

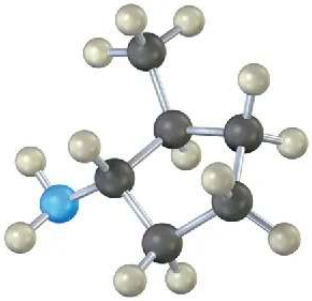
13.16: Additional Problems

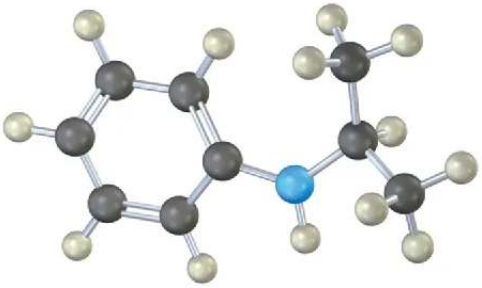
24 • Additional Problems

Visualizing Chemistry

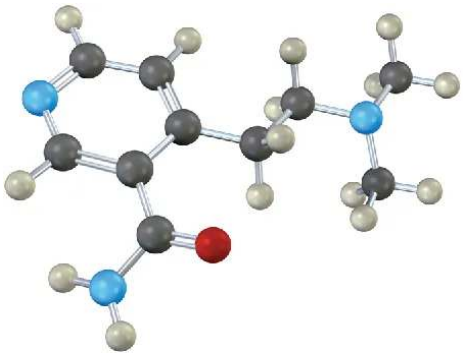
PROBLEM 24.26 Name the following amines, and identify each as primary, secondary, or tertiary:


(a)

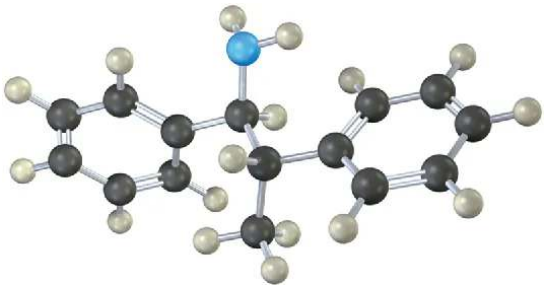

(b)


(c)

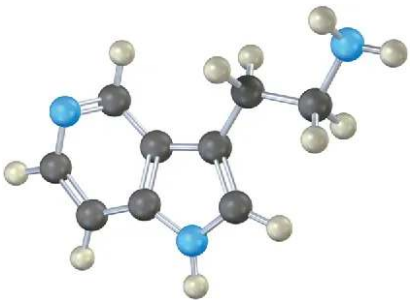
PROBLEM 24.27 The following compound contains three nitrogen atoms. Rank them in order of increasing basicity.



PROBLEM 24.28 Name the following amine, including *R*,*S* stereochemistry, and draw the product of its reaction with excess iodomethane followed by heating with Ag_2O (Hofmann elimination). Is the stereochemistry of the alkene product *Z* or *E*? Explain.

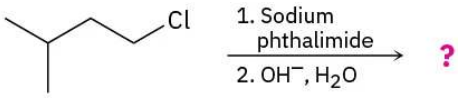


PROBLEM 24.29 Which nitrogen atom in the following compound is most basic? Explain.

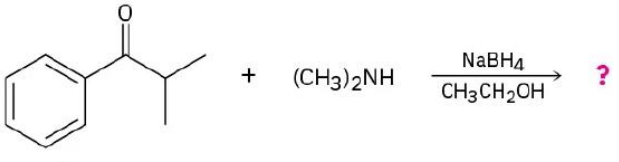


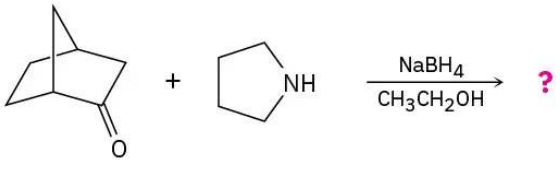
Mechanism Problems

PROBLEM 24.30

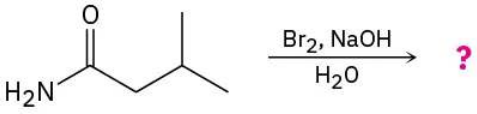
(a) (b) 

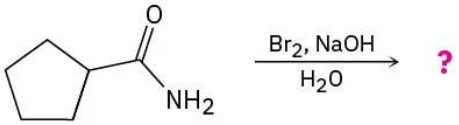
Problem 24-31 Predict the product(s) and write the mechanism for each of the following reactions:

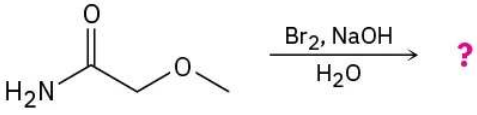
(a) 

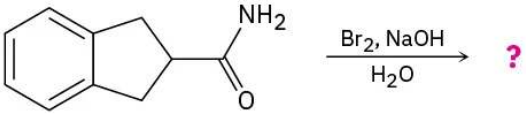
(b) 

Problem 24-32 Predict the product(s) and write the mechanism for each of the following reactions:

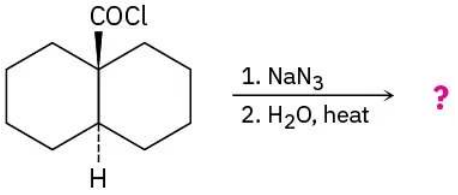
(a) 

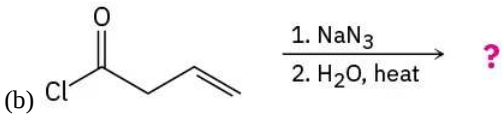
(b) 

(c) 

(d) 

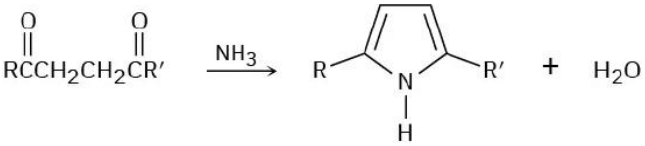
Problem 24-33 Predict the product(s) and write the mechanism for each of the following reactions:

(a) 

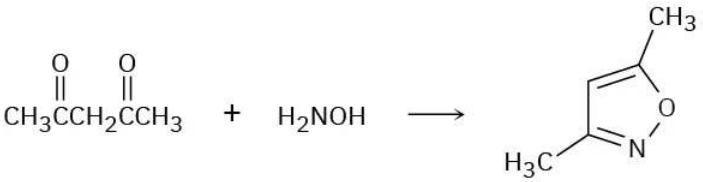
(b) 

Problem 24-34 The diazotization of aniline first involves the formation of NO^+ (nitrosonium ion) by the dehydration of nitrous acid with sulfuric acid. The aniline nitrogen then acts as a nucleophile and eventually loses water. Propose a mechanism for the formation of the dizaonium salt of aniline using curved arrows to show all electron movement.

Problem 24-35 Substituted pyrroles are often prepared by treatment of a 1,4-diketone with ammonia. Propose a mechanism.



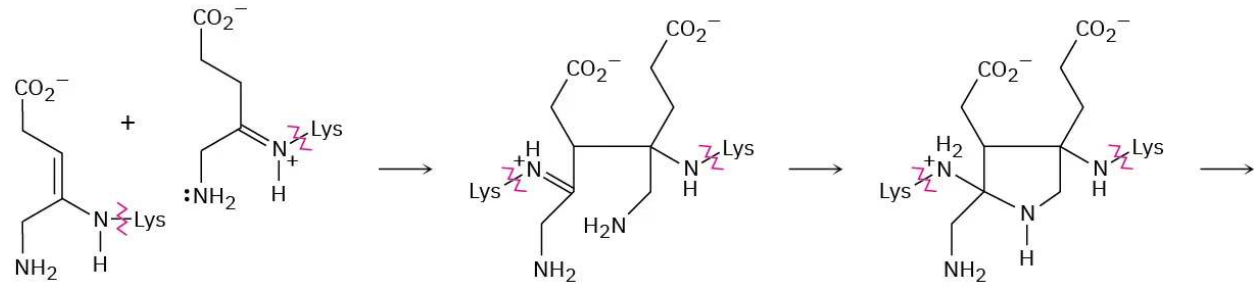
Problem 24-36 3,5-Dimethylisoxazole is prepared by reaction of 2,4-pentanedione with hydroxylamine. Propose a mechanism.



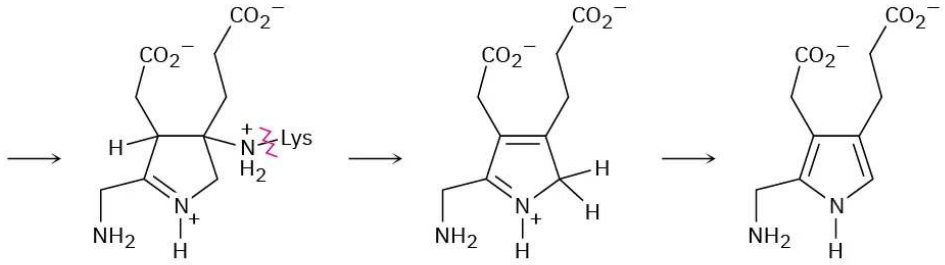
3,5-Dimethylisoxazole

Problem 24-37 One problem with reductive amination as a method of amine synthesis is that by-products are sometimes obtained. For example, reductive amination of benzaldehyde with methylamine leads to a mixture of *N*-methylbenzylamine and *N*-methyldibenzylamine. How do you suppose the tertiary amine by-product is formed? Propose a mechanism.

Problem 24-38 Chlorophyll, heme, vitamin B_{12}, and a host of other substances are biosynthesized from porphobilinogen (PBG), which is itself formed from condensation of two molecules of 5-aminolevulinate. The two 5-aminolevulinates are bound to lysine (Lys) amino acids in the enzyme, one in the enamine form and one in the imine form, and their condensation is thought to occur by the following steps. Use curved arrows to show the mechanism of each step.

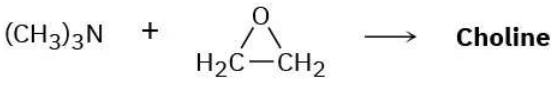


Enzyme-bound 5-aminolevulinate



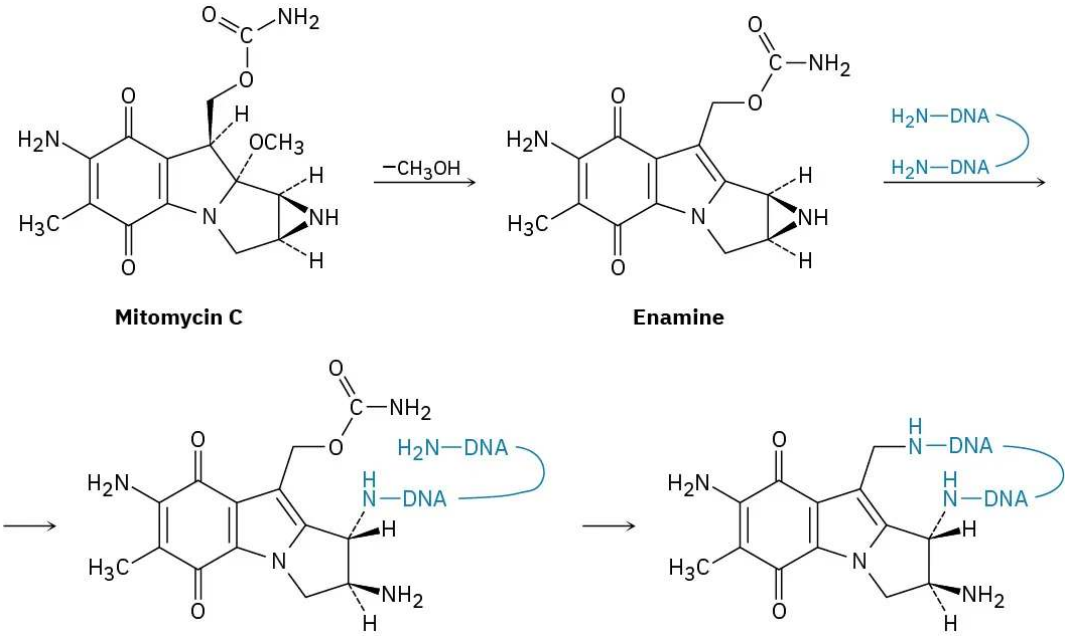
Porphobilinogen (PBG)

Problem 24-39 Choline, a component of the phospholipids in cell membranes, can be prepared by S_N2 reaction of trimethylamine with ethylene oxide. Show the structure of choline, and propose a mechanism for the reaction.



Choline

Problem 24-40 The antitumor antibiotic mitomycin C functions by forming cross-links in DNA chains.

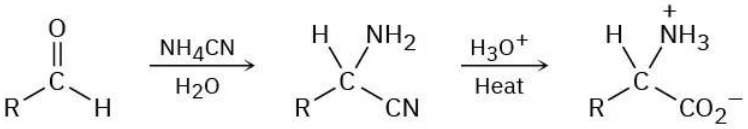


(a)The first step is loss of methoxide and formation of an iminium ion intermediate that is deprotonated to give an enamine. Show the mechanism.

(b) The second step is reaction of the enamine with DNA to open the three-membered, nitrogen-containing (aziridine) ring. Show the mechanism.

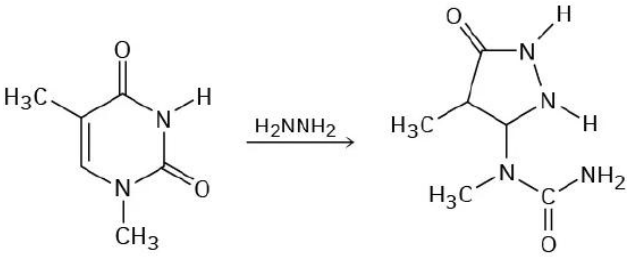
(c) The third step is loss of carbamate ($NH_2CO_2^-$) and formation of an unsaturated iminium ion, followed by a conjugate addition of another part of the DNA chain. Show the mechanism.

Problem 24-41 α-Amino acids can be prepared by the Strecker synthesis, a two-step process in which an aldehyde is treated with ammonium cyanide followed by hydrolysis of the amino nitrile intermediate with aqueous acid. Propose a mechanism for the reaction.

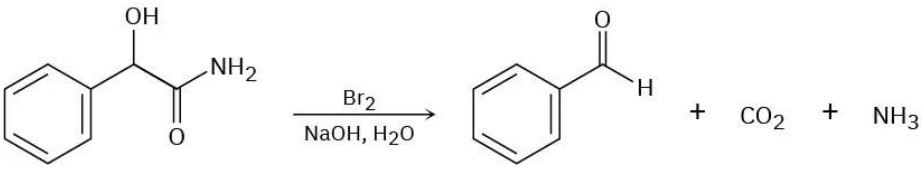


An α-amino acid

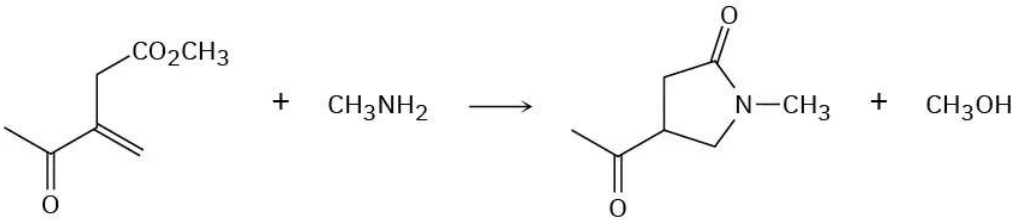
Problem 24-42 One of the reactions used in determining the sequence of nucleotides in a strand of DNA is reaction with hydrazine. Propose a mechanism for the following reaction, which occurs by an initial conjugate addition followed by internal amide formation.



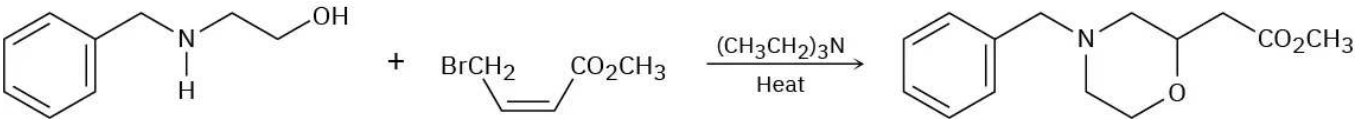
Problem 24-43 When an α-hydroxy amide is treated with Br_2 in aqueous NaOH under Hofmann rearrangement conditions, loss of CO_2 occurs and a chain-shortened aldehyde is formed. Propose a mechanism.



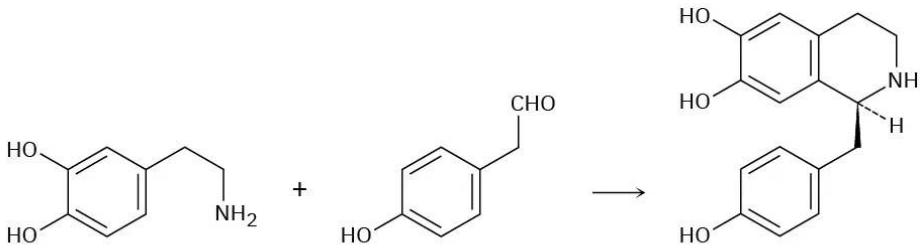
Problem 24-44 The following transformation involves a conjugate nucleophilic addition reaction (**Section 19.13**) followed by an intramolecular nucleophilic acyl substitution reaction (**Section 21.2**). Show the mechanism.



Problem 24-45 Propose a mechanism for the following reaction:



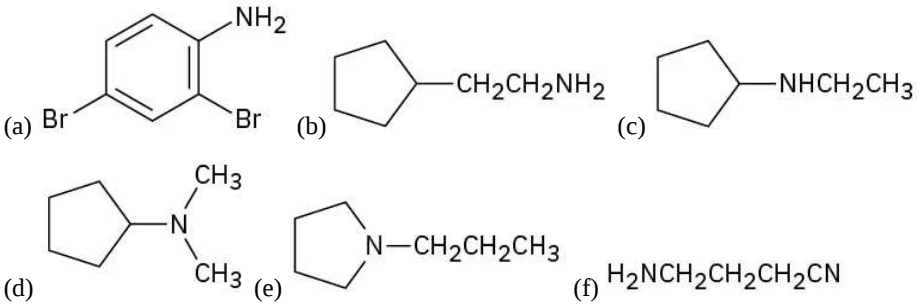
Problem 24-46 One step in the biosynthesis of morphine is the reaction of dopamine with *p*-hydroxyphenylacetaldehyde to give (*S*)-norcoclaurine. Assuming that the reaction is acid-catalyzed, propose a mechanism.



Dopamine | ***p*-Hydroxyphenyl-acetaldehyde** | **(*S*)-Norcoclaurine**

Naming Amines

Problem 24-47 Name the following compounds:

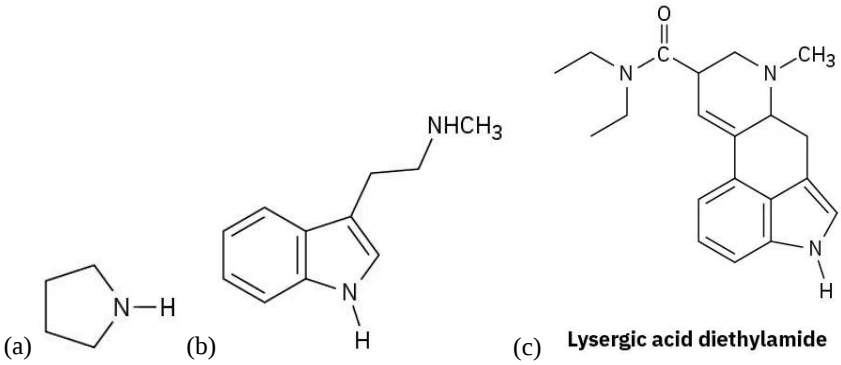


Problem 24-48 Draw structures corresponding to the following IUPAC names:

(a) *N*,*N*-Dimethylaniline **(b)** (Cyclohexylmethyl)amine **(c)** *N*-Methylcyclohexylamine

(d) (2-Methylcyclohexyl)amine **(e)** 3-(*N*,*N*-Dimethylamino)propanoic acid

Problem 24-49 Classify each of the amine nitrogen atoms in the following substances as primary, secondary, or tertiary:

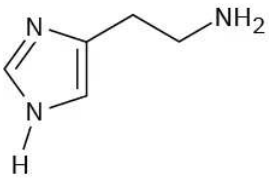


Lysergic acid diethylamide

Amine Basicity

Problem 24-50 Although pyrrole is a much weaker base than most other amines, it is a much stronger acid ($pK_a \approx 15$ for the pyrrole versus 35 for diethylamine). The N–H hydrogen is readily abstracted by base to yield the pyrrole anion, $C_4H_4N^-$. Explain.

Problem 24-51 Histamine, whose release in the body triggers nasal secretions and constricted airways, has three nitrogen atoms. List them in order of increasing basicity and explain your ordering.



Histamine

Problem 24-52 Account for the fact that *p*-nitroaniline ($pK_a = 1.0$) is less basic than *m*-nitroaniline ($pK_a = 2.5$) by a factor of 30. Draw resonance structures to support your argument. (The pK_a values refer to the corresponding ammonium ions.)

Synthesis of Amines

Problem 24-53 How would you prepare the following substances from 1-butanol?

(a) Butylamine (b) Dibutylamine (c) Propylamine (d) Pentylamine (e) *N*,*N*-Dimethylbutylamine (f) Propene

Problem 24-54 How would you prepare the following substances from pentanoic acid?

(a) Pentanamide (b) Butylamine (c) Pentylamine (d) 2-Bromopentanoic acid (e) Hexanenitrile (f) Hexylamine

Problem 24-55 How would you prepare aniline from the following starting materials?

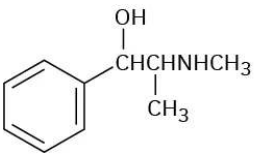
(a) Benzene (b) Benzamide (c) Toluene

Problem 24-56 How would you prepare benzylamine, $C_6H_5CH_2NH_2$, from benzene? More than one step is needed.

Problem 24-57 How might you prepare pentylamine from the following starting materials?

(a) Pentanamide (b) Pentanenitrile (c) 1-Butene (d) Hexanamide (e) 1-Butanol (f) 5-Decene (g) Pentanoic acid

Problem 24-58 How might a reductive amination be used to synthesize ephedrine, an amino alcohol that was widely used for the treatment of bronchial asthma?



Ephedrine

Reactions of Amines

Problem 24-59 How would you convert aniline into each of the following products?

(a) Benzene (b) Benzamide (c) Toluene

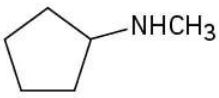
Problem 24-60 Write the structures of the major organic products you would expect from reaction of <i">m-toluidine (*m*-methylaniline) with the following reagents:

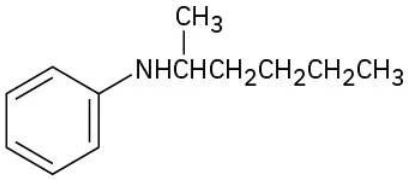
(a) Br_2 (1 equivalent) (b) CH_3I (excess) (c) CH_3COCl in pyridine (d) The product of (c), then HSO_3Cl

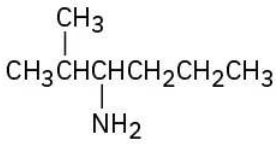
Problem 24-61 Show the products from reaction of *p*-bromoaniline with the following reagents:

(a) CH_3I (excess) (b) HCl (c) HNO_2, H_2SO_4 (d) CH_3COCl (e) CH_3MgBr (f) CH_3CH_2Cl, $AlCl_3$ (g) Product of (c) with CuCl, HCl (h) Product of (d) with CH_3CH_2Cl, $AlCl_3$

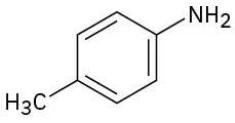
Problem 24-62 What are the major products you would expect from Hofmann elimination of the following amines?

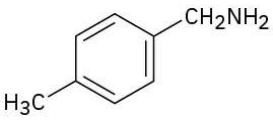
(a) 

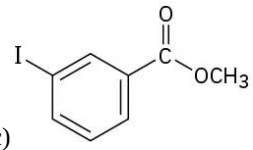
(b) 

(c) 

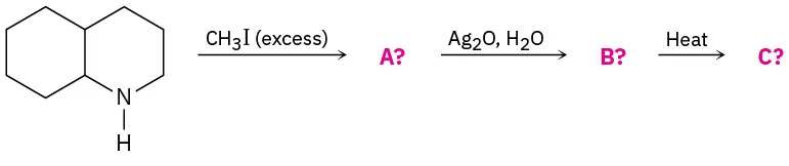
Problem 24-63 How would you prepare the following compounds from toluene? A diazonio replacement reaction is needed in some instances.

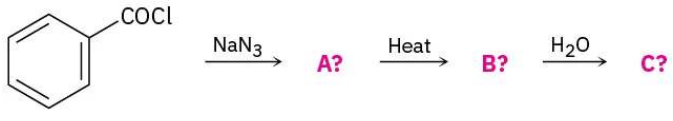
(a) 

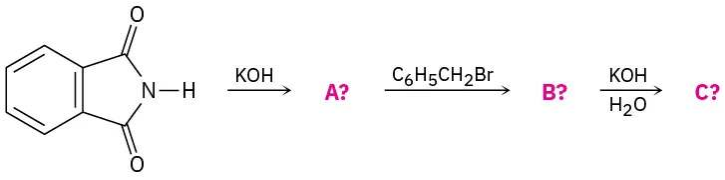
(b) 

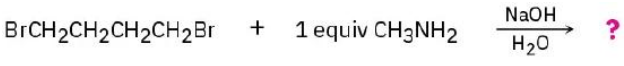
(c) 

Problem 24-64 Predict the product(s) of the following reactions. If more than one product is formed, tell which is major.

(a) 

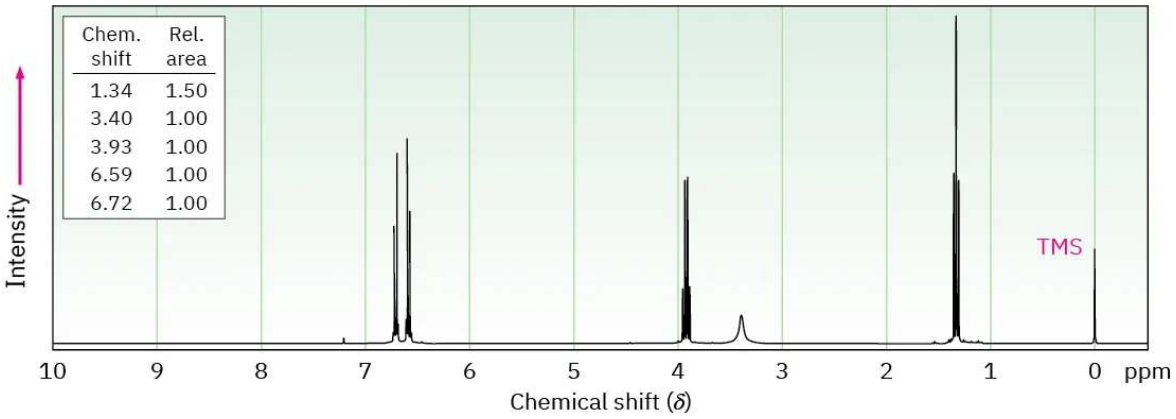
(b) 

(c) 

(d) 

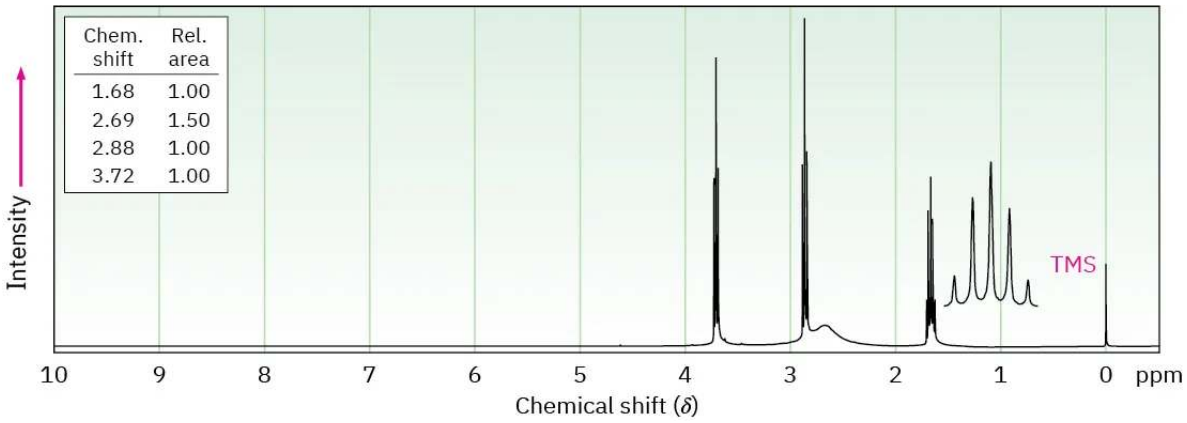
Spectroscopy

Problem 24-65 Phenacetin, a substance formerly used in over-the-counter headache remedies, has the formula $C_{10}H_{13}NO_2$. Phenacetin is neutral and does not dissolve in either acid or base. When warmed with aqueous NaOH, phenacetin yields an amine, $C_8H_{11}NO$, whose ^1H NMR spectrum is shown. When heated with HI, the amine is cleaved to an aminophenol, C_6H_7NO. What is the structure of phenacetin, and what are the structures of the amine and the aminophenol?

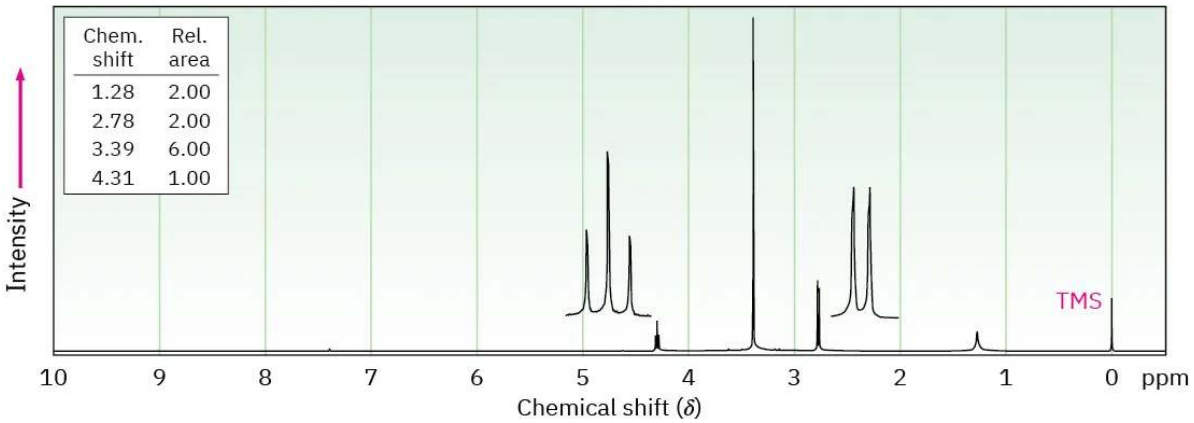


Problem 24-66 Propose structures for amines with the following 1H NMR spectra:

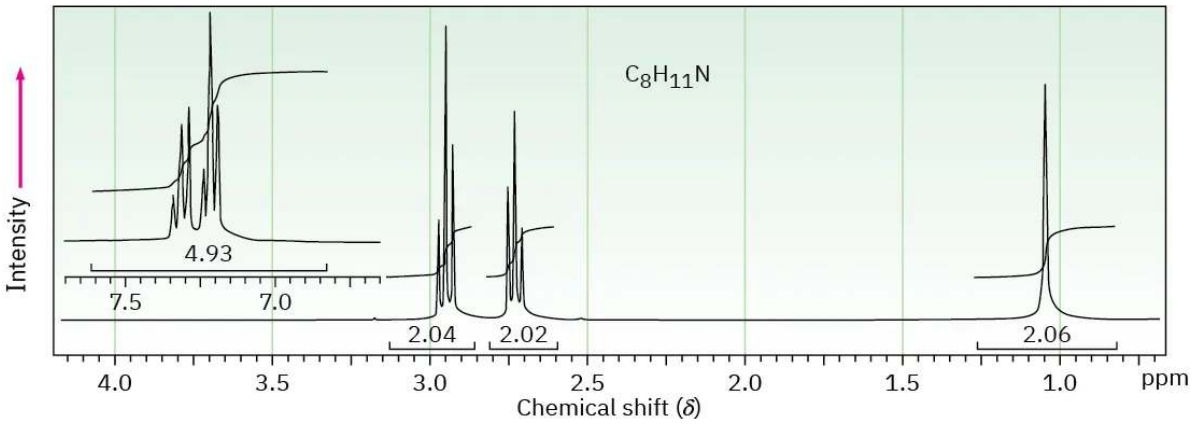
(a) C_3H_9NO



(b) $C_4H_{11}NO_2$



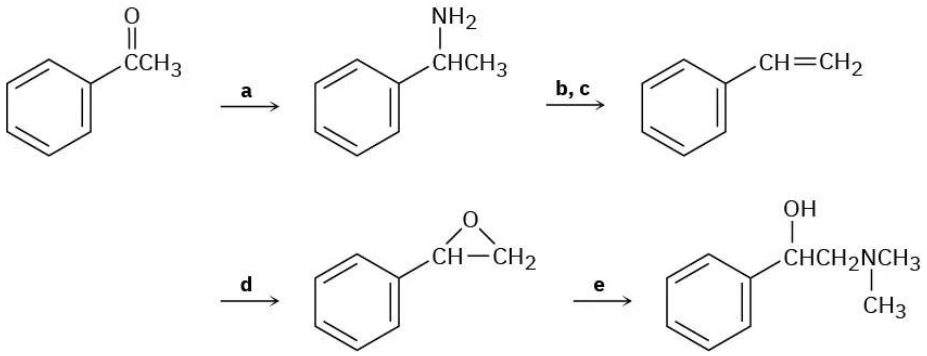
(c) $C_8H_{11}N$



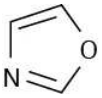
Problem 24-67 Draw the structure of the amine that produced the ^{1}H NMR spectrum shown in Problem 24-66(c). This compound has a single strong peak in its IR spectrum at 3280 cm^{-1}.

General Problems

Problem 24-68 Fill in the missing reagents **a**–**e** in the following scheme:

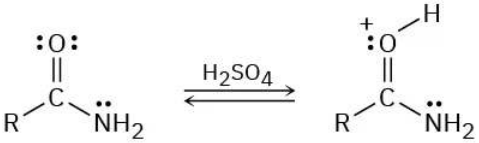


Problem 24-69 Oxazole is a five-membered aromatic heterocycle. Would you expect oxazole to be more basic or less basic than pyrrole? Explain.

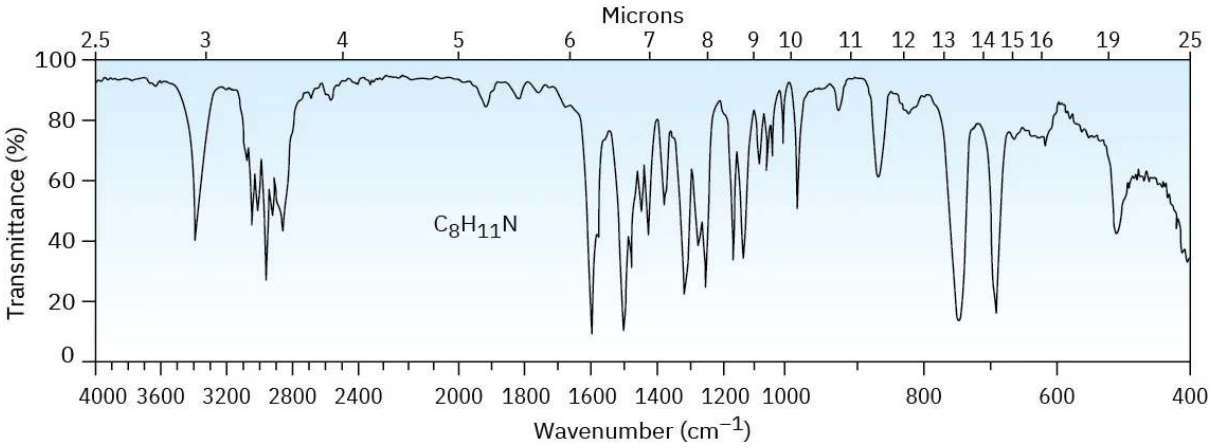


Oxazole

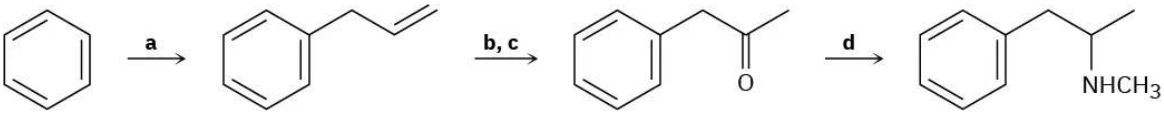
Problem 24-70 Protonation of an amide using strong acid occurs on oxygen rather than on nitrogen. Suggest a reason for this behavior, taking resonance into account.



Problem 24-71 What is the structure of the compound with formula $C_8H_{11}N$ that produced the following IR spectrum?

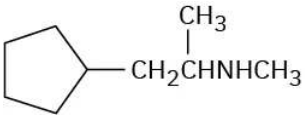


Problem 24-72 Fill in the missing reagents a–d in the following synthesis of racemic methamphetamine from benzene.



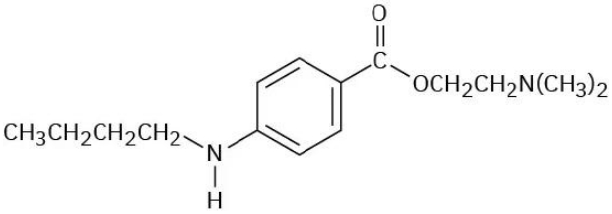
(*R*,*S*)-Methamphetamine

Problem 24-73 Cyclopentamine is an amphetamine-like central nervous system stimulant. Propose a synthesis of cyclopentamine from materials of five carbons or less.



Cyclopentamine

Problem 24-74 Tetracaine is a substance used as a spinal anesthetic.



Tetracaine

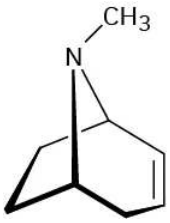
(a) How would you prepare tetracaine from the corresponding aniline derivative, $ArNH_2$?

(b) How would you prepare tetracaine from *p*-nitrobenzoic acid?

(c) How would you prepare tetracaine from benzene?

Problem 24-75 Atropine, $C_{17}H_{23}NO_3$, is a poisonous alkaloid isolated from the leaves and roots of *Atropa belladonna*, the deadly nightshade. In small doses, atropine acts as a muscle relaxant; 0.5 ng (nanogram, 10^{-9} g) is sufficient to cause pupil dilation. On basic hydrolysis, atropine yields tropic acid, $C_6H_5CH(CH_2OH)CO_2H$, and tropine, $C_8H_{15}NO$. Tropine is an optically inactive alcohol that yields tropidene on dehydration with H_2SO_4. Propose a structure for atropine.

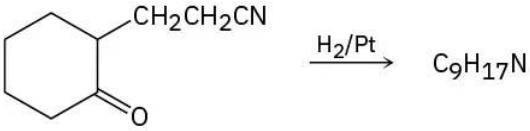
https://chem.libretexts.org/@go/page/564360



Tropidene

Problem 24-76 Tropidene (Problem 24-75) can be converted by a series of steps into tropilidene (1,3,5-cycloheptatriene). How would you accomplish this conversion?

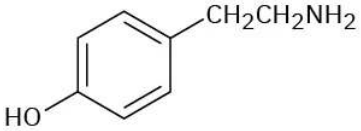
Problem 24-77 Propose a structure for the product with formula $C_9H_{17}N$ that results when 2-(2-cyanoethyl)cyclohexanone is reduced catalytically.



Problem 24-78 Coniine, $C_8H_{17}N$, is the toxic principle of the poison hemlock drunk by Socrates. When subjected to Hofmann elimination, coniine yields 5-(*N*,*N*-dimethylamino)-1-octene. If coniine is a secondary amine, what is its structure?

Problem 24-79 How would you synthesize coniine (Problem 24-78) from acrylonitrile ($H_2C{=}CHCN$) and ethyl 3-oxohexanoate ($CH_3CH_2CH_2COCH_2CO_2Et$)? (See Problem 24-77.)

Problem 24-80 Tyramine is an alkaloid found, among other places, in mistletoe and ripe cheese. How would you synthesize tyramine from benzene? From toluene?

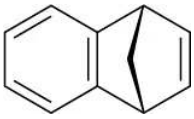


Tyramine

Problem 24-81 Reaction of anthranilic acid (*o*-aminobenzoic acid) with HNO_2 and H_2SO_4 yields a diazonium salt that can be treated with base to yield a neutral diazonium carboxylate.

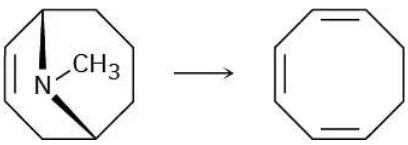
(a) What is the structure of the neutral diazonium carboxylate?

(b) Heating the diazonium carboxylate results in the formation of CO_2, N_2, and an intermediate that reacts with 1,3-cyclopentadiene to yield the following product:



What is the structure of the intermediate, and what kind of reaction does it undergo with cyclopentadiene?

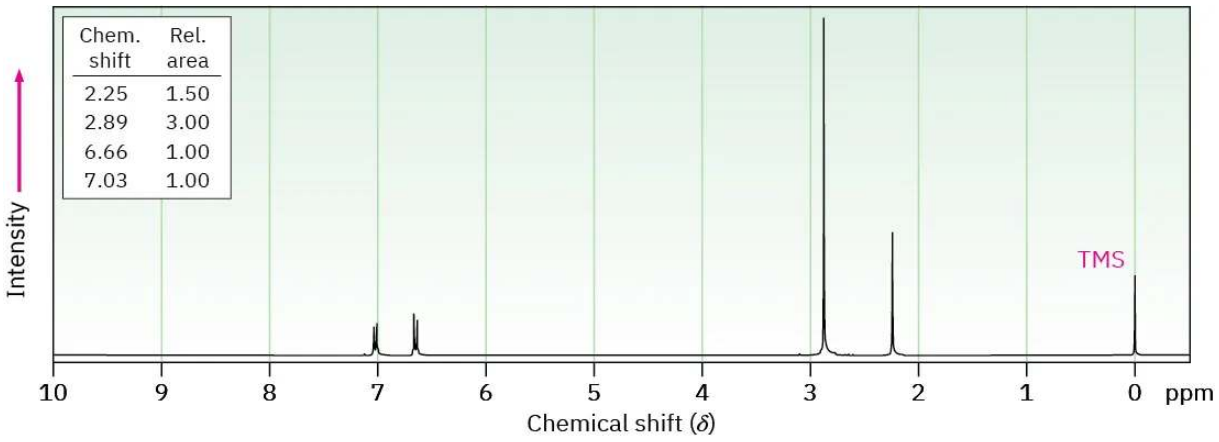
Problem 24-82 Cyclooctatetraene was first synthesized in 1911 by a route that involved the following transformation:



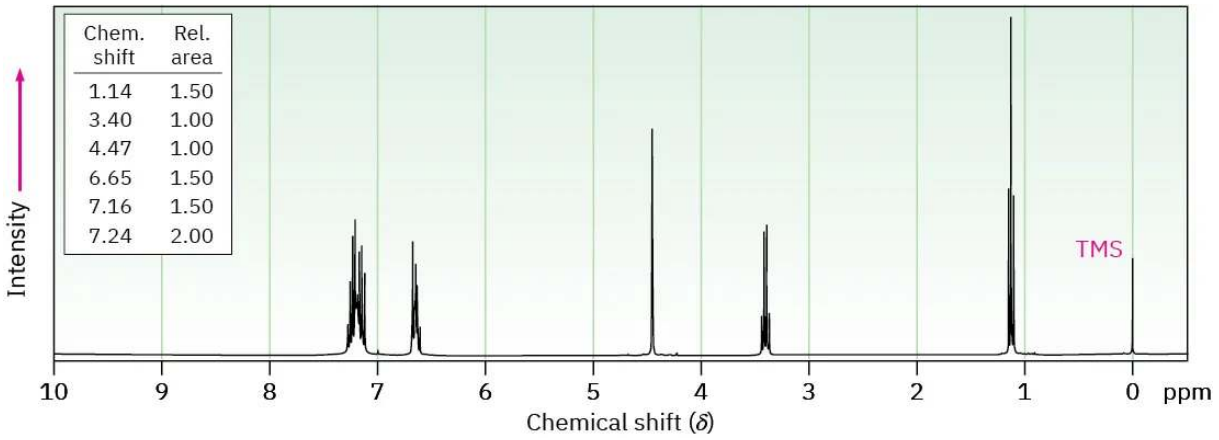
How might you use the Hofmann elimination to accomplish this reaction? How would you finish the synthesis by converting cyclooctatriene into cyclooctatetraene?

Problem 24-83 Propose structures for compounds that show the following ^1H NMR spectra.

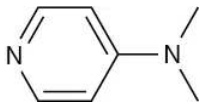
(a) $C_9H_{13}N$



(b) $C_{15}H_{17}N$



Problem 24-844-Dimethylaminopyridine (DMAP) acts as a catalyst in acyl transfer reactions. DMAP's catalytic activity stems from its nucleophilic character at the pyridine nitrogen, not the dimethylamino group. Explain this behavior, taking resonance into account.



This page titled 13.16: Additional Problems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **24.15: Additional Problems** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

CHAPTER OVERVIEW

14: Orbitals and Organic Chemistry - Pericyclic Reactions

14.1: Why This Chapter?
14.2: Molecular Orbitals of Conjugated Pi Systems
14.3: Electrocyclic Reactions
14.4: Stereochemistry of Thermal Electrocyclic Reactions
14.5: Photochemical Electrocyclic Reactions
14.6: Cycloaddition Reactions
14.7: Stereochemistry of Cycloadditions
14.8: Sigmatropic Rearrangements
14.9: Some Examples of Sigmatropic Rearrangements
14.10: A Summary of Rules for Pericyclic Reactions
14.11: Chemistry Matters—Vitamin D, the Sunshine Vitamin
14.12: Key Terms
14.13: Summary
14.14: Additional Problems

This page titled 14: Orbitals and Organic Chemistry - Pericyclic Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

14.1: Why This Chapter?

Broad outlines of both polar and radical reactions have been in place for more than a century, but our understanding of pericyclic reactions has emerged more recently. Prior to the mid-1960s, in fact, they were even occasionally referred to as “no-mechanism reactions.” They occur largely in the laboratory rather than in biological processes, but a knowledge of them is necessary, both for completeness in studying organic chemistry and in understanding biological pathways where they do occur.

Figure 14.1.1: It may look easy, but these sunbathers are working hard to carry out a pericyclic reaction. (credit: “Tanning” by Meraj Chhaya/Flickr, CC BY 2.0).

Most organic reactions take place by polar mechanisms, in which a nucleophile donates two electrons to an electrophile in forming a new bond. Other reactions take place by radical mechanisms, in which each of two reactants donates one electron in forming a new bond. Both kinds of reactions occur frequently in the laboratory and in living organisms. Less common, however, is the third major class of organic reactions—*pericyclic reactions.*

A pericyclic reaction is one that occurs by a concerted process through a cyclic transition state. A *concerted reaction* is one in which all bonding changes occur simultaneously; no intermediates are involved. Rather than try to expand this definition now, we’ll begin by briefly reviewing some of the ideas of molecular orbital theory introduced in the chapters on Structure and Bonding and Conjugated Compounds and Ultraviolet Spectroscopy and then looking individually at the three main classes of pericyclic reactions: *electrocyclic reactions*, *cycloadditions*, and *sigmatropic rearrangements.*

This page titled 14.1: Why This Chapter? is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **30.0: Why This Chapter?** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

14.2: Molecular Orbitals of Conjugated Pi Systems

A conjugated polyene, as we saw in Section 14.1, is one with alternating double and single bonds. According to molecular orbital (MO) theory, the *p* orbitals on the sp^2-hybridized carbons of a conjugated polyene interact to form a set of π molecular orbitals whose energies depend on the number of nodes they have between nuclei. Molecular orbitals with fewer nodes are lower in energy than isolated *p* atomic orbitals and are bonding MOs; molecular orbitals with more nodes are higher in energy than isolated *p* orbitals and are antibonding MOs. Pi molecular orbitals of ethylene and 1,3-butadiene are shown in Figure 14.2.1.

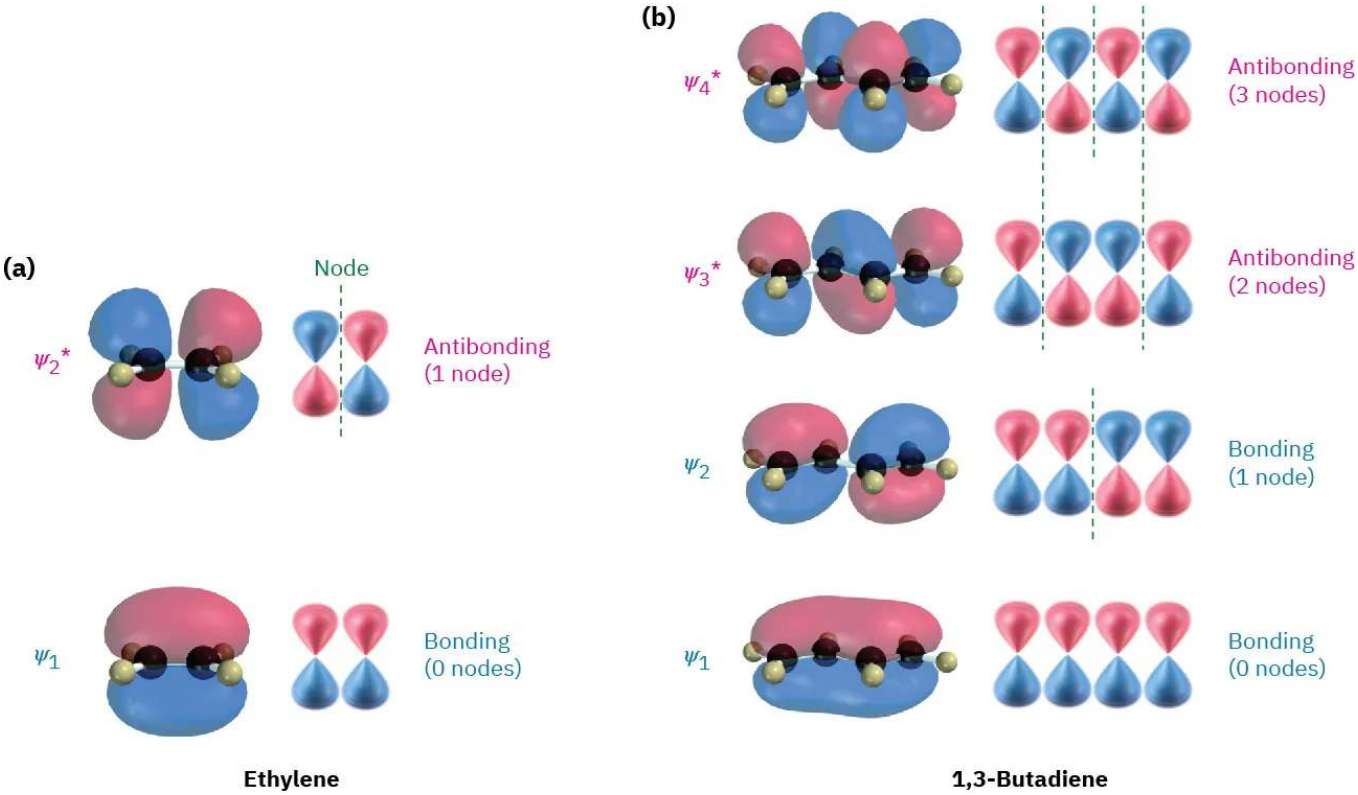


Figure 14.2.1: Pi molecular orbitals of **(a)** ethylene and **(b)** 1,3-butadiene.

A similar sort of molecular orbital description can be derived for any conjugated π electron system. 1,3,5-Hexatriene, for example, has three double bonds and six π MOs, as shown in Figure 14.2.2. In the ground state, only the three bonding orbitals, ψ_1, ψ_2, and ψ_3, are filled. On irradiation with ultraviolet light, however, an electron is promoted from the highest-energy filled orbital (ψ_3) to the lowest-energy unfilled orbital (ψ_4*) to give an excited state (Section 14.7), in which ψ_3 and ψ_4* are each half-filled. (An asterisk denotes an antibonding orbital.)

What do molecular orbitals and their nodes have to do with pericyclic reactions? The answer is, *everything*. According to a series of rules formulated in the mid-1960s by R. B. Woodward and Roald Hoffmann at Harvard University, a pericyclic reaction can take place only if the symmetries of the reactant MOs are the same as the symmetries of the product MOs. In other words, the lobes of reactant MOs must be of the correct algebraic sign for bonding to occur in the transition state leading to product.

If the symmetries of reactant and product orbitals match up, or *correlate*, the reaction is said to be symmetry-allowed. If the symmetries of reactant and product orbitals don't correlate, the reaction is symmetry-disallowed. Symmetry-allowed reactions often occur under relatively mild conditions, but symmetry-disallowed reactions can't occur by concerted paths. They either take place by nonconcerted, higher-energy pathways, or they don't take place at all.

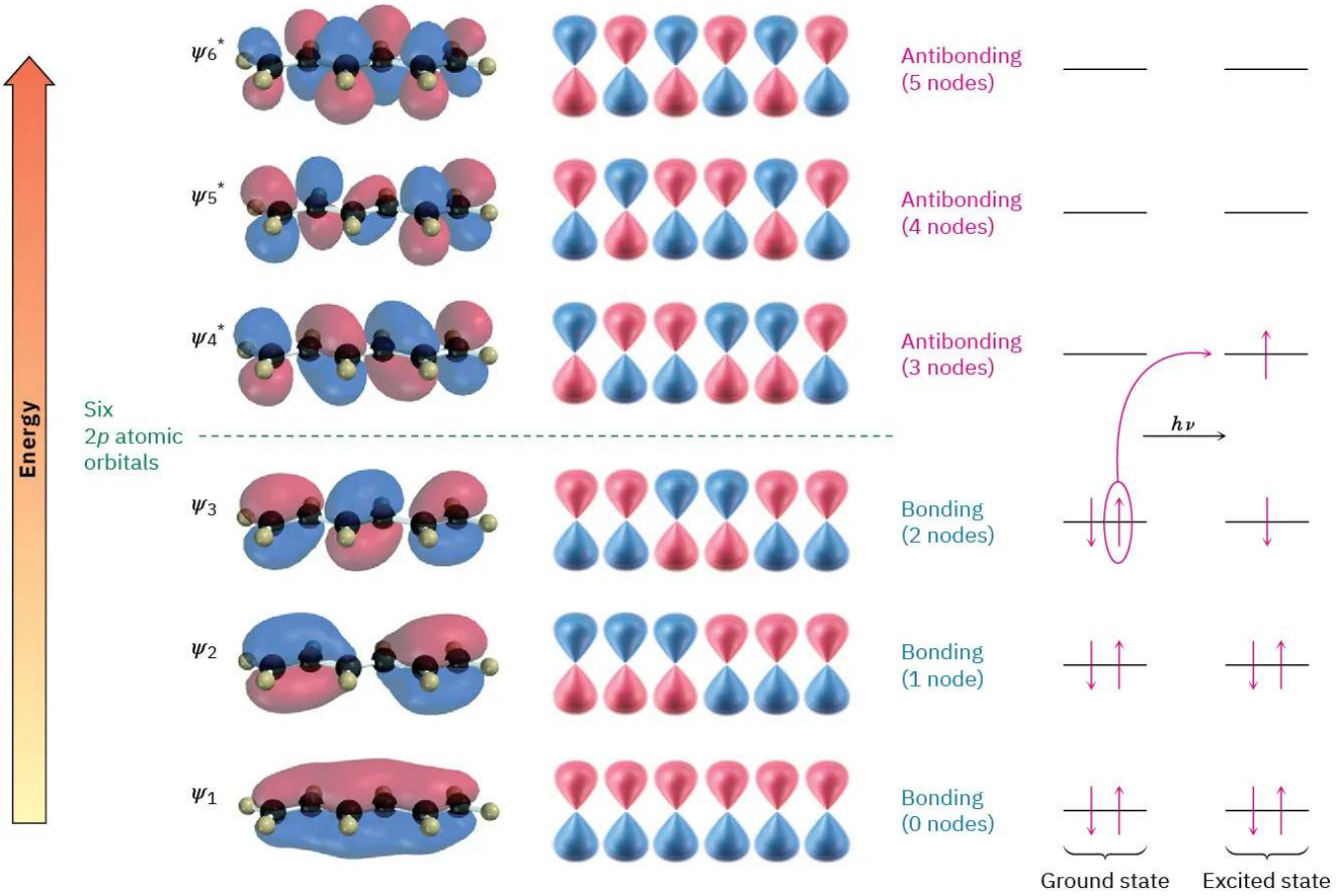


Figure 14.2.2: The six π molecular orbitals of 1,3,5-hexatriene. In the ground state, the three bonding MOs, ψ_1, ψ_2, and ψ_3, are filled. In the excited state, ψ_3 and ψ_4* are both half-filled.

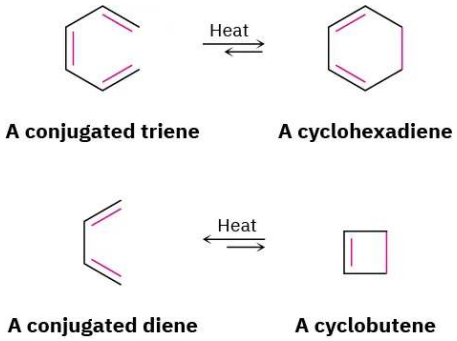
The Woodward–Hoffmann rules for pericyclic reactions require an analysis of all reactant and product molecular orbitals, but Kenichi Fukui at Kyoto Imperial University in Japan introduced a simplified version. Hoffman and Fukui shared a Nobel Prize for their work, and Woodward would have joined them (for his second Nobel Prize) had he not passed away before the award was made. According to Fukui's simplified version, we need to consider only two molecular orbitals, called the frontier orbitals. These frontier orbitals are the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). In ground-state 1,3,5-hexatriene, for example, ψ_3 is the HOMO and ψ_4* is the LUMO (Figure 14.2.2). In excited-state 1,3,5-hexatriene, however, ψ_4* is the HOMO and ψ_5* is the LUMO.

This page titled 14.2: Molecular Orbitals of Conjugated Pi Systems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **30.1: Molecular Orbitals of Conjugated Pi Systems** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

14.3: Electrocyclic Reactions

The best way to understand how orbital symmetry affects pericyclic reactions is to look at some examples. Let's look first at a group of polyene rearrangements called *electrocyclic reactions*. An electrocyclic reaction is a pericyclic process that involves the cyclization of a conjugated acyclic polyene. One π bond is broken, the other π bonds change position, a new σ bond is formed, and a cyclic compound results. For example, a conjugated triene can be converted into a cyclohexadiene, and a conjugated diene can be converted into a cyclobutene.



Pericyclic reactions are reversible, and the position of the equilibrium depends on the specific case. In general, the triene $\rightleftarrows$ cyclohexadiene equilibrium favors the cyclic product, whereas the diene $\rightleftarrows$ cyclobutene equilibrium favors the less strained open-chain product.

The most striking feature of electrocyclic reactions is their stereochemistry. For example, (2*E*,4*Z*,6*E*)-2,4,6-octatriene yields only *cis*-5,6-dimethyl-1,3-cyclohexadiene when heated, and (2*E*,4*Z*,6*Z*)-2,4,6-octatriene yields only *trans*-5,6-dimethyl-1,3-cyclohexadiene. Remarkably, however, the stereochemical results change completely when the reactions are carried out under what are called *photochemical*, rather than *thermal*, conditions. Irradiation of (2*E*,4*Z*,6*E*)-2,4,6-octatriene with ultraviolet light (denoted hν) yields *trans*-5,6-dimethyl-1,3-cyclohexadiene (Figure 14.3.1).

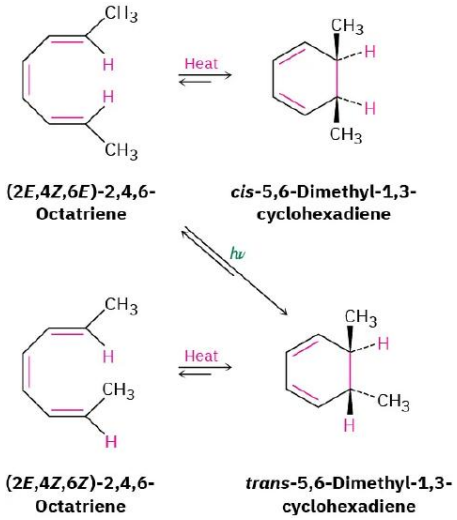


Figure 14.3.1: Electrocyclic interconversions of 2,4,6-octatriene isomers and 5,6-dimethyl-1,3-cyclohexadiene isomers.

A similar result is obtained for the thermal electrocyclic ring-opening of 3,4-dimethylcyclobutene. The trans isomer yields only (2*E*,4*E*)-2,4-hexadiene when heated, and the cis isomer yields only (2*E*,4*Z*)-2,4-hexadiene. On UV irradiation, however, the results are opposite. Cyclization of the 2*E*,4*E* isomer under photochemical conditions yields cis product (Figure 14.3.2).

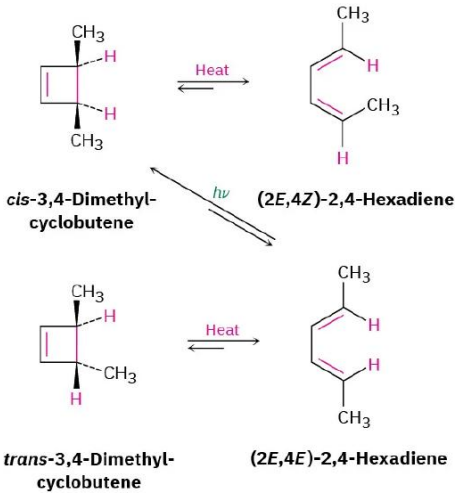
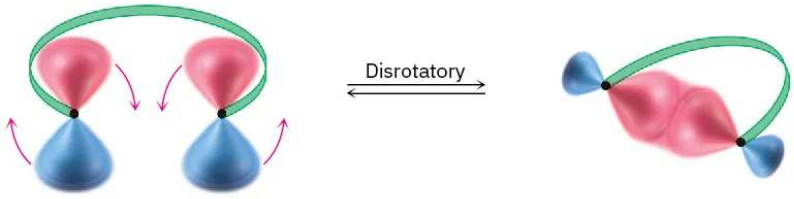


Figure 14.3.2: Electrocyclic interconversions of 2,4-hexadiene isomers and 3,4-dimethylcyclobutene isomers.

To account for these results, we need to look at the two outermost lobes of the polyene MOs—the lobes that interact when cyclization occurs. There are two possibilities: lobes of like sign can be either on the same side of the molecule or on opposite sides.

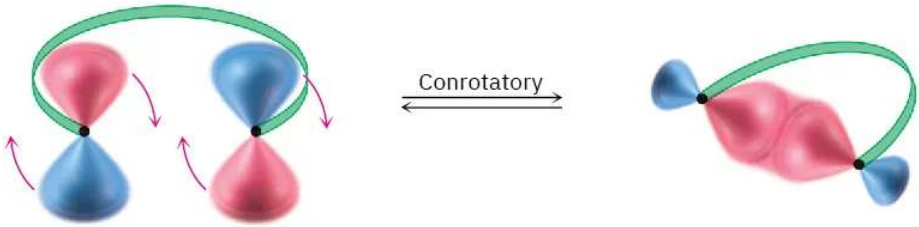
Like lobes on same side **Like lobes on opposite side**

For a bond to form, the outermost π lobes must rotate so that favorable bonding interaction is achieved—a positive lobe with a positive lobe or a negative lobe with a negative lobe. If two lobes of like sign are on the same side of the molecule, the two orbitals must rotate in *opposite* directions—one clockwise and one counterclockwise. This kind of motion is referred to as **disrotatory**.



Clockwise **Counterclockwise**

Conversely, if lobes of like sign are on opposite sides of the molecule, both orbitals must rotate in the *same* direction, either both clockwise or both counterclockwise. This kind of motion is called **conrotatory**.



Clockwise **Clockwise**

This page titled 14.3: Electrocyclic Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **30.2: Electrocyclic Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

14.4: Stereochemistry of Thermal Electrocyclic Reactions

How can we predict whether conrotatory or disrotatory motion will occur in a given case? According to frontier orbital theory, the stereochemistry of an electrocyclic reaction is determined by the symmetry of the polyene HOMO. The electrons in the HOMO are the highest-energy, most loosely held electrons and are therefore most easily moved during reaction. For thermal reactions, the ground-state electron configuration is used to identify the HOMO; for photochemical reactions, the excited-state electron configuration is used.

Let's look again at the thermal ring-closure of conjugated trienes. According to Figure 30.3, the HOMO of a conjugated triene in its ground state has lobes of like sign on the same side of the molecule, a symmetry that predicts disrotatory ring-closure. This disrotatory cyclization is precisely what is observed in the thermal cyclization of 2,4,6-octatriene. The 2*E*,4*Z*,6*E* isomer yields cis product; the 2*E*,4*Z*,6*Z* isomer yields trans product (Figure 14.4.1).

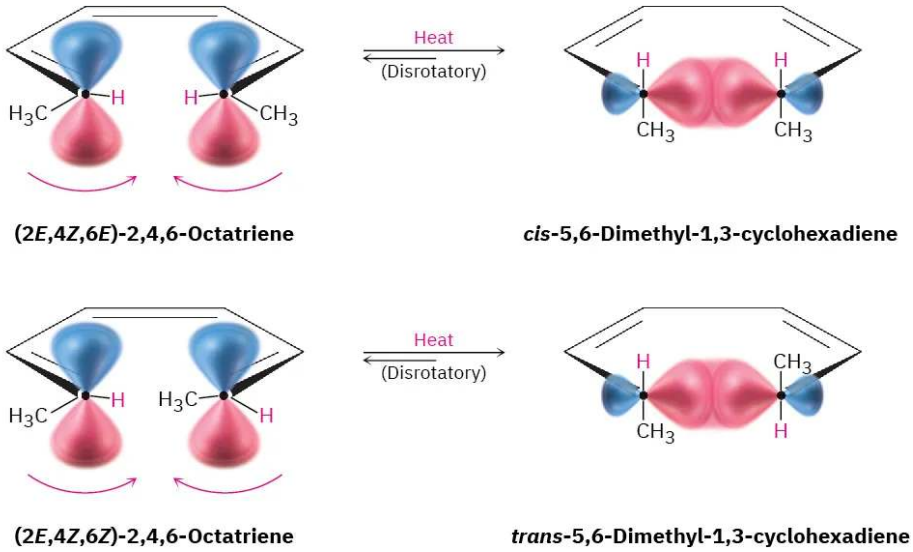


Figure 14.4.1: Thermal cyclizations of 2,4,6-octatrienes occur by disrotatory ring-closures.

In the same way, the ground-state HOMO of conjugated dienes (Figure 30.2) has a symmetry that predicts conrotatory ring-closure. In practice, however, the conjugated diene reaction can be observed only in the reverse direction (cyclobutene → diene) because of the position of the equilibrium. We therefore find that the 3,4-dimethylcyclobutene ring *opens* in a conrotatory fashion. *cis*-3,4-Dimethylcyclobutene yields (2*E*,4*Z*)-2,4-hexadiene, and *trans*-3,4-dimethylcyclobutene yields (2*E*,4*E*)-2,4-hexadiene by conrotatory opening (Figure 14.4.2).

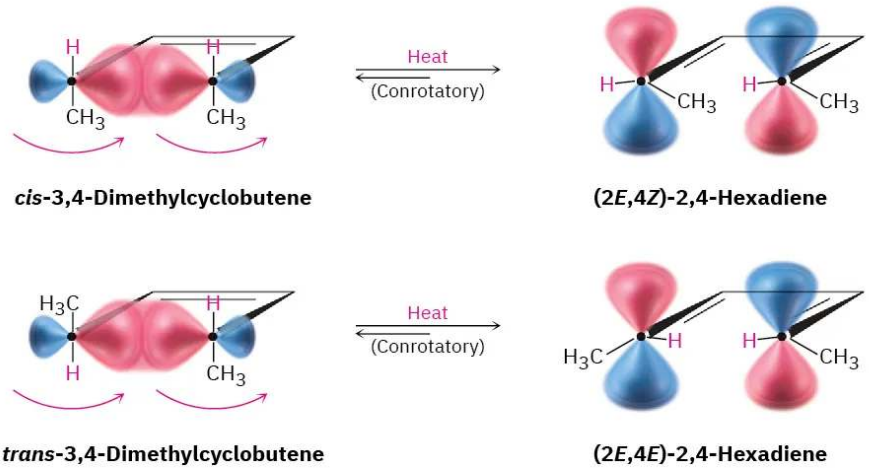
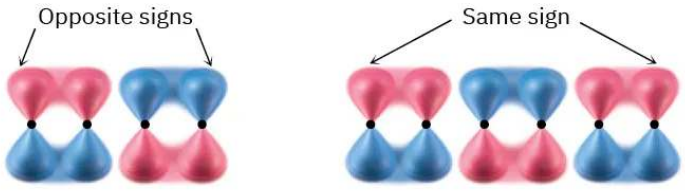


Figure 14.4.2: Thermal ring-openings of *cis*- and *trans*-dimethylcyclobutene occur by conrotatory paths.

Note that a conjugated diene and a conjugated triene react with opposite stereochemistry. The diene opens and closes by a conrotatory path, whereas the triene opens and closes by a disrotatory path. This is due to the different symmetries of the diene and triene HOMOs.



Diene HOMO **Triene HOMO**

It turns out that there is an alternating relationship between the number of electron pairs (double bonds) undergoing bond reorganization and the stereochemistry of ring-opening or -closure. Polyenes with an even number of electron pairs undergo thermal electrocyclic reactions in a conrotatory sense, whereas polyenes with an odd number of electron pairs undergo the same reactions in a disrotatory sense.

? Exercise 14.4.1

Draw the products you would expect from conrotatory and disrotatory cyclizations of (2*Z*,4*Z*,6*Z*)-2,4,6-octatriene. Which of the two paths would you expect the thermal reaction to follow?

Answer

Disrotatory: *cis*-5,6-dimethyl-1,3-cyclohexadiene;
conrotatory: *trans*-5,6-dimethyl-1,3-cyclohexadiene. Disrotatory closure occurs.

? Exercise 14.4.2

trans-3,4-Dimethylcyclobutene can open by two conrotatory paths to give either (2*E*,4*E*)-2,4-hexadiene or (2*Z*,4*Z*)-2,4-hexadiene. Explain why both products are symmetry-allowed, and then account for the fact that only the 2*E*,4*E* isomer is obtained in practice.

Answer

The more stable of two allowed products is formed.

This page titled 14.4: Stereochemistry of Thermal Electrocyclic Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **30.3: Stereochemistry of Thermal Electrocyclic Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

14.5: Photochemical Electrocyclic Reactions

We noted previously that photochemical electrocyclic reactions take a different stereochemical course than their thermal counterparts, and we can now explain this difference. Ultraviolet irradiation of a polyene causes an excitation of one electron from the ground-state HOMO to the ground-state LUMO, thus changing their symmetries. But because electronic excitation changes the symmetries of HOMO and LUMO, it also changes the reaction stereochemistry. (2*E*,4*E*)-2,4-Hexadiene, for instance, undergoes photochemical cyclization by a disrotatory path, whereas the thermal reaction is conrotatory. Similarly, (2*E*,4*Z*,6*E*)-2,4,6-octatriene undergoes photochemical cyclization by a conrotatory path, whereas the thermal reaction is disrotatory (Figure 14.5.1).

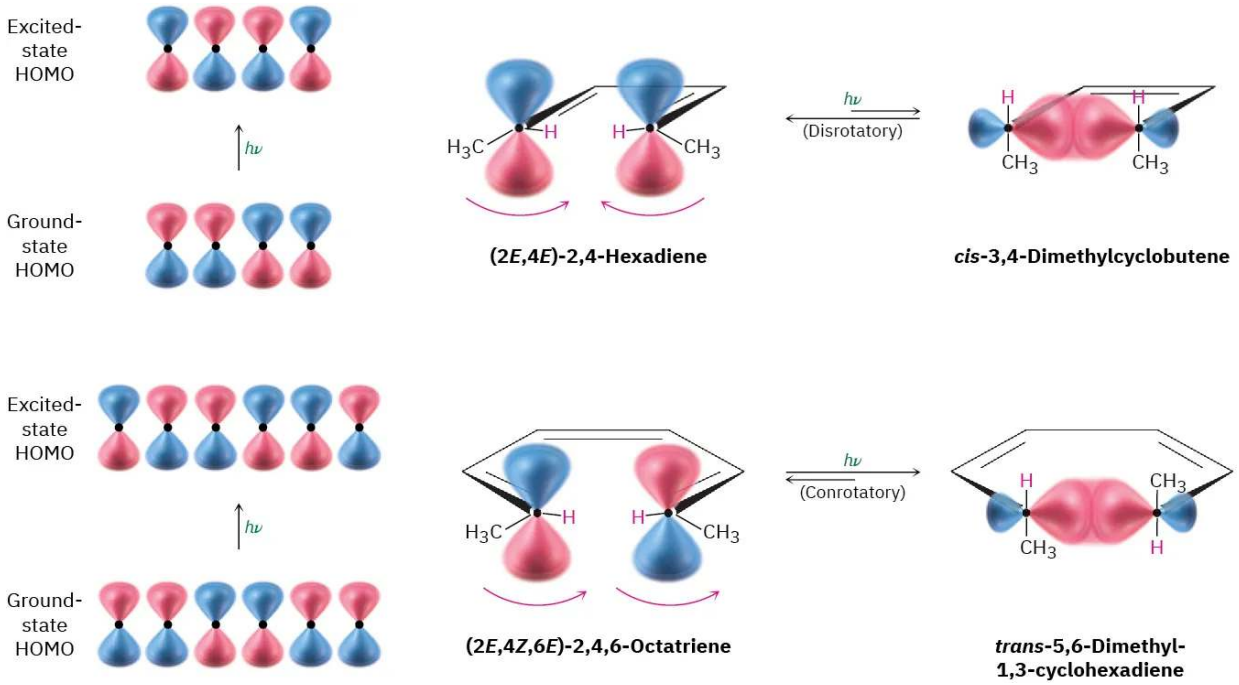


Figure 14.5.1: Photochemical cyclizations of conjugated dienes and trienes. The two processes occur with different stereochemistry because of their different orbital symmetries.

Thermal and photochemical electrocyclic reactions always take place with opposite stereochemistry because the symmetries of the frontier orbitals are always different. Table 14.5.1 gives some simple rules that make it possible to predict the stereochemistry of electrocyclic reactions.

Table 14.5.1: Stereochemical Rules for Electrocyclic Reactions

Electron pairs (double bonds)	Thermal reaction	Photochemical reaction
Even number	Conrotatory	Disrotatory
Odd number	Disrotatory	Conrotatory

? Exercise 14.5.1

What product would you expect to obtain from the photochemical cyclization of (2*E*,4*Z*,6*E*)-2,4,6-octatriene? Of (2*E*,4*Z*,6*Z*)-2,4,6-octatriene?

Answer

trans-5,6-Dimethyl-1,3-cyclohexadiene; *cis*-5,6-dimethyl-1,3-cyclohexadiene

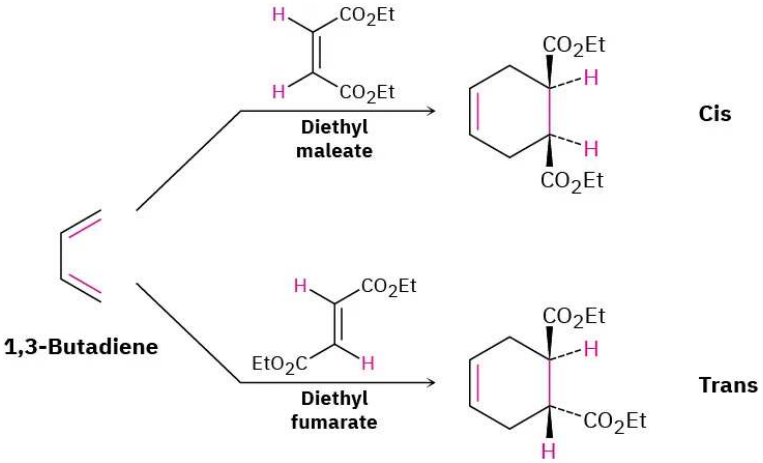
This page titled 14.5: Photochemical Electrocyclic Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **30.4: Photochemical Electrocyclic Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

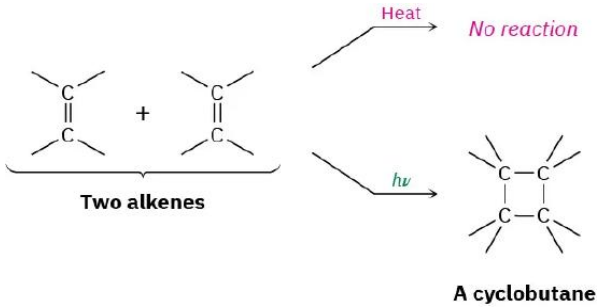
14.6: Cycloaddition Reactions

A cycloaddition reaction is one in which two unsaturated molecules add to one another to yield a cyclic product. As with electrocyclic reactions, cycloadditions are governed by the orbital symmetry of the reactants. Symmetry-allowed processes often take place readily, but symmetry-disallowed processes take place with difficulty, if at all, and then only by nonconcerted pathways. Let's look at two examples to see how they differ.

As we saw in Section 14.4, the Diels–Alder cycloaddition reaction is a pericyclic process that takes place between a diene (four π electrons) and a dienophile (two π electrons) to yield a cyclohexene product. Many thousands of Diels–Alder reactions are known. They often take place easily at room temperature or slightly above, and they are stereospecific with respect to substituents. For example, room-temperature reaction between 1,3-butadiene and diethyl maleate (cis) exclusively yields the cis-disubstituted cyclohexene product. A similar reaction between 1,3-butadiene and diethyl fumarate (trans) exclusively yields the trans-disubstituted product.



In contrast to the [4 + 2]-π-electron Diels–Alder reaction, the [2 + 2]-π-electron cycloaddition between two alkenes does not occur thermally. The [2 + 2] cycloaddition takes place only on irradiation, yielding cyclobutane products.



For a successful cycloaddition, the terminal π lobes of the two reactants must have the correct symmetry for bonding to occur. This can happen in either of two ways, called *suprafacial* and *antarafacial*. Suprafacial cycloadditions take place when a bonding interaction occurs between lobes on the same face of one reactant and lobes on the same face of the other reactant. Antarafacial cycloadditions take place when a bonding interaction occurs between lobes on the same face of one reactant and lobes on opposite faces of the other reactant (Figure 14.6.1).

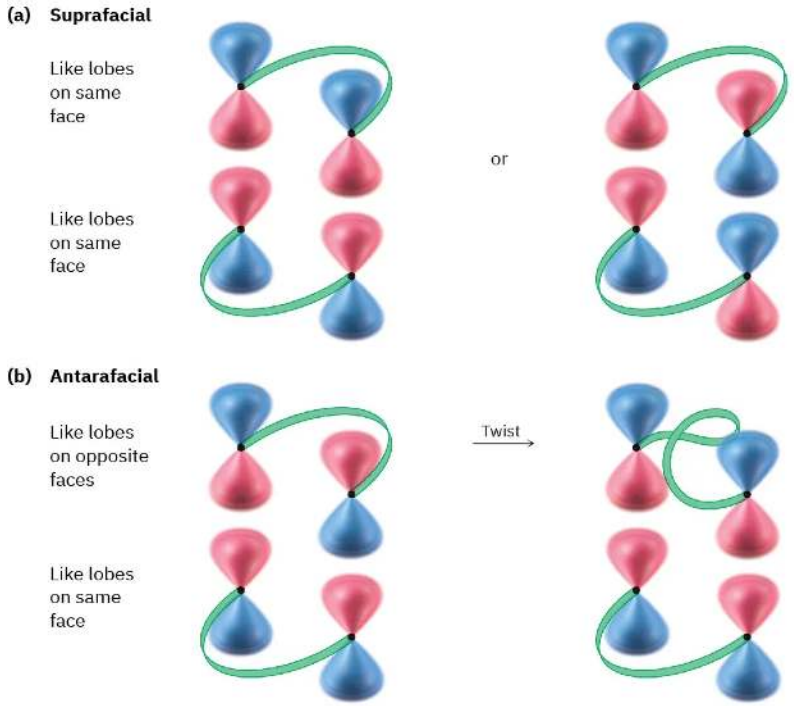


Figure 14.6.1: (a) Suprafacial cycloaddition occurs when there is bonding between lobes on the same face of one reactant and lobes on the same face of the other reactant. (b) Antarafacial cycloaddition occurs when there is bonding between lobes on the same face of one reactant and lobes on opposite faces of the other, which requires a twist in one π system.

Note that both suprafacial and antarafacial cycloadditions are symmetry-allowed. Geometric constraints often make antarafacial reactions difficult, however, because there must be a twisting of the π orbital system in one of the reactants. Thus, suprafacial cycloadditions are much more common for small π systems.

This page titled 14.6: Cycloaddition Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **30.5: Cycloaddition Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

14.7: Stereochemistry of Cycloadditions

How can we predict whether a given cycloaddition reaction will occur with suprafacial or with antarafacial geometry? According to frontier orbital theory, a cycloaddition reaction takes place when a bonding interaction occurs between the HOMO of one reactant and the LUMO of the other. An intuitive explanation of this rule is to imagine that one reactant donates electrons to the other. As with electrocyclic reactions, it's the electrons in the HOMO of the first reactant that are least tightly held and most likely to be donated. Of course when the second reactant accepts those electrons, they must go into a vacant, unoccupied orbital—the LUMO.

For a [4 + 2] cycloaddition (Diels–Alder reaction), let's arbitrarily select the diene LUMO and the alkene HOMO. The symmetries of the two ground-state orbitals are such that bonding of the terminal lobes can occur with suprafacial geometry (Figure 14.7.1), so the Diels–Alder reaction takes place readily under thermal conditions. Note that, as with electrocyclic reactions, we need be concerned only with the terminal lobes. For purposes of prediction, interactions among the interior lobes need not be considered.

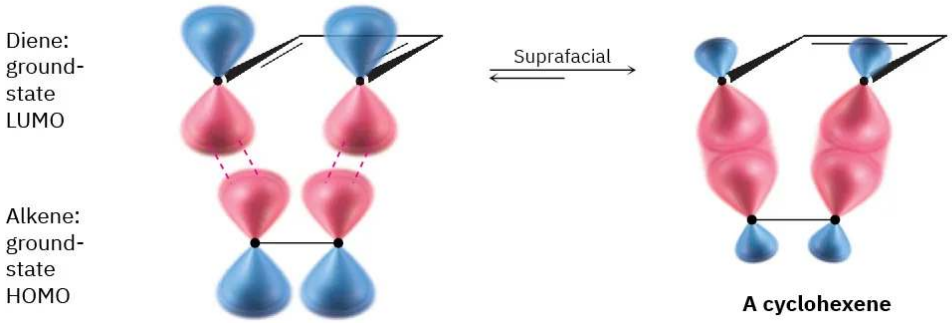


Figure 14.7.1: Interaction of diene LUMO and alkene HOMO in a suprafacial [4 + 2] cycloaddition reaction (Diels–Alder reaction).

In contrast with the thermal [4 + 2] Diels–Alder reaction, the [2 + 2] cycloaddition of two alkenes to yield a cyclobutane can only occur photochemically. The explanation for this follows from orbital-symmetry arguments. Looking at the ground-state HOMO of one alkene and the LUMO of the second alkene, it's apparent that a thermal [2 + 2] cycloaddition must take place by an antarafacial pathway (Figure 14.7.2a). Geometric constraints make the antarafacial transition state difficult, however, and so concerted thermal [2 + 2] cycloadditions are not observed.

In contrast with the thermal process, photochemical [2 + 2] cycloadditions *are* observed. Irradiation of an alkene with UV light excites an electron from ψ_1, the ground-state HOMO, to ψ_2*, which becomes the excited-state HOMO. Interaction between the excited-state HOMO of one alkene and the LUMO of the second alkene allows a photochemical [2 + 2] cycloaddition reaction to occur by a suprafacial pathway (Figure 14.7.2*b*).

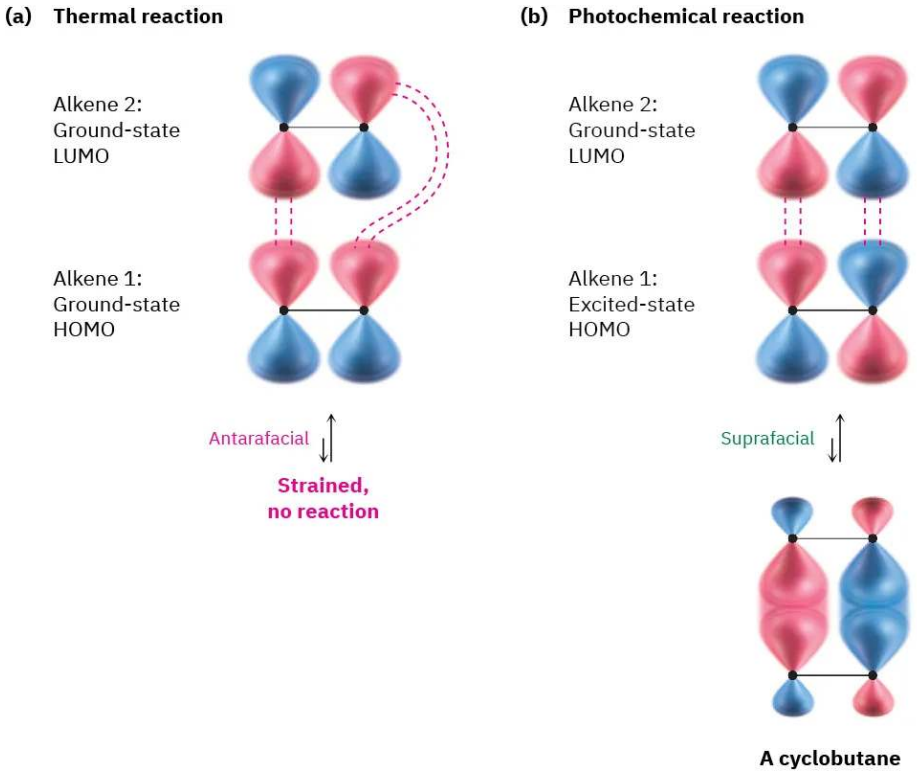
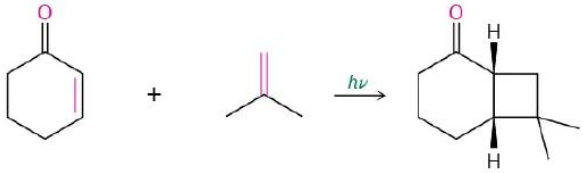


Figure 14.7.2: (a) Interaction of a ground-state HOMO and a ground-state LUMO in a potential [2 + 2] cycloaddition does not occur thermally because the antarafacial geometry is too strained. (b) Interaction of an excited-state HOMO and a ground-state LUMO in a photochemical [2 + 2] cycloaddition reaction is less strained, however, and occurs with suprafacial geometry.

The photochemical [2 + 2] cycloaddition reaction occurs smoothly, particularly with α,β-unsaturated carbonyl compounds, and represents one of the best methods known for synthesizing cyclobutane rings. For example:



2-Cyclohexenone **2-Methylpropene** **(40%)**

Thermal and photochemical cycloaddition reactions always take place with opposite stereochemistry. As with electrocyclic reactions, we can categorize cycloadditions according to the total number of electron pairs (double bonds) involved in the rearrangement. Thus, a thermal [4 + 2] Diels–Alder reaction between a diene and a dienophile involves an odd number (three) of electron pairs and takes place by a suprafacial pathway. A thermal [2 + 2] reaction between two alkenes involves an even number (two) of electron pairs and must take place by an antarafacial pathway. For photochemical cyclizations, these selectivities are reversed. These general rules are given in Table 14.7.1.

Table 14.7.1: Stereochemical Rules for Cycloaddition Reactions

Electron pairs (double bonds)	Thermal reaction	Photochemical reaction
Even number	Antarafacial	Suprafacial
Odd number	Suprafacial	Antarafacial

Exercise 14.7.1

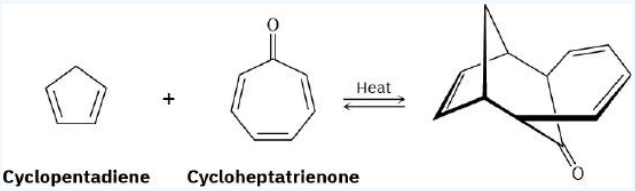
What stereochemistry would you expect for the product of the Diels–Alder reaction between (2*E*,4*E*)-2,4-hexadiene and ethylene? What stereochemistry would you expect if (2*E*,4*Z*)-2,4-hexadiene were used instead?

Answer

cis-3,6-Dimethylcyclohexene; *trans*-3,6-dimethylcyclohexene

Exercise 14.7.2

1,3-Cyclopentadiene reacts with cycloheptatrienone to give the product shown. Tell what kind of reaction is involved, and explain the observed result. Is the reaction suprafacial or antarafacial?



Answer

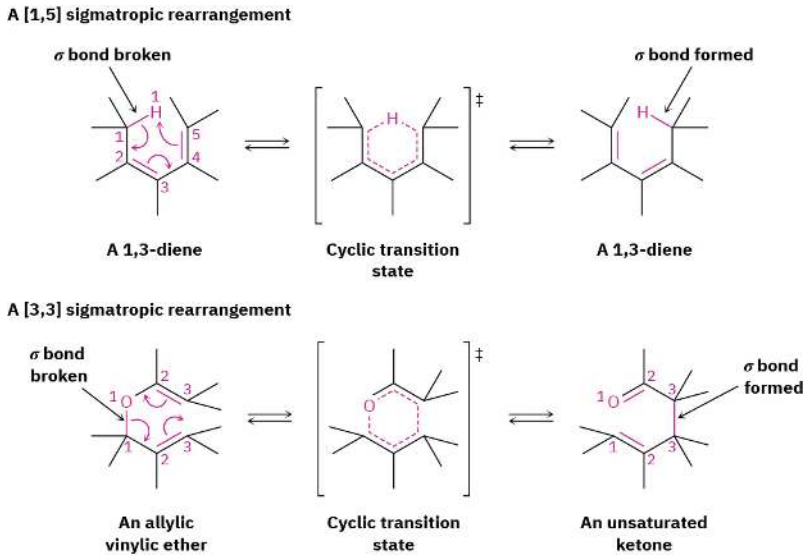
A [6 + 4] suprafacial cycloaddition

This page titled 14.7: Stereochemistry of Cycloadditions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **30.6: Stereochemistry of Cycloadditions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

14.8: Sigmatropic Rearrangements

A sigmatropic rearrangement, the third general kind of pericyclic reaction, is a process in which a σ-bonded substituent atom or group migrates across a π electron system from one position to another. A σ bond is broken in the reactant, the π bonds move, and a new σ bond is formed in the product. The σ-bonded group can be either at the end or in the middle of the π system, as the following [1,5] and [3,3] rearrangements illustrate:



The notations [1,5] and [3,3] describe the kind of rearrangement that is occurring. The numbers refer to the two groups connected by the σ bond in the reactant and designate the positions in those groups to which migration occurs. For example, in the [1,5] sigmatropic rearrangement of a 1,3-diene, the two groups connected by the σ bond are a hydrogen atom and a pentadienyl group. Migration occurs to position 1 of the H group (the only possibility) and to position 5 of the pentadienyl group. In the [3,3] rearrangement of an allylic vinylic ether, the two groups connected by the σ bond are an allylic group and the vinylic ether. Migration occurs to position 3 of the allylic group and also to position 3 of the vinylic ether.

Like electrocyclic reactions and cycloadditions, sigmatropic rearrangements are controlled by orbital symmetries. There are two possible modes of reaction: migration of a group across the same face of the π system is suprafacial, and migration of a group from one face of the π system to the other face is antarafacial (Figure 14.8.1).

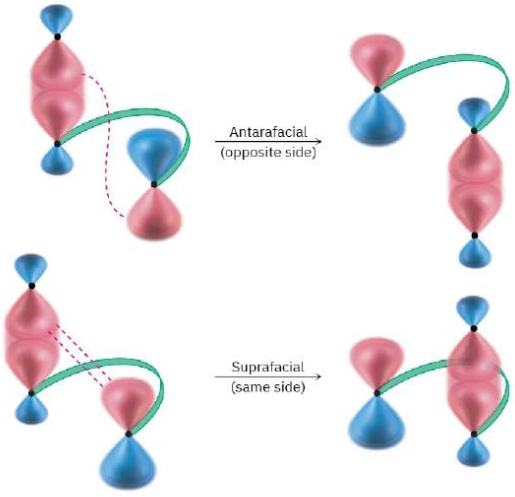


Figure 14.8.1: Suprafacial and antarafacial sigmatropic rearrangements.

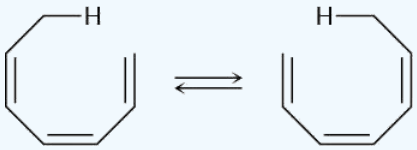
Both suprafacial and antarafacial sigmatropic rearrangements are symmetry-allowed, but suprafacial rearrangements are often easier for geometric reasons. The rules for sigmatropic rearrangements are identical to those for cycloaddition reactions (Table 14.8.1).

Table 14.8.1: Stereochemical Rules for Sigmatropic Rearrangements

Electron pairs (double bonds)	Thermal reaction	Photochemical reaction
Even number	Antarafacial	Suprafacial
Odd number	Suprafacial	Antarafacial

? Exercise 14.8.1

Classify the following sigmatropic reaction by order [*x*,*y*], and tell whether it will proceed with suprafacial or antarafacial stereochemistry:



Answer

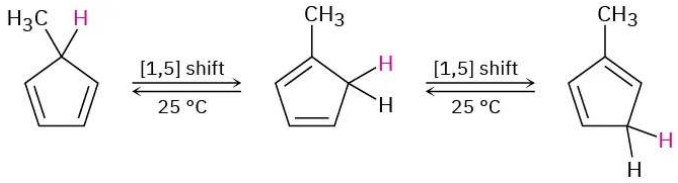
An antarafacial [1,7] sigmatropic rearrangement

This page titled 14.8: Sigmatropic Rearrangements is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

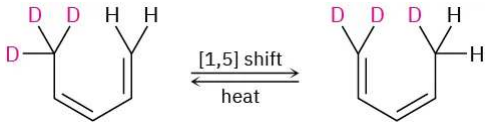
- **30.7: Sigmatropic Rearrangements** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

14.9: Some Examples of Sigmatropic Rearrangements

Because a [1,5] sigmatropic rearrangement involves three electron pairs (two π bonds and one σ bond), the orbital-symmetry rules in Table 30.3 predict a suprafacial reaction. In fact, the [1,5] suprafacial shift of a hydrogen atom across two double bonds of a π system is a commonly observed sigmatropic rearrangements. For example, 5-methyl-1,3-cyclopentadiene rapidly rearranges at room temperature to yield a mixture of 1-methyl-, 2-methyl-, and 5-methyl-isomers.



As another example, heating 5,5,5-trideuterio-(3*Z*)-1,3-pentadiene causes scrambling of deuterium between positions 1 and 5.



Both these [1,5] hydrogen shifts occur by a symmetry-allowed suprafacial pathway, as illustrated in Figure 14.9.1. In contrast with these thermal [1,5] sigmatropic hydrogen shifts, however, thermal [1,*3*] hydrogen shifts are unknown. If they were to occur, they would have to proceed by a strained antarafacial reaction pathway.

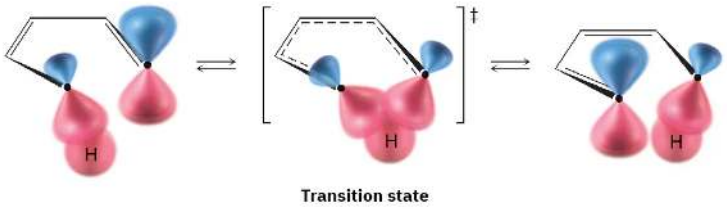
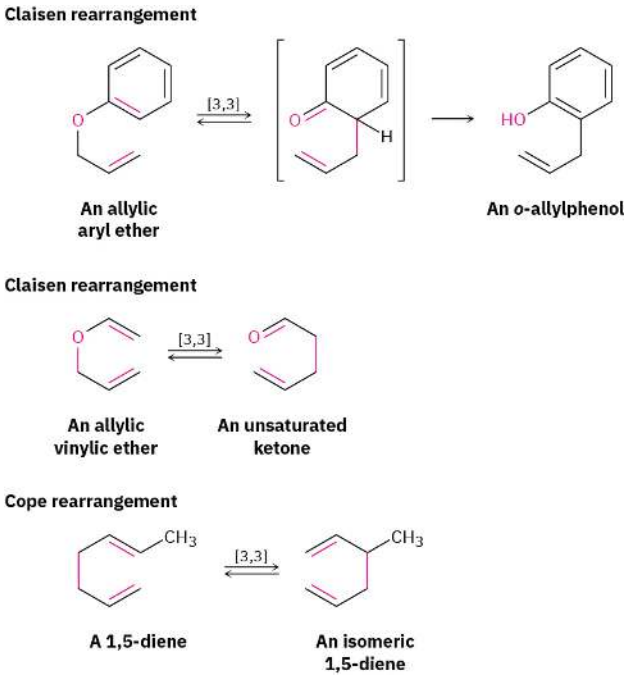


Figure 14.9.1: An orbital view of a suprafacial [1,5] hydrogen shift.

Two other important sigmatropic reactions are the **Claisen rearrangement** of either an allyl aryl ether ($H_2C{=}CHCH_2{-}O{-}$) or an allyl vinyl ($H_2C{=}CHCH_2{-}O{-}CH{=}$) ether, and the **Cope rearrangement** of a 1,5 hexadiene to an isomeric 1,5-diene. These two rearrangements, along with the Diels–Alder reaction, are among the most generally useful pericyclic reactions for organic synthesis. Thousands of examples of all three are known.



Like the Diels–Alder reaction discussed in Section 14.4 and Section 14.5, the Claisen rearrangement takes place in a single step through a pericyclic mechanism in which a reorganization of bonding electrons occurs in a six-membered, cyclic transition state. The 6-allyl-2,4-cyclohexadienone intermediate then isomerizes to *o*-allylphenol (Figure 14.9.2).

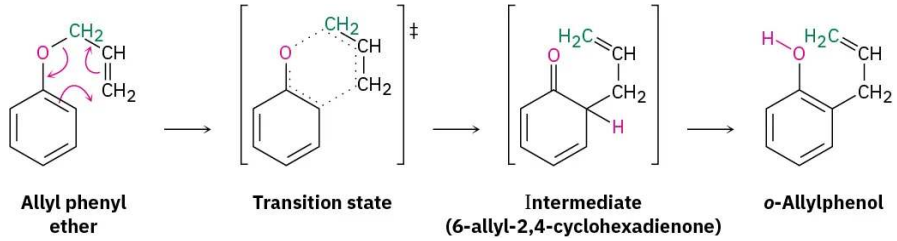


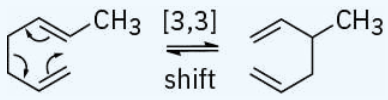
Figure 14.9.2: Mechanism of Claisen rearrangement. C─O bond-breaking and C─C bond-making occur simultaneously.

Evidence for this mechanism comes from the observation that the rearrangement takes place with transposition of the allyl group. That is, allyl phenyl ether containing a ^{14}C label on the allyl *ether* carbon atom yields *o*-allylphenol in which the label is on the *terminal* vinylic carbon (green in Figure 14.9.2).

? Exercise 14.9.1

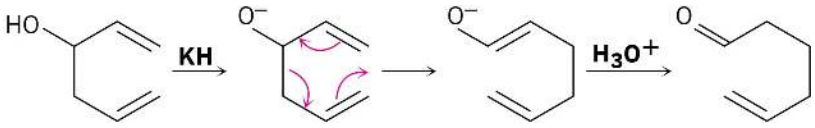
Draw a curved-arrow mechanism for the Cope arrangement just shown.

Answer



The Cope rearrangement that converts a 1,5-diene to an isomeric 1,5-diene is somewhat limited but a modification called the **Oxy Cope Rearrangement** is wider in scope. As shown in the following example, a 1-5 diene with an –OH next to the double bond can

be converted into an oxy-anion by reaction with a strong base such as potassium hydride (KH). A Cope rearrangement then occurs, and reaction with aqueous acid gives an enol that tautomerizes to an aldehyde.



Although biological examples of pericyclic reactions are relatively rare, a much-studied example occurs in bacteria during biosynthesis of the essential amino acid phenylalanine. Phenylalanine arises from the precursor chorismate through a Claisen rearrangement to prephenate, followed by decarboxylation to phenylpyruvate and reductive amination (Figure 14.9.4).

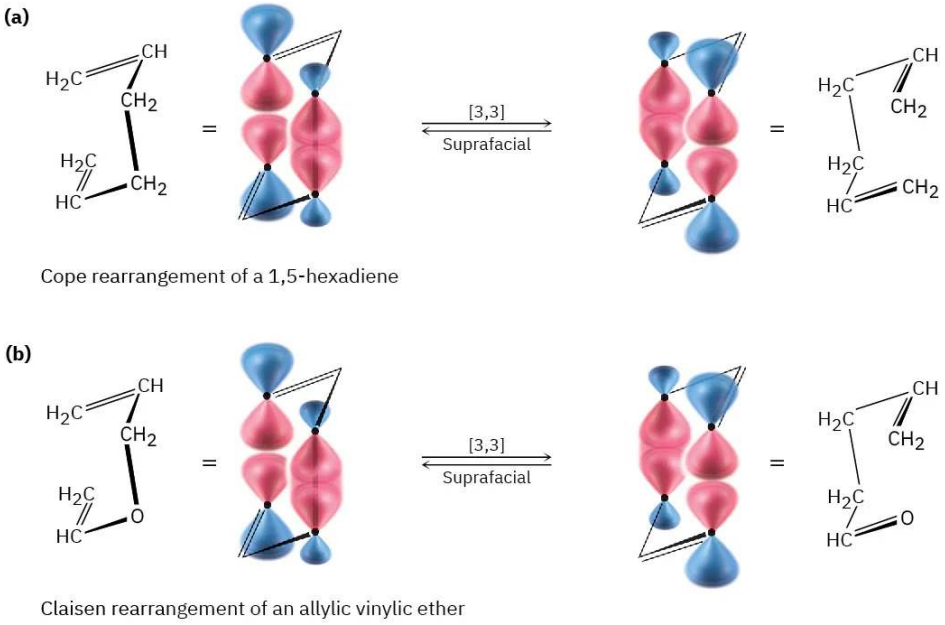


Figure 14.9.3: Suprafacial [3,3] **(a)** Cope and **(b)** Claisen rearrangements.

You might note that the reductive amination of phenylpyruvate is the exact reverse of the transamination process shown in Figure 29.17, by which amino acids are deaminated. In addition, the reductive amination of ketones is a standard method for preparing amines in the laboratory, as we saw in Section 24.6.

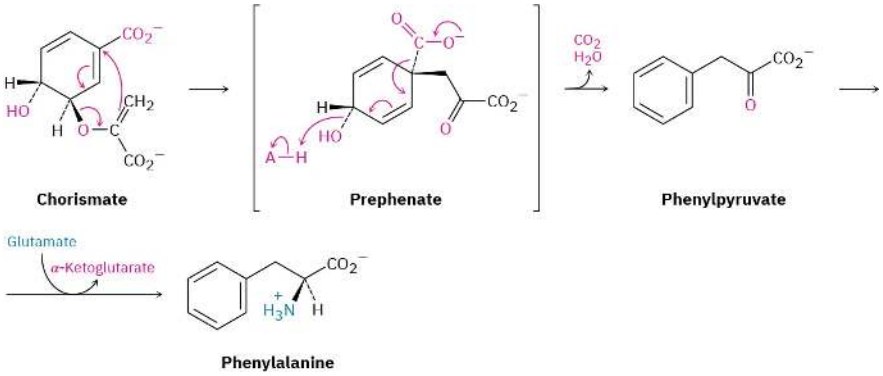
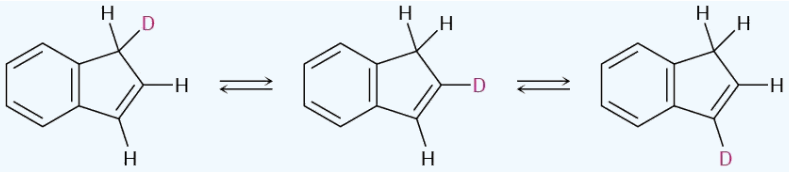


Figure 14.9.4: Pathway for the bacterial biosynthesis of phenylalanine from chorismate, involving a Claisen rearrangement.

? Exercise 14.9.3

Propose a mechanism to account for the fact that heating 1-deuterioindene scrambles the isotope label to all three positions on the five-membered ring.



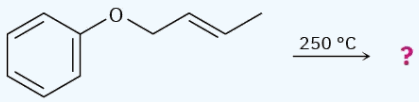
1-Deuterioindene

Answer

A series of [1,5] hydrogen shifts occur.

Exercise 14.9.4

What product would you expect from Claisen rearrangement of 2-butenyl phenyl ether?



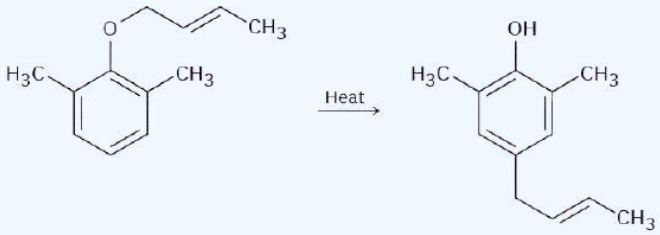
2-Butenyl phenyl ether

Answer

o-(1-Methylallyl)phenol

Exercise 14.9.1

When a 2,6-disubstituted allyl phenyl ether is heated in an attempted Claisen rearrangement, migration occurs to give the *p*-allyl product as the result of two sequential pericyclic reactions. Explain.



Answer

Claisen rearrangement is followed by a Cope rearrangement.

This page titled 14.9: Some Examples of Sigmatropic Rearrangements is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **30.8: Some Examples of Sigmatropic Rearrangements** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

14.10: A Summary of Rules for Pericyclic Reactions

How can you keep straight all the rules about pericyclic reactions? The summary in Table 30.1, Table 30.2, and Table 30.3 can be distilled into a mnemonic phrase that provides an easy way to predict the stereochemical outcome of any pericyclic reaction:

The Electrons Circle Around (TECA)

Thermal reactions with an **E**ven number of electron pairs are **C**onrotatory or **A**ntarafacial.

A change either from thermal to photochemical or from an even to an odd number of electron pairs changes the outcome from conrotatory/antarafacial to disrotatory/suprafacial. A change from both thermal and even to photochemical and odd causes no change because two negatives make a positive.

These selection rules are summarized in 14.10.1; knowing them gives you the ability to predict the stereochemistry of literally thousands of pericyclic reactions.

Table 14.10.1: Stereochemical Rules for Pericyclic Reactions

Electronic state	Electron pairs	Stereochemistry
Ground state (thermal)	Even number Odd number	Antara–con Supra–dis
Excited state (photochemical)	Even number Odd number	Supra–dis Antara–con

Exercise 14.10.1

Predict the stereochemistry of the following pericyclic reactions:

a. The thermal cyclization of a conjugated tetraene
b. The photochemical cyclization of a conjugated tetraene
c. A photochemical [4 + 4] cycloaddition
d. A thermal [2 + 6] cycloaddition
e. A photochemical [3,5] sigmatropic rearrangement

Answer

a. Conrotatory
b. Disrotatory
c. Suprafacial
d. Antarafacial
e. Suprafacial

This page titled 14.10: A Summary of Rules for Pericyclic Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **30.9: A Summary of Rules for Pericyclic Reactions** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

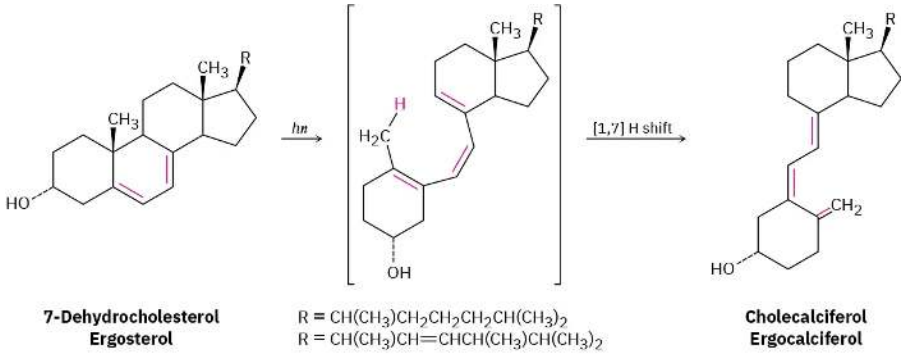
14.11: Chemistry Matters—Vitamin D, the Sunshine Vitamin

Vitamin D, discovered in 1918, is a general name for two related compounds, **cholecalciferol** (vitamin D_3) and **ergocalciferol** (vitamin D_2). Both are derived from steroids (Section 27.6) and differ only in the nature of the hydrocarbon side chain attached to the five-membered ring. Cholecalciferol comes primarily from dairy products and fish; ergocalciferol comes from some vegetables.

Figure 14.11.1: Here are the sunbathers, again, with their chemical work complete. (credit: "Tanning" by Meraj Chhaya/Flickr, CC BY 2.0)

The function of vitamin D in the body is to control the calcification of bones by increasing intestinal absorption of calcium. When sufficient vitamin D is present, approximately 30% of ingested calcium is absorbed, but in the absence of vitamin D, calcium absorption falls to about 10%. A deficiency of vitamin D thus leads to poor bone growth and to the diseases *rickets* in children and *osteoporosis* in adults.

Actually, neither vitamin D_2 nor D_3 is present in foods. Rather, foods contain the precursor molecules 7-dehydrocholesterol and ergosterol. In the presence of sunlight, both precursors are converted in the outer, epidermal layer of skin to the active vitamins, hence the nickname for vitamin D, the "sunshine vitamin."



Pericyclic reactions are unusual in living organisms, and the photochemical synthesis of vitamin D is one of only a few well-studied examples. The reaction takes place in two steps, an electrocyclic ring-opening of a cyclohexadiene to yield an open-chain hexatriene, followed by a sigmatropic [1,7] H shift to yield an isomeric hexatriene. Only the initial electrocyclic ring-opening requires irradiation by so-called UVB light of 295 to 300 nm wavelength. The subsequent sigmatropic [1,7] H shift occurs spontaneously by a thermal isomerization.

Following synthesis under the skin, further metabolic processing of cholecalciferol and ergocalciferol in the liver and kidney introduces two additional –OH groups to give the active forms of the vitamin, calcitriol and ergocalcitriol.

This page titled 14.11: Chemistry Matters—Vitamin D, the Sunshine Vitamin is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **30.10: Chemistry Matters—Vitamin D, the Sunshine Vitamin** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

https://chem.libretexts.org/@go/page/564372

14.12: Key Terms

- antarafacial
- conrotatory
- cycloaddition reaction
- disrotatory
- electrocyclic reaction
- frontier orbitals
- highest occupied molecular orbital (HOMO)
- lowest unoccupied molecular orbital (LUMO)
- pericyclic reaction
- photochemical reaction
- sigmatropic rearrangement
- suprafacial
- symmetry-allowed
- symmetry-disallowed

This page titled 14.12: Key Terms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **30.11: Key Terms** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

14.13: Summary

A **pericyclic reaction** takes place in a single step through a cyclic transition state without intermediates. There are three major classes of pericyclic processes: electrocyclic reactions, cycloaddition reactions, and sigmatropic rearrangements. The stereochemistry of these reactions is controlled by the symmetry of the orbitals involved in bond reorganization.

Electrocyclic reactions involve the cyclization of conjugated acyclic polyenes. For example, 1,3,5-hexatriene cyclizes to 1,3-cyclohexadiene on heating. Electrocyclic reactions can occur by either **conrotatory** or **disrotatory** pathways, depending on the symmetry of the terminal lobes of the π system. Conrotatory cyclization requires that both lobes rotate in the same direction, whereas disrotatory cyclization requires that the lobes rotate in opposite directions. The reaction course in a specific case can be found by looking at the symmetry of the **highest occupied molecular orbital (HOMO)**.

Cycloaddition reactions are those in which two unsaturated molecules add together to yield a cyclic product. For example, Diels–Alder reaction between a diene (four π electrons) and a dienophile (two π electrons) yields a cyclohexene. Cycloadditions can take place either by **suprafacial** or **antarafacial** pathways. Suprafacial cycloaddition involves interaction between lobes on the same face of one component and on the same face of the second component. Antarafacial cycloaddition involves interaction between lobes on the same face of one component and on opposite faces of the other component. The reaction course in a specific case can be found by looking at the symmetry of the HOMO of one component and the **lowest unoccupied molecular orbital (LUMO)** of the other.

Sigmatropic rearrangements involve the migration of a σ-bonded group across a π electron system. For example, Claisen rearrangement of an allylic vinylic ether yields an unsaturated carbonyl compound, and Cope rearrangement of a 1,5-hexadiene yields an isomeric 1,5-hexadiene. Sigmatropic rearrangements can occur with either suprafacial or antarafacial stereochemistry; the selection rules for a given case are the same as those for cycloaddition reactions.

The stereochemistry of any pericyclic reaction can be predicted by counting the total number of electron pairs (bonds) involved in bond reorganization and then applying the mnemonic "**T**he **E**lectrons **C**ircle **A**round." That is, **thermal** (ground-state) reactions involving an even number of electron pairs occur with either conrotatory or antarafacial stereochemistry. Exactly the opposite rules apply to **photochemical** (excited-state) reactions.

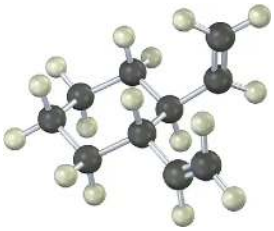
This page titled 14.13: Summary is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **30.12: Summary** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

14.14: Additional Problems

Visualizing Chemistry

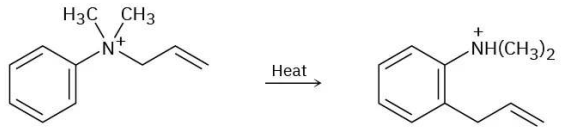
PROBLEM 30.13 Predict the product obtained when the following substance is heated:



PROBLEM 30.14 The ^{13}C NMR spectrum of homotropilidene taken at room temperature shows only three peaks. Explain.

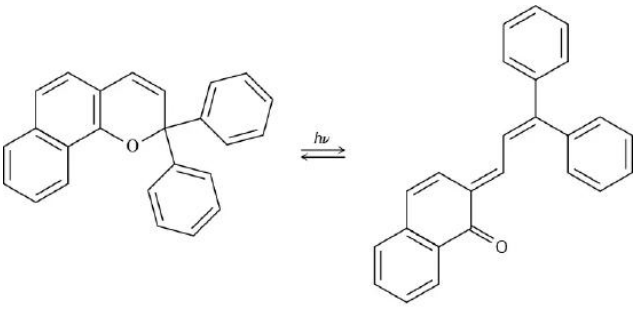
Mechanism Problems

PROBLEM 30.15 The following rearrangement of *N*-allyl-*N*,*N*-dimethylanilinium ion has been observed. Propose a mechanism.



***N*-Allyl-*N*,*N*-dimethylanilinium ion** **o-Allyl-*N*,*N*-dimethylanilinium ion**

PROBLEM 30.16 Plastic photochromic sunglasses are based on the following reversible rearrangement of a dye inside the lenses that occurs when the lenses are exposed to sunlight. The original dye absorbs UV light but not visible light and is thus colorless, while the rearrangement product absorbs visible light and is thus darkened.

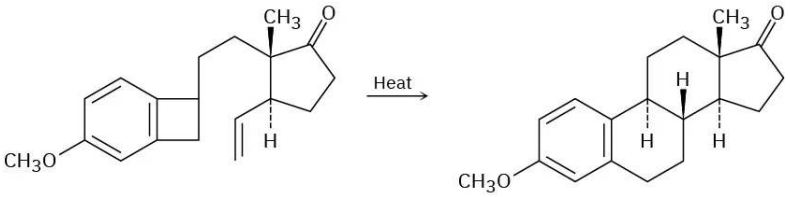


(Colorless) **(Dark)**

(a) Show the mechanism of the rearrangement.

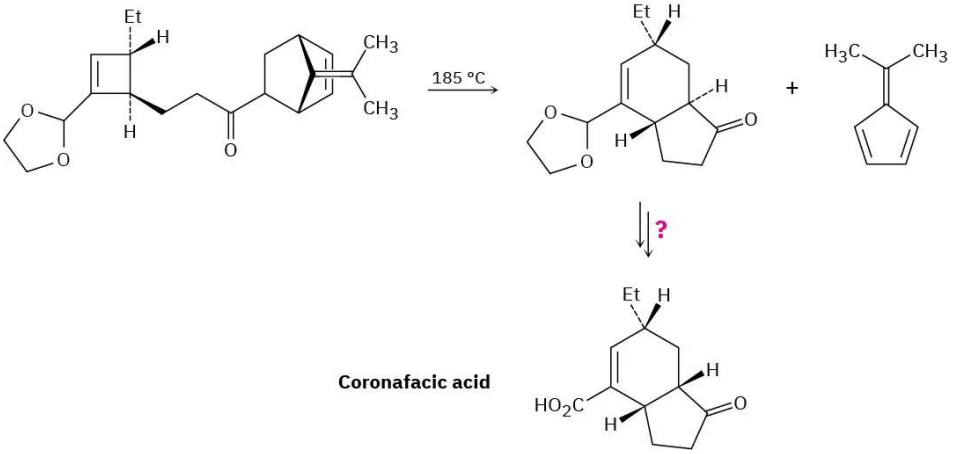
(b) Why does the rearrangement product absorb at a longer wavelength (visible light) than the original dye (UV)?

PROBLEM 30.17 The sex hormone estrone has been synthesized by a route that involves the following step. Identify the pericyclic reactions involved, and propose a mechanism.



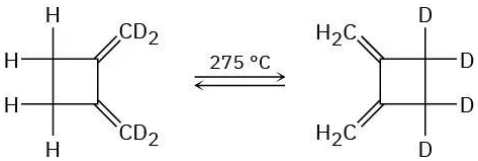
Estrone methyl ether

PROBLEM 30.18 Coronafacic acid, a bacterial toxin, was synthesized using a key step that involves three sequential pericyclic reactions. Identify them, and propose a mechanism for the overall transformation. How would you complete the synthesis?



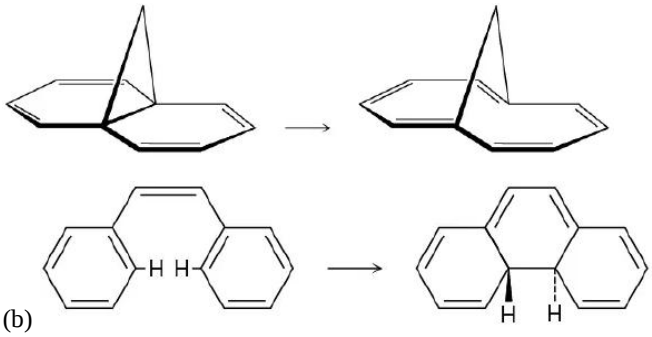
Coronafacic acid

PROBLEM 30.19 The following thermal rearrangement involves two pericyclic reactions in sequence. Identify them, and propose a mechanism to account for the observed result.



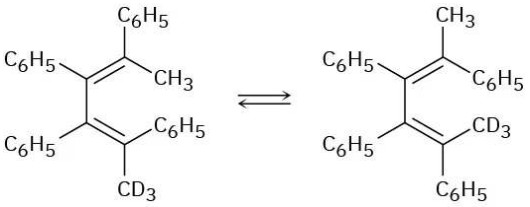
Electrocyclic Reactions

PROBLEM 30.20

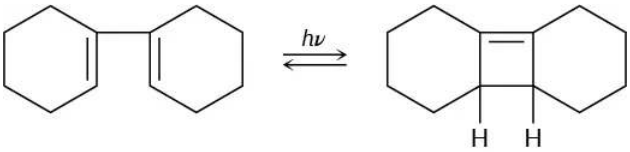


(b)

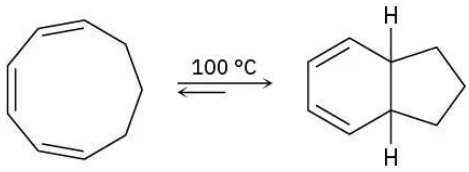
PROBLEM 30.21 The following thermal isomerization occurs under relatively mild conditions. Identify the pericyclic reactions involved, and show how the rearrangement occurs.



PROBLEM 30.22 Would you expect the following reaction to proceed in a conrotatory or disrotatory manner? Show the stereochemistry of the cyclobutene product, and explain your answer.



PROBLEM 30.23 Heating (1*Z*,3*Z*,5*Z*)-1,3,5-cyclononatriene to 100 °C causes cyclization and formation of a bicyclic product. Is the reaction conrotatory or disrotatory? What is the stereochemical relationship of the two hydrogens at the ring junctions, cis or trans?

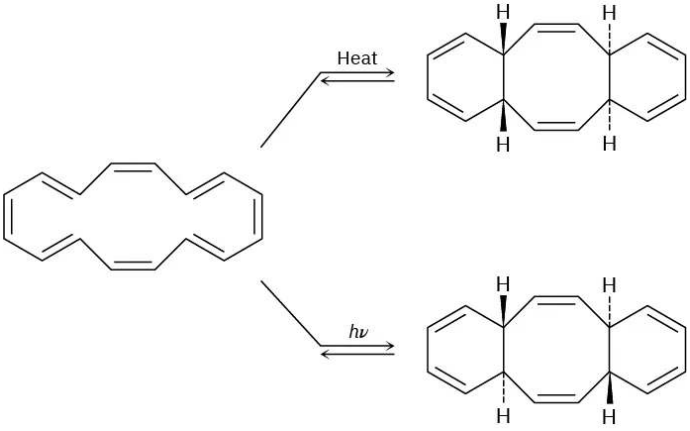


(1*Z*,3*Z*,5*Z*)-1,3,5-Cyclononatriene

PROBLEM 30.24 (2*E*,4*Z*,6*Z*,8*E*)-2,4,6,8-Decatetraene has been cyclized to give 7,8-dimethyl-1,3,5-cyclooctatriene. Predict the manner of ring-closure—conrotatory or disrotatory—for both thermal and photochemical reactions, and predict the stereochemistry of the product in each case.

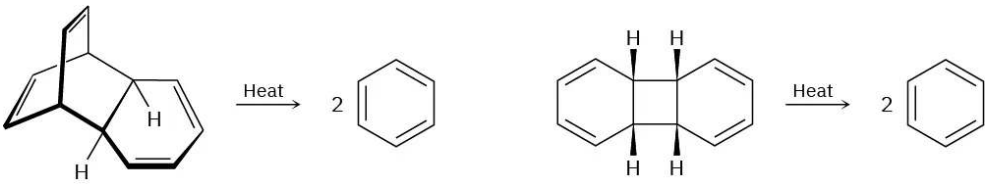
PROBLEM 30.25 Answer Problem 30-24 for the thermal and photochemical cyclizations of (2*E*,4*Z*,6*Z*,8*Z*)-2,4,6,8-decatetraene.

PROBLEM 30.26 The cyclohexadecaoctaene shown isomerizes to two different isomers, depending on reaction conditions. Explain the observed results, and indicate whether each reaction is conrotatory or disrotatory.

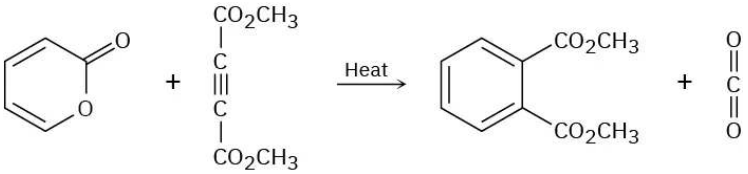


Cycloaddition Reactions

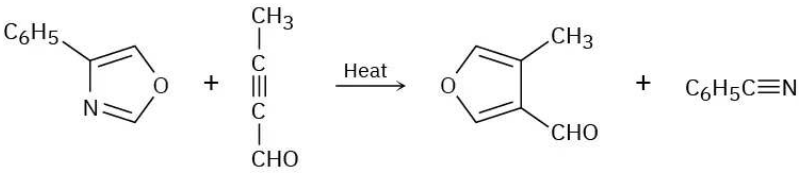
PROBLEM 30.27 Which of the following reactions is more likely to occur? Explain.



PROBLEM 30.28 The following reaction takes place in two steps, one of which is a cycloaddition while the other is a *reverse* cycloaddition. Identify the two pericyclic reactions, and show how they occur.

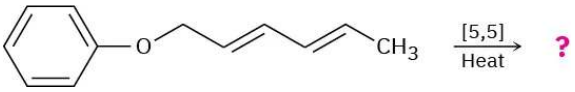


PROBLEM 30.29 Two sequential pericyclic reactions are involved in the following furan synthesis. Identify them, and propose a mechanism for the transformation.

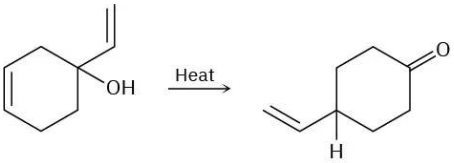


Sigmatropic Rearrangements

PROBLEM 30.30 Predict the product of the following pericyclic reaction. Is this [5,5] shift a suprafacial or an antarafacial process?



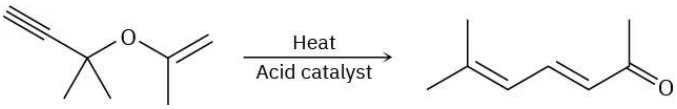
PROBLEM 30.31 Propose a pericyclic mechanism to account for the following transformation:



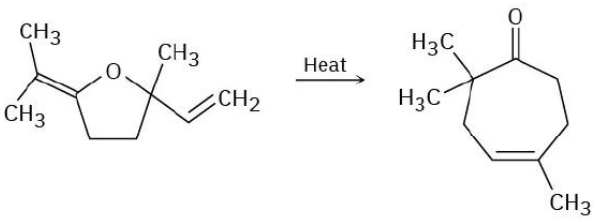
PROBLEM 30.32 Vinyl-substituted cyclopropanes undergo thermal rearrangement to yield cyclopentenes. Propose a mechanism for the reaction, and identify the pericyclic process involved.

Vinylcyclopropane **Cyclopentene**

PROBLEM 30.33 The following synthesis of dienones occurs readily. Propose a mechanism to account for the results, and identify the kind of pericyclic reaction involved.



PROBLEM 30.34 Karahanaenone, a terpenoid isolated from oil of hops, has been synthesized by the thermal reaction shown. Identify the kind of pericyclic reaction, and explain how karahanaenone is formed.



Karahanaenone

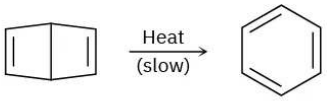
General Problems

PROBLEM 30.35

A photochemical [1,5] sigmatropic rearrangement

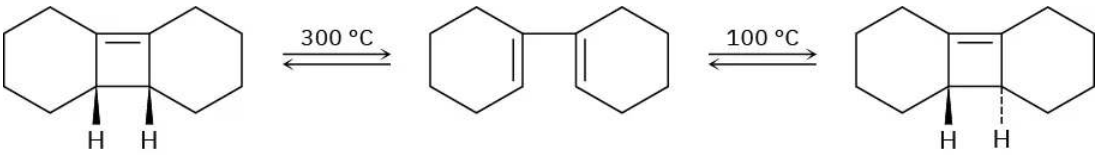
(b) A thermal [4 + 6] cycloaddition (c) A thermal [1,7] sigmatropic rearrangement (d) A photochemical [2 + 6] cycloaddition

PROBLEM 30.36 Bicyclohexadiene, also known as *Dewar benzene*, is extremely stable despite the fact that its rearrangement to benzene is energetically favored. Explain why the rearrangement is so slow.

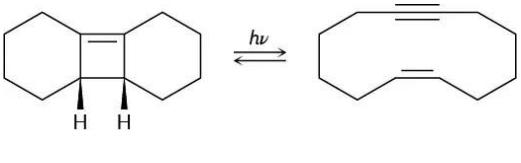


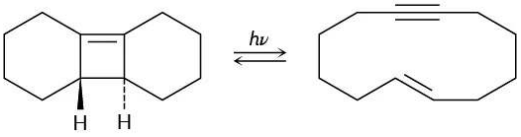
Dewar benzene **Benzene**

PROBLEM 30.37 Ring-opening of the *trans*-cyclobutene isomer shown takes place at much lower temperature than a similar ring-opening of the *cis*-cyclobutene isomer. Explain the temperature effect, and identify the stereochemistry of each reaction as either conrotatory or disrotatory.

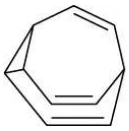


PROBLEM 30.38 Photolysis of the *cis*-cyclobutene isomer in Problem 30-37 yields *cis*-cyclododecaen-7-yne, but photolysis of the trans isomer yields *trans*-cyclododecaen-7-yne. Explain these results, and identify the type and stereochemistry of the pericyclic reaction.



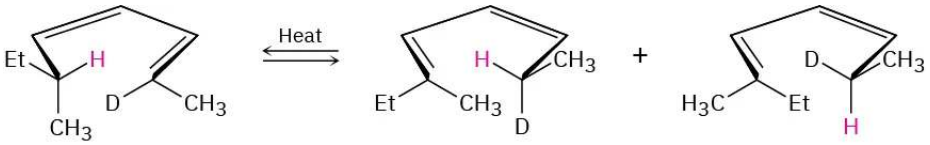


PROBLEM 30.39 The ^{1}H NMR spectrum of bullvalene at 100 °C consists only of a single peak at 4.22 δ. Explain.

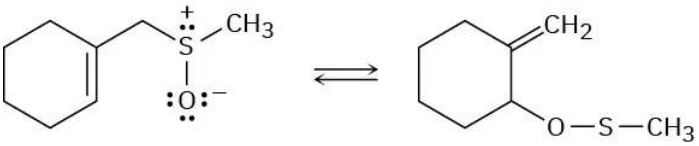


Bullvalene

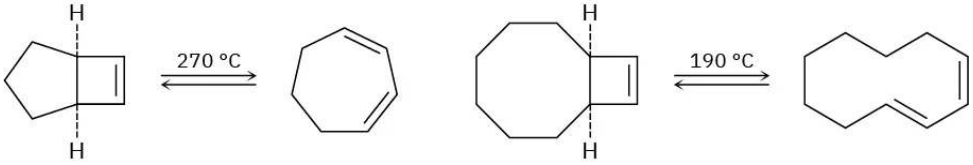
PROBLEM 30.40 The following rearrangement was devised and carried out to prove the stereochemistry of [1,5] sigmatropic hydrogen shifts. Explain how the observed result confirms the predictions of orbital symmetry.



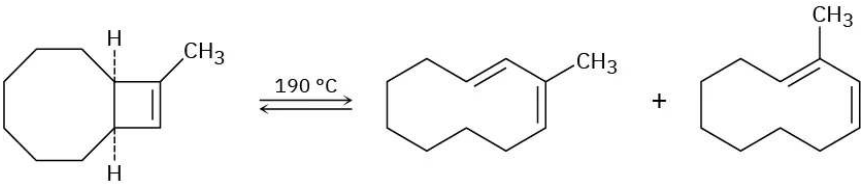
PROBLEM 30.41 The following reaction is an example of a [2,3] sigmatropic rearrangement. Would you expect the reaction to be suprafacial or antarafacial? Explain.



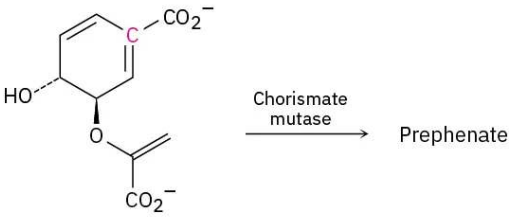
PROBLEM 30.42 When the compound having a cyclobutene fused to a five-membered ring is heated, (1*Z*,3*Z*)-1,3-cycloheptadiene is formed. When the related compound having a cyclobutene fused to an eight-membered ring is heated, however, (1*E*,3*Z*)-1,3-cyclodecadiene is formed. Explain these results, and suggest a reason why opening of the eight-membered ring occurs at a lower temperature.



PROBLEM 30.43 In light of your answer to Problem 30-42, explain why a mixture of products occurs in the following reaction:

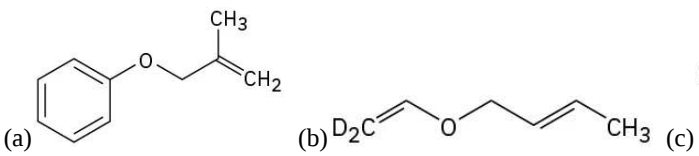


PROBLEM 30.44 In nature, the enzyme chorismate mutase catalyzes a Claisen rearrangement of chorismate that involves both the terminal double bond and the double bond with the highlighted carbon. What is the structure of prephenate, the biological precursor to the amino acids phenylalanine and tyrosine?



Chorismate

PROBLEM 30.45 Predict the product(s) if the starting materials underwent a Claisen rearrangement. Draw arrows to illustrate the rearrangement of electrons.



https://chem.libretexts.org/@go/page/564375

This page titled 14.14: Additional Problems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by OpenStax via source content that was edited to the style and standards of the LibreTexts platform.

- **30.13: Additional Problems** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

Index

A

acetals
8.11: Nucleophilic Addition of Alcohols - Acetal Formation
acetyl group
8.2: Naming Aldehydes and Ketones
acid anhydrides
10.6: Chemistry of Acid Anhydrides
acid halides
10.5: Chemistry of Acid Halides
acyl group
5.4: Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction
acyl phosphates
10.9: Chemistry of Thioesters and Acyl Phosphates - Biological Carboxylic Acid Derivatives
acylation
5.1: Why This Chapter?
alcohol
6.1: Why This Chapter?
alcoholysis
10.5: Chemistry of Acid Halides
aldol
12.2: Carbonyl Condensations - The Aldol Reaction
aldol reaction
12.2: Carbonyl Condensations - The Aldol Reaction
aldolases
12.14: Some Biological Carbonyl Condensation Reactions
alkoxymercuration
7.3: Preparing Ethers
alkylation
5.1: Why This Chapter?
Allylic Carbocations
3.3: Electrophilic Additions to Conjugated Dienes- Allylic Carbocations
alpha bromination
11.5: Alpha Bromination of Carboxylic Acids
alpha cleavage
1.4: Mass Spectrometry of Some Common Functional Groups
6.12: Spectroscopy of Alcohols and Phenols
alpha position
11.1: Why This Chapter?
Alpha Substitutions
12.3: Carbonyl Condensations versus Alpha Substitutions
alpha-substitution reaction
11.1: Why This Chapter?
amide
8.13.1.4: Basicity of Amines
13.4: Basicity of Amines
amides
10.8: Chemistry of Amides
aminolysis
10.5: Chemistry of Acid Halides
aniline
8.13.1.5: Basicity of Arylamines
8.13.1.9: Reactions of Arylamines
13.5: Basicity of Arylamines
13.9: Reactions of Arylamines
antarafacial cycloaddition
14.6: Cycloaddition Reactions
arene
4.2: Naming Aromatic Compounds
arenediazonium salt
8.13.1.9: Reactions of Arylamines
13.9: Reactions of Arylamines
aromatic
4.1: Why This Chapter?
Aromatic Halogenation
5.3: Other Aromatic Substitutions
Aromatic Hydroxylation
5.3: Other Aromatic Substitutions
Aromatic Ions
4.5: Aromatic Ions
Aromatic Nitration
5.3: Other Aromatic Substitutions
Aromatic Sulfonation
5.3: Other Aromatic Substitutions
aroyl group
8.2: Naming Aldehydes and Ketones
arylamines
8.13.1.5: Basicity of Arylamines
8.13.1.9: Reactions of Arylamines
13.5: Basicity of Arylamines
13.9: Reactions of Arylamines
Arynes
5.12: Chemistry Matters—Combinatorial Chemistry
azide synthesis
8.13.1.7: Synthesis of Amines
13.7: Synthesis of Amines
azo compound
8.13.1.9: Reactions of Arylamines
13.9: Reactions of Arylamines

B

barbiturates
11.9: Chemistry Matters—Barbiturates
benzoyl group
8.2: Naming Aldehydes and Ketones
benzyl group
4.2: Naming Aromatic Compounds
benzylic oxidation
5.9: Oxidation of Aromatic Compounds
benzylic position
5.9: Oxidation of Aromatic Compounds
benzyne
5.8: Benzyne
5.12: Chemistry Matters—Combinatorial Chemistry
betaine
8.12: Nucleophilic Addition of Phosphorus Ylides- The Wittig Reaction
biomarkers
1.5: Mass Spectrometry in Biological - Time-of-flight (TOF) Instruments
Birch reduction
5.10: Reduction of Aromatic Compounds
bromination
5.2: Electrophilic Aromatic Substitution Reactions - Bromination
buffer
8.13.1.6: Biological Amines and the Henderson-Hasselbalch Equation
9.4: Biological Acids and the Henderson-Hasselbalch Equation
13.6: Biological Amines and the Henderson-Hasselbalch Equation

C

C13 NMR
2.12: Characteristics of ^{13}C NMR Spectroscopy
2.14: Uses of ^{13}C NMR Spectroscopy
Cannizzaro reaction
8.13: Biological Reductions
carbaldehyde
8.2: Naming Aldehydes and Ketones
carbocycles
4.6: Aromatic Heterocycles - Pyridine and Pyrrole
carbonyl condensation reaction
12.2: Carbonyl Condensations - The Aldol Reaction
Carbonyl Condensations
12.3: Carbonyl Condensations versus Alpha Substitutions
carboxylic acid derivatives
10.11: Spectroscopy of Carboxylic Acid Derivatives
carboxylic acids
9.2: Naming Carboxylic Acids and Nitriles
9.3: Structure and Properties of Carboxylic Acids
chain-growth polymer
10.10: Polyamides and Polyesters - Step-Growth Polymers
chemical shift
2.4: Chemical Shifts
2.5: Chemical Shifts in ^{1}H NMR Spectroscopy
chromophores
3.9: Interpreting Ultraviolet Spectra- The Effect of Conjugation
Claisen condensation
12.8: The Claisen Condensation Reaction
Claisen rearrangement
7.12: Summary
14.9: Some Examples of Sigmatropic Rearrangements
Claisen–Schmidt condensation
12.6: Mixed Aldol Reactions
combinatorial chemistry
5.12: Chemistry Matters—Combinatorial Chemistry
Conjugate Addition
8.14: Conjugate Nucleophilic Addition to α,β-Unsaturated Aldehydes and Ketones
conjugated diene
3.1: Why This Chapter?
Conjugated Dienes
3.2: Stability of Conjugated Dienes- Molecular Orbital Theory
conjugated double bonds
3.1: Why This Chapter?
conjugation
3.2: Stability of Conjugated Dienes- Molecular Orbital Theory
3.9: Interpreting Ultraviolet Spectra- The Effect of Conjugation
Conversion of Acid Chlorides into Alcohols
10.5: Chemistry of Acid Halides

Conversion of Acid Chlorides into Ketones
10.5: Chemistry of Acid Halides
Conversion of Acid Halides into Anhydrides
10.5: Chemistry of Acid Halides
Conversion of Acid Halides into Carboxylic Acids
10.5: Chemistry of Acid Halides
Conversion of Acid Halides into Esters
10.5: Chemistry of Acid Halides
Conversion of Carboxylic Acids into Acid Anhydrides
10.4: Reactions of Carboxylic Acids
Conversion of Carboxylic Acids into Acid Chlorides
10.4: Reactions of Carboxylic Acids
Conversion of Carboxylic Acids into Esters
10.4: Reactions of Carboxylic Acids
Cope rearrangement
14.9: Some Examples of Sigmatropic Rearrangements
coupling constant
2.7: Spin-Spin Splitting in ¹H NMR Spectra
Crossed Claisen reactions
12.9: Mixed Claisen Condensations
crown ether
7.7: Crown Ethers
Curtius rearrangement
8.13.1.7: Synthesis of Amines
13.7: Synthesis of Amines
cyclic ethers
7.1: Why This Chapter?
7.5: Cyclic Ethers - Epoxides
cycloaddition
14.7: Stereochemistry of Cycloadditions
cyclobutadienyl ring
4.4: Aromaticity and the Hückel 4n + 2 Rule
cyclopentadiene ion
4.5: Aromatic Ions
cyclopentadienyl ring
4.4: Aromaticity and the Hückel 4n + 2 Rule
cyclopropenyl ring
4.4: Aromaticity and the Hückel 4n + 2 Rule

D

D2O shake
6.12: Spectroscopy of Alcohols and Phenols
degenerate
4.3: Structure and Stability of Benzene
dehydration
6.12: Spectroscopy of Alcohols and Phenols
delta scale
2.4: Chemical Shifts
DEPT
2.13: DEPT ¹³C NMR Spectroscopy
Dess-Martin periodinane
6.8: Oxidation of Alcohols
Dess–Martin periodinane
8.3: Preparing Aldehydes and Ketones
diamagnetic anisotropy
4.8: Spectroscopy of Aromatic Compounds
diastereotopic
2.8: ¹H NMR Spectroscopy and Proton Equivalence
diazotization reaction
8.13.1.9: Reactions of Arylamines
13.9: Reactions of Arylamines
Dieckmann Cyclization
12.10: Intramolecular Claisen Condensations - The Dieckmann Cyclization
diene
3.1: Why This Chapter?
dienophile
3.6: Characteristics of the Diels-Alder Reaction
14.6: Cycloaddition Reactions
dimerization
3.6: Characteristics of the Diels-Alder Reaction
Diorganocopper Reaction
10.5: Chemistry of Acid Halides
Distortions Enhancement by Polarization Transfer
2.13: DEPT ¹³C NMR Spectroscopy
disubstituted benzenes
4.2: Naming Aromatic Compounds
doublet
2.7: Spin-Spin Splitting in ¹H NMR Spectra
downfield
2.4: Chemical Shifts
drift tube
1.5: Mass Spectrometry in Biological - Time-of-flight (TOF) Instruments

E

electrocyclic reactions
14.3: Electrocyclic Reactions
electromagnetic spectrum
1.6: Spectroscopy and the Electromagnetic Spectrum
Electrophilic Aromatic Substitution Reactions
5.2: Electrophilic Aromatic Substitution Reactions - Bromination
electrophilic substitution
5.1: Why This Chapter?
electrophilic substitutions
5.5: Substituent Effects in Electrophilic Substitutions
enamines
8.9: Nucleophilic Addition of Amines- Imine and Enamine Formation
12.12: Carbonyl Condensations with Enamines - The Stork Enamine Reaction
enantioselective synthesis
8.16: Chemistry Matters—Enantioselective Synthesis
enantiotopic
2.8: ¹H NMR Spectroscopy and Proton Equivalence
enol
6.1: Why This Chapter?
11.2: Keto-Enol Tautomerism
enolate ion
11.2: Keto-Enol Tautomerism
enone
3.1: Why This Chapter?
enones
12.4: Dehydration of Aldol Products - Synthesis of Enones
epoxides
7.5: Cyclic Ethers - Epoxides
esters
10.7: Chemistry of Esters
ether
7.1: Why This Chapter?
ethers
7.2: Names and Properties of Ethers

F

fermentation
6.1: Why This Chapter?
fingerprint region
1.8: Interpreting Infrared Spectra
Fremy’s salt
6.11: Reactions of Phenols
frontier molecular orbital theory
14.2: Molecular Orbitals of Conjugated Pi Systems

G

Gabriel synthesis
8.13.1.7: Synthesis of Amines
13.7: Synthesis of Amines
gem diols
8.6: Nucleophilic Addition of Water- Hydration
geminal diols
8.6: Nucleophilic Addition of Water- Hydration
glutathione
7.8: Thiols and Sulfides
Grignard reagents
6.6: Alcohols from Carbonyl Compounds - Grignard Reagents

H

Hückel's rule
4.4: Aromaticity and the Hückel 4n + 2 Rule
haloform reaction
11.7: Reactivity of Enolate Ions
halogenation
5.1: Why This Chapter?
hemiacetal
8.11: Nucleophilic Addition of Alcohols - Acetal Formation
heterocycles
4.6: Aromatic Heterocycles - Pyridine and Pyrrole
Hofmann Elimination
8.13.1.8: Reactions of Amines
13.8: Reactions of Amines
Hofmann rearrangement
8.13.1.7: Synthesis of Amines
13.7: Synthesis of Amines
HOMO
14.2: Molecular Orbitals of Conjugated Pi Systems
HOMO–LUMO gap
14.2: Molecular Orbitals of Conjugated Pi Systems
homotopic
2.8: ¹H NMR Spectroscopy and Proton Equivalence
hydride ion
6.5: Alcohols from Carbonyl Compounds - Reduction
hydroquinone
6.11: Reactions of Phenols
hydroxylation
5.1: Why This Chapter?

I

imide
- 8.13.1.7: Synthesis of Amines
- 13.7: Synthesis of Amines

imines
- 8.9: Nucleophilic Addition of Amines- Imine and Enamine Formation

inductive effect
- 9.5: Substituent Effects on Acidity

Infrared Spectroscopy of Ethers
- 7.9: Spectroscopy of Ethers

infrared spectrum
- 1.7: Infrared Spectroscopy

intramolecular aldol reaction
- 12.7: Intramolecular Aldol Reactions

intramolecular claisen condensation
- 12.10: Intramolecular Claisen Condensations - The Dieckmann Cyclization

Ionic Liquids
- 8.13.1.12: Chemistry Matters - Green Chemistry II- Ionic Liquids
- 13.12: Chemistry Matters - Green Chemistry II- Ionic Liquids

ionophores
- 7.7: Crown Ethers

J

Jones Reagent
- 6.8: Oxidation of Alcohols

K

ketals
- 8.11: Nucleophilic Addition of Alcohols - Acetal Formation

keto
- 11.2: Keto-Enol Tautomerism

kinetic control
- 3.4: Kinetic vs. Thermodynamic Control of Reactions

L

lactone
- 10.7: Chemistry of Esters

LUMO
- 14.2: Molecular Orbitals of Conjugated Pi Systems

M

Magnetic resonance imaging
- 2.15: Chemistry Matters—Magnetic Resonance Imaging (MRI)

Malonic Ester Synthesis
- 11.8: Alkylation of Enolate Ions

mass spectra
- 1.3: Interpreting Mass Spectra

McLafferty rearrangement
- 1.4: Mass Spectrometry of Some Common Functional Groups
- 8.15: Spectroscopy of Aldehydes and Ketones

Meisenheimer complex
- 5.7: Nucleophilic Aromatic Substitution
- 5.8: Benzyne

mercaptans
- 7.8: Thiols and Sulfides

metabolism
- 12.15: Chemistry Matters - A Prologue to Metabolism

Michael addition
- 12.11: Conjugate Carbonyl Additions - The Michael Reaction

mixed aldol reactions
- 12.6: Mixed Aldol Reactions

molar absorptivity
- 3.8: Ultraviolet Spectroscopy

multiplet
- 2.7: Spin-Spin Splitting in ^{1}H NMR Spectra

N

naming amines
- 8.13.1.2: Naming Amines
- 13.2: Naming Amines

nitration
- 5.1: Why This Chapter?

nitriles
- 9.2: Naming Carboxylic Acids and Nitriles
- 9.8: Chemistry of Nitriles

nitrogen rule
- 1.4: Mass Spectrometry of Some Common Functional Groups
- 8.13.1.11: Spectroscopy of Amines
- 13.11: Spectroscopy of Amines

nitronium ion
- 5.3: Other Aromatic Substitutions

nuclear magnetic resonance
- 2.2: Nuclear Magnetic Resonance Spectroscopy

Nuclear Magnetic Resonance Spectroscopy of Ethers
- 7.9: Spectroscopy of Ethers

nucleophilic aromatic substitution
- 5.8: Benzyne

O

oxaphosphetane
- 8.12: Nucleophilic Addition of Phosphorus Ylides- The Wittig Reaction

oximes
- 8.9: Nucleophilic Addition of Amines- Imine and Enamine Formation

oxirane
- 7.5: Cyclic Ethers - Epoxides

oxymercuration
- 7.3: Preparing Ethers

P

PAH
- 4.7: Polycyclic Aromatic Compounds

pericyclic reaction
- 3.5: The Diels-Alder Cycloaddition Reaction

pericyclic reactions
- 14.10: A Summary of Rules for Pericyclic Reactions

phenol
- 6.1: Why This Chapter?
- 6.10: Phenols and Their Uses

phenyl group
- 4.2: Naming Aromatic Compounds

phosphorane
- 8.12: Nucleophilic Addition of Phosphorus Ylides- The Wittig Reaction

photolithography
- 3.11: Chemistry Matters—Photolithography

physiological pH
- 9.4: Biological Acids and the Henderson-Hasselbalch Equation

polyalkylation
- 5.4: Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction

polyamides
- 10.10: Polyamides and Polyesters - Step-Growth Polymers

polycyclic aromatic compounds
- 4.7: Polycyclic Aromatic Compounds

polycyclic aromatic hydrocarbons
- 4.7: Polycyclic Aromatic Compounds

polyene
- 3.1: Why This Chapter?

polyesters
- 10.10: Polyamides and Polyesters - Step-Growth Polymers

polysubstituted benzenes
- 5.11: Synthesis of Polysubstituted Benzenes

Preparation of Acid Halides
- 10.5: Chemistry of Acid Halides

protection groups
- 6.9: Protection of Alcohols

proteomics
- 1.5: Mass Spectrometry in Biological - Time-of-flight (TOF) Instruments

pyramidal inversion
- 8.13.1.3: Structure and Properties of Amines
- 13.3: Structure and Properties of Amines

Pyridine
- 4.6: Aromatic Heterocycles - Pyridine and Pyrrole

pyrimidine
- 4.6: Aromatic Heterocycles - Pyridine and Pyrrole

Pyrrole
- 4.6: Aromatic Heterocycles - Pyridine and Pyrrole
- 8.13.1.10: Heterocyclic Amines
- 13.10: Heterocyclic Amines

Q

quanta
- 1.6: Spectroscopy and the Electromagnetic Spectrum

quartet
- 2.7: Spin-Spin Splitting in ^{1}H NMR Spectra

quinones
- 6.11: Reactions of Phenols

R

Reactions of Acid Halides A type of functional group with an acyl group bonded to a halogen atom, RCOX.
- 10.5: Chemistry of Acid Halides

reductive amination
- 8.13.1.7: Synthesis of Amines
- 13.7: Synthesis of Amines

rhodopsin
- 3.10: Conjugation, Color, and the Chemistry of Vision

ring current
- 4.8: Spectroscopy of Aromatic Compounds

Robinson annulation reaction
- 12.13: The Robinson Annulation Reaction

S

Sandmeyer reaction
- 8.13.1.9: Reactions of Arylamines
- 13.9: Reactions of Arylamines

Sanger’s reagent
- 5.7: Nucleophilic Aromatic Substitution

saponification
- 10.7: Chemistry of Esters

Schiemann reaction
- 8.13.1.9: Reactions of Arylamines
- 13.9: Reactions of Arylamines

Schiff bases
- 8.9: Nucleophilic Addition of Amines- Imine and Enamine Formation

Sharpless epoxidation
- 8.16: Chemistry Matters—Enantioselective Synthesis

shielding
- 2.3: The Nature of NMR Absorptions

sigmatropic rearrangements
- 14.8: Sigmatropic Rearrangements
- 14.9: Some Examples of Sigmatropic Rearrangements

signal averaging
- 2.11: ^{13}C NMR Spectroscopy - Signal Averaging and FT-NMR

signal integration
- 2.6: Integration of ^{1}H NMR Absorptions- Proton Counting

spectroscopy
- 1.1: Why This Chapter?

steric effect
- 5.6: Trisubstituted Benzenes- Additivity of Effects

steric hindrance
- 5.6: Trisubstituted Benzenes- Additivity of Effects

Stork enamine reaction
- 12.12: Carbonyl Condensations with Enamines - The Stork Enamine Reaction

structure determination
- 1: Structure Determination - Mass Spectrometry and Infrared Spectroscopy

Substituent Effects
- 5.6: Trisubstituted Benzenes- Additivity of Effects

substitution reactions
- 4.3: Structure and Stability of Benzene

sulfa drug
- 8.13.1.9: Reactions of Arylamines
- 13.9: Reactions of Arylamines

sulfide
- 7.1: Why This Chapter?

sulfides
- 7.8: Thiols and Sulfides

sulfonation
- 5.1: Why This Chapter?

suprafacial cycloaddition
- 14.6: Cycloaddition Reactions

T

tautomerism
- 11.2: Keto-Enol Tautomerism

Theory of Conservation of Orbital Symmetry
- 14.2: Molecular Orbitals of Conjugated Pi Systems

thermal electrocyclic reactions
- 14.4: Stereochemistry of Thermal Electrocyclic Reactions

thermodynamic control
- 3.4: Kinetic vs. Thermodynamic Control of Reactions

thioesters
- 10.9: Chemistry of Thioesters and Acyl Phosphates - Biological Carboxylic Acid Derivatives

thiol
- 7.1: Why This Chapter?

thiols
- 7.8: Thiols and Sulfides

tree diagram
- 2.9: More Complex Spin-Spin Splitting Patterns

triplet
- 2.7: Spin-Spin Splitting in ^{1}H NMR Spectra

trisubstituted benzenes
- 5.7: Nucleophilic Aromatic Substitution

U

ubiquinone
- 6.11: Reactions of Phenols

ultraviolet spectroscopy
- 3.8: Ultraviolet Spectroscopy

upfield
- 2.4: Chemical Shifts

V

vision
- 3.10: Conjugation, Color, and the Chemistry of Vision

vitamin A
- 3.10: Conjugation, Color, and the Chemistry of Vision

vulcanization
- 3.7: Diene Polymers - Natural and Synthetic Rubbers

W

wavenumber
- 1.7: Infrared Spectroscopy

Williamson Ether Synthesis
- 7.3: Preparing Ethers

Wittig reaction
- 8.12: Nucleophilic Addition of Phosphorus Ylides- The Wittig Reaction

Wolff–Kishner reaction
- 8.10: Nucleophilic Addition of Hydrazine - The Wolff-Kishner Reaction

Y

Ylides
- 8.12: Nucleophilic Addition of Phosphorus Ylides- The Wittig Reaction

Glossary

Sample Word 1 | Sample Definition 1

Detailed Licensing

Some of the pages in this book can be re-mixes of open content from other books in the LibreTexts Library. Sometimes sections from several sources are used on the same page and there may be no unique open license. Where there is a conflict, the licensing may appear as *undeclared*. On any page, by toggling AutoAttibution on the Tools menu, you can display the detailed attribution on a paragraph level. Material from different books will be color coded and the source displayed by mousing over the paragraph.

Content in the Front and Back Matter, directories and similar can be uncopywriteable, being simple listings and these are also shown as *undeclared*.

Overview

Title: Organic Chemistry II

Webpages: 262

Applicable Restrictions: Noncommercial

All licenses found:

- CC BY-NC-SA 4.0: 95.8% (251 pages)
- Undeclared: 3.4% (9 pages)
- CC BY 4.0: 0.4% (1 page)
- Other: 0.4% (1 page)

By Page

- Organic Chemistry II - *CC BY 4.0*
  - Front Matter - *Undeclared*
    - TitlePage - *Undeclared*
    - InfoPage - *Other*
    - Table of Contents - *Undeclared*
    - Licensing - *Undeclared*
  - 1: Structure Determination - Mass Spectrometry and Infrared Spectroscopy - *CC BY-NC-SA 4.0*
    - 1.1: Why This Chapter? - *CC BY-NC-SA 4.0*
    - 1.2: Mass Spectrometry of Small Molecules - Magnetic-Sector Instruments - *CC BY-NC-SA 4.0*
    - 1.3: Interpreting Mass Spectra - *CC BY-NC-SA 4.0*
    - 1.4: Mass Spectrometry of Some Common Functional Groups - *CC BY-NC-SA 4.0*
    - 1.5: Mass Spectrometry in Biological - Time-of-flight (TOF) Instruments - *CC BY-NC-SA 4.0*
    - 1.6: Spectroscopy and the Electromagnetic Spectrum - *CC BY-NC-SA 4.0*
    - 1.7: Infrared Spectroscopy - *CC BY-NC-SA 4.0*
    - 1.8: Interpreting Infrared Spectra - *CC BY-NC-SA 4.0*
    - 1.9: Infrared Spectra of Some Common Functional Groups - *CC BY-NC-SA 4.0*
    - 1.10: Chemistry Matters—X-Ray Crystallography - *CC BY-NC-SA 4.0*
    - 1.11: Key Terms - *CC BY-NC-SA 4.0*
    - 1.12: Summary - *CC BY-NC-SA 4.0*
    - 1.13: Additional Problems - *CC BY-NC-SA 4.0*
  - 2: Structure Determination - Nuclear Magnetic Resonance Spectroscopy - *CC BY-NC-SA 4.0*
    - 2.1: Why This Chapter? - *CC BY-NC-SA 4.0*
    - 2.2: Nuclear Magnetic Resonance Spectroscopy - *CC BY-NC-SA 4.0*
    - 2.3: The Nature of NMR Absorptions - *CC BY-NC-SA 4.0*
    - 2.4: Chemical Shifts - *CC BY-NC-SA 4.0*
    - 2.5: Chemical Shifts in ^{1}H NMR Spectroscopy - *CC BY-NC-SA 4.0*
    - 2.6: Integration of ^{1}H NMR Absorptions- Proton Counting - *CC BY-NC-SA 4.0*
    - 2.7: Spin-Spin Splitting in ^{1}H NMR Spectra - *CC BY-NC-SA 4.0*
    - 2.8: ^{1}H NMR Spectroscopy and Proton Equivalence - *CC BY-NC-SA 4.0*
    - 2.9: More Complex Spin-Spin Splitting Patterns - *CC BY-NC-SA 4.0*
    - 2.10: Uses of ^{1}H NMR Spectroscopy - *CC BY-NC-SA 4.0*
    - 2.11: ^{13}C NMR Spectroscopy - Signal Averaging and FT-NMR - *CC BY-NC-SA 4.0*
    - 2.12: Characteristics of ^{13}C NMR Spectroscopy - *CC BY-NC-SA 4.0*
    - 2.13: DEPT ^{13}C NMR Spectroscopy - *CC BY-NC-SA 4.0*

- 2.14: Uses of ^{13}C NMR Spectroscopy - *CC BY-NC-SA 4.0*
- 2.15: Chemistry Matters—Magnetic Resonance Imaging (MRI) - *CC BY-NC-SA 4.0*
- 2.16: Key Terms - *CC BY-NC-SA 4.0*
- 2.17: Summary - *CC BY-NC-SA 4.0*
- 2.18: Additional Problems - *CC BY-NC-SA 4.0*

3: Conjugated Compounds and Ultraviolet Spectroscopy - *CC BY-NC-SA 4.0*

- 3.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 3.2: Stability of Conjugated Dienes- Molecular Orbital Theory - *CC BY-NC-SA 4.0*
- 3.3: Electrophilic Additions to Conjugated Dienes- Allylic Carbocations - *CC BY-NC-SA 4.0*
- 3.4: Kinetic vs. Thermodynamic Control of Reactions - *CC BY-NC-SA 4.0*
- 3.5: The Diels-Alder Cycloaddition Reaction - *CC BY-NC-SA 4.0*
- 3.6: Characteristics of the Diels-Alder Reaction - *CC BY-NC-SA 4.0*
- 3.7: Diene Polymers - Natural and Synthetic Rubbers - *CC BY-NC-SA 4.0*
- 3.8: Ultraviolet Spectroscopy - *CC BY-NC-SA 4.0*
- 3.9: Interpreting Ultraviolet Spectra- The Effect of Conjugation - *CC BY-NC-SA 4.0*
- 3.10: Conjugation, Color, and the Chemistry of Vision - *CC BY-NC-SA 4.0*
- 3.11: Chemistry Matters—Photolithography - *CC BY-NC-SA 4.0*
- 3.12: Key Terms - *CC BY-NC-SA 4.0*
- 3.13: Summary - *CC BY-NC-SA 4.0*
- 3.14: Summary of Reactions - *CC BY-NC-SA 4.0*
- 3.15: Additional Problems - *CC BY-NC-SA 4.0*

4: Benzene and Aromaticity - *CC BY-NC-SA 4.0*

- 4.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 4.2: Naming Aromatic Compounds - *CC BY-NC-SA 4.0*
- 4.3: Structure and Stability of Benzene - *CC BY-NC-SA 4.0*
- 4.4: Aromaticity and the Hückel 4n + 2 Rule - *CC BY-NC-SA 4.0*
- 4.5: Aromatic Ions - *CC BY-NC-SA 4.0*
- 4.6: Aromatic Heterocycles - Pyridine and Pyrrole - *CC BY-NC-SA 4.0*
- 4.7: Polycyclic Aromatic Compounds - *CC BY-NC-SA 4.0*
- 4.8: Spectroscopy of Aromatic Compounds - *CC BY-NC-SA 4.0*
- 4.9: Chemistry Matters—Aspirin, NSAIDs, and COX-2 Inhibitors - *CC BY-NC-SA 4.0*
- 4.10: Key Terms - *CC BY-NC-SA 4.0*
- 4.11: Summary - *CC BY-NC-SA 4.0*
- 4.12: Additional Problems - *CC BY-NC-SA 4.0*

5: Chemistry of Benzene - Electrophilic Aromatic Substitution - *CC BY-NC-SA 4.0*

- 5.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 5.2: Electrophilic Aromatic Substitution Reactions - Bromination - *CC BY-NC-SA 4.0*
- 5.3: Other Aromatic Substitutions - *CC BY-NC-SA 4.0*
- 5.4: Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction - *CC BY-NC-SA 4.0*
- 5.5: Substituent Effects in Electrophilic Substitutions - *CC BY-NC-SA 4.0*
- 5.6: Trisubstituted Benzenes- Additivity of Effects - *CC BY-NC-SA 4.0*
- 5.7: Nucleophilic Aromatic Substitution - *CC BY-NC-SA 4.0*
- 5.8: Benzyne - *CC BY-NC-SA 4.0*
- 5.9: Oxidation of Aromatic Compounds - *CC BY-NC-SA 4.0*
- 5.10: Reduction of Aromatic Compounds - *CC BY-NC-SA 4.0*
- 5.11: Synthesis of Polysubstituted Benzenes - *CC BY-NC-SA 4.0*
- 5.12: Chemistry Matters—Combinatorial Chemistry - *CC BY-NC-SA 4.0*
- 5.13: Key Terms - *CC BY-NC-SA 4.0*
- 5.14: Summary - *CC BY-NC-SA 4.0*
- 5.15: Summary of Reactions - *CC BY-NC-SA 4.0*
- 5.16: Additional Problems - *CC BY-NC-SA 4.0*

6: Alcohols and Phenols - *CC BY-NC-SA 4.0*

- 6.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 6.2: Naming Alcohols and Phenols - *CC BY-NC-SA 4.0*
- 6.3: Properties of Alcohols and Phenols - *CC BY-NC-SA 4.0*
- 6.4: Preparation of Alcohols- A Review - *CC BY-NC-SA 4.0*
- 6.5: Alcohols from Carbonyl Compounds - Reduction - *CC BY-NC-SA 4.0*
- 6.6: Alcohols from Carbonyl Compounds - Grignard Reagents - *CC BY-NC-SA 4.0*
- 6.7: Reactions of Alcohols - *CC BY-NC-SA 4.0*
- 6.8: Oxidation of Alcohols - *CC BY-NC-SA 4.0*
- 6.9: Protection of Alcohols - *CC BY-NC-SA 4.0*
- 6.10: Phenols and Their Uses - *CC BY-NC-SA 4.0*
- 6.11: Reactions of Phenols - *CC BY-NC-SA 4.0*

- 6.12: Spectroscopy of Alcohols and Phenols - *CC BY-NC-SA 4.0*
- 6.13: Chemistry Matters—Ethanol- Chemical, Drug, and Poison - *CC BY-NC-SA 4.0*
- 6.14: Key Terms - *CC BY-NC-SA 4.0*
- 6.15: Summary - *CC BY-NC-SA 4.0*
- 6.16: Summary of Reactions - *CC BY-NC-SA 4.0*
- 6.17: Additional Problems - *CC BY-NC-SA 4.0*

7: Ethers and Epoxides; Thiols and Sulfides - *CC BY-NC-SA 4.0*

- 7.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 7.2: Names and Properties of Ethers - *CC BY-NC-SA 4.0*
- 7.3: Preparing Ethers - *CC BY-NC-SA 4.0*
- 7.4: Reactions of Ethers - Acidic Cleavage - *CC BY-NC-SA 4.0*
- 7.5: Cyclic Ethers - Epoxides - *CC BY-NC-SA 4.0*
- 7.6: Reactions of Epoxides - Ring-opening - *CC BY-NC-SA 4.0*
- 7.7: Crown Ethers - *CC BY-NC-SA 4.0*
- 7.8: Thiols and Sulfides - *CC BY-NC-SA 4.0*
- 7.9: Spectroscopy of Ethers - *CC BY-NC-SA 4.0*
- 7.10: Chemistry Matters—Epoxy Resins and Adhesives - *CC BY-NC-SA 4.0*
- 7.11: Key Terms - *CC BY-NC-SA 4.0*
- 7.12: Summary - *CC BY-NC-SA 4.0*
- 7.13: Summary of Reactions - *CC BY-NC-SA 4.0*
- 7.14: Additional Problems - *CC BY-NC-SA 4.0*
- 7.15: Preview of Carbonyl Chemistry - *CC BY-NC-SA 4.0*

8: Aldehydes and Ketones- Nucleophilic Addition Reactions - *CC BY-NC-SA 4.0*

- 8.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 8.2: Naming Aldehydes and Ketones - *CC BY-NC-SA 4.0*
- 8.3: Preparing Aldehydes and Ketones - *CC BY-NC-SA 4.0*
- 8.4: Oxidation of Aldehydes and Ketones - *CC BY-NC-SA 4.0*
- 8.5: Nucleophilic Addition Reactions of Aldehydes and Ketones - *CC BY-NC-SA 4.0*
- 8.6: Nucleophilic Addition of Water- Hydration - *CC BY-NC-SA 4.0*
- 8.7: Nucleophilic Addition of HCN - Cyanohydrin Formation - *CC BY-NC-SA 4.0*
- 8.8: Nucleophilic Addition of Hydride and Grignard Reagents- Alcohol Formation - *CC BY-NC-SA 4.0*
- 8.9: Nucleophilic Addition of Amines- Imine and Enamine Formation - *CC BY-NC-SA 4.0*
- 8.10: Nucleophilic Addition of Hydrazine - The Wolff-Kishner Reaction - *CC BY-NC-SA 4.0*
- 8.11: Nucleophilic Addition of Alcohols - Acetal Formation - *CC BY-NC-SA 4.0*
- 8.12: Nucleophilic Addition of Phosphorus Ylides- The Wittig Reaction - *CC BY-NC-SA 4.0*
- 8.13: Biological Reductions - *CC BY-NC-SA 4.0*
  - 8.13.1: Amines and Heterocycles - *CC BY-NC-SA 4.0*
    - 8.13.1.1: Why This Chapter? - *CC BY-NC-SA 4.0*
    - 8.13.1.2: Naming Amines - *CC BY-NC-SA 4.0*
    - 8.13.1.3: Structure and Properties of Amines - *CC BY-NC-SA 4.0*
    - 8.13.1.4: Basicity of Amines - *CC BY-NC-SA 4.0*
    - 8.13.1.5: Basicity of Arylamines - *CC BY-NC-SA 4.0*
    - 8.13.1.6: Biological Amines and the Henderson-Hasselbalch Equation - *CC BY-NC-SA 4.0*
    - 8.13.1.7: Synthesis of Amines - *CC BY-NC-SA 4.0*
    - 8.13.1.8: Reactions of Amines - *CC BY-NC-SA 4.0*
    - 8.13.1.9: Reactions of Arylamines - *CC BY-NC-SA 4.0*
    - 8.13.1.10: Heterocyclic Amines - *CC BY-NC-SA 4.0*
    - 8.13.1.11: Spectroscopy of Amines - *CC BY-NC-SA 4.0*
    - 8.13.1.12: Chemistry Matters - Green Chemistry II- Ionic Liquids - *CC BY-NC-SA 4.0*
    - 8.13.1.13: Key Terms - *CC BY-NC-SA 4.0*
    - 8.13.1.14: Summary - *CC BY-NC-SA 4.0*
    - 8.13.1.15: Summary of Reactions - *CC BY-NC-SA 4.0*
    - 8.13.1.16: Additional Problems - *CC BY-NC-SA 4.0*
- 8.14: Conjugate Nucleophilic Addition to α,β-Unsaturated Aldehydes and Ketones - *CC BY-NC-SA 4.0*
- 8.15: Spectroscopy of Aldehydes and Ketones - *CC BY-NC-SA 4.0*
- 8.16: Chemistry Matters—Enantioselective Synthesis - *CC BY-NC-SA 4.0*
- 8.17: Key Terms - *CC BY-NC-SA 4.0*
- 8.18: Summary - *CC BY-NC-SA 4.0*

- 8.19: Summary of Reactions - *CC BY-NC-SA 4.0*
- 8.20: Additional Problems - *CC BY-NC-SA 4.0*
- 8.21: Carbonyl Condensation Reactions - *CC BY-NC-SA 4.0*

9: Carboxylic Acids and Nitriles - *CC BY-NC-SA 4.0*

- 9.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 9.2: Naming Carboxylic Acids and Nitriles - *CC BY-NC-SA 4.0*
- 9.3: Structure and Properties of Carboxylic Acids - *CC BY-NC-SA 4.0*
- 9.4: Biological Acids and the Henderson-Hasselbalch Equation - *CC BY-NC-SA 4.0*
- 9.5: Substituent Effects on Acidity - *CC BY-NC-SA 4.0*
- 9.6: Preparing Carboxylic Acids - *CC BY-NC-SA 4.0*
- 9.7: Reactions of Carboxylic Acids - An Overview - *CC BY-NC-SA 4.0*
- 9.8: Chemistry of Nitriles - *CC BY-NC-SA 4.0*
- 9.9: Spectroscopy of Carboxylic Acids and Nitriles - *CC BY-NC-SA 4.0*
- 9.10: Chemistry Matters—Vitamin C - *CC BY-NC-SA 4.0*
- 9.11: Key Terms - *CC BY-NC-SA 4.0*
- 9.12: Summary - *CC BY-NC-SA 4.0*
- 9.13: Summary of Reactions - *CC BY-NC-SA 4.0*
- 9.14: Additional Problems - *CC BY-NC-SA 4.0*

10: Carboxylic Acid Derivatives- Nucleophilic Acyl Substitution Reactions - *CC BY-NC-SA 4.0*

- 10.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 10.2: Naming Carboxylic Acid Derivatives - *CC BY-NC-SA 4.0*
- 10.3: Nucleophilic Acyl Substitution Reactions - *CC BY-NC-SA 4.0*
- 10.4: Reactions of Carboxylic Acids - *CC BY-NC-SA 4.0*
- 10.5: Chemistry of Acid Halides - *CC BY-NC-SA 4.0*
- 10.6: Chemistry of Acid Anhydrides - *CC BY-NC-SA 4.0*
- 10.7: Chemistry of Esters - *CC BY-NC-SA 4.0*
- 10.8: Chemistry of Amides - *CC BY-NC-SA 4.0*
- 10.9: Chemistry of Thioesters and Acyl Phosphates - Biological Carboxylic Acid Derivatives - *CC BY-NC-SA 4.0*
- 10.10: Polyamides and Polyesters - Step-Growth Polymers - *CC BY-NC-SA 4.0*
- 10.11: Spectroscopy of Carboxylic Acid Derivatives - *CC BY-NC-SA 4.0*
- 10.12: Chemistry Matters—β-Lactam Antibiotics - *CC BY-NC-SA 4.0*
- 10.13: Key Terms - *CC BY-NC-SA 4.0*
- 10.14: Summary - *CC BY-NC-SA 4.0*
- 10.15: Summary of Reactions - *CC BY-NC-SA 4.0*
- 10.16: Additional Problems - *CC BY-NC-SA 4.0*
- 10.17: Carbonyl Condensation Reactions - *CC BY-NC-SA 4.0*

11: Carbonyl Alpha-Substitution Reactions - *CC BY-NC-SA 4.0*

- 11.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 11.2: Keto-Enol Tautomerism - *CC BY-NC-SA 4.0*
- 11.3: Reactivity of Enols- α-Substitution Reactions - *CC BY-NC-SA 4.0*
- 11.4: Alpha Halogenation of Aldehydes and Ketones - *CC BY-NC-SA 4.0*
- 11.5: Alpha Bromination of Carboxylic Acids - *CC BY-NC-SA 4.0*
- 11.6: Acidity of Alpha Hydrogen Atoms- Enolate Ion Formation - *CC BY-NC-SA 4.0*
- 11.7: Reactivity of Enolate Ions - *CC BY-NC-SA 4.0*
- 11.8: Alkylation of Enolate Ions - *CC BY-NC-SA 4.0*
- 11.9: Chemistry Matters—Barbiturates - *CC BY-NC-SA 4.0*
- 11.10: Key Terms - *CC BY-NC-SA 4.0*
- 11.11: Summary - *CC BY-NC-SA 4.0*
- 11.12: Summary of Reactions - *CC BY-NC-SA 4.0*
- 11.13: Additional Problems - *CC BY-NC-SA 4.0*

12: Carbonyl Condensation Reactions - *CC BY-NC-SA 4.0*

- 12.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 12.2: Carbonyl Condensations - The Aldol Reaction - *CC BY-NC-SA 4.0*
- 12.3: Carbonyl Condensations versus Alpha Substitutions - *CC BY-NC-SA 4.0*
- 12.4: Dehydration of Aldol Products - Synthesis of Enones - *CC BY-NC-SA 4.0*
- 12.5: Using Aldol Reactions in Synthesis - *CC BY-NC-SA 4.0*
- 12.6: Mixed Aldol Reactions - *CC BY-NC-SA 4.0*
- 12.7: Intramolecular Aldol Reactions - *CC BY-NC-SA 4.0*
- 12.8: The Claisen Condensation Reaction - *CC BY-NC-SA 4.0*
- 12.9: Mixed Claisen Condensations - *CC BY-NC-SA 4.0*
- 12.10: Intramolecular Claisen Condensations - The Dieckmann Cyclization - *CC BY-NC-SA 4.0*
- 12.11: Conjugate Carbonyl Additions - The Michael Reaction - *CC BY-NC-SA 4.0*

- 12.12: Carbonyl Condensations with Enamines - The Stork Enamine Reaction - *CC BY-NC-SA 4.0*
- 12.13: The Robinson Annulation Reaction - *CC BY-NC-SA 4.0*
- 12.14: Some Biological Carbonyl Condensation Reactions - *CC BY-NC-SA 4.0*
- 12.15: Chemistry Matters - A Prologue to Metabolism - *CC BY-NC-SA 4.0*
- 12.16: Key Terms - *CC BY-NC-SA 4.0*
- 12.17: Summary - *CC BY-NC-SA 4.0*
- 12.18: Summary of Reactions - *CC BY-NC-SA 4.0*
- 12.19: Additional Problems - *CC BY-NC-SA 4.0*

13: Amines and Heterocycles - *CC BY-NC-SA 4.0*

- 13.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 13.2: Naming Amines - *CC BY-NC-SA 4.0*
- 13.3: Structure and Properties of Amines - *CC BY-NC-SA 4.0*
- 13.4: Basicity of Amines - *CC BY-NC-SA 4.0*
- 13.5: Basicity of Arylamines - *CC BY-NC-SA 4.0*
- 13.6: Biological Amines and the Henderson-Hasselbalch Equation - *CC BY-NC-SA 4.0*
- 13.7: Synthesis of Amines - *CC BY-NC-SA 4.0*
- 13.8: Reactions of Amines - *CC BY-NC-SA 4.0*
- 13.9: Reactions of Arylamines - *CC BY-NC-SA 4.0*
- 13.10: Heterocyclic Amines - *CC BY-NC-SA 4.0*
- 13.11: Spectroscopy of Amines - *CC BY-NC-SA 4.0*
- 13.12: Chemistry Matters - Green Chemistry II- Ionic Liquids - *CC BY-NC-SA 4.0*
- 13.13: Key Terms - *CC BY-NC-SA 4.0*
- 13.14: Summary - *CC BY-NC-SA 4.0*
- 13.15: Summary of Reactions - *CC BY-NC-SA 4.0*
- 13.16: Additional Problems - *CC BY-NC-SA 4.0*

14: Orbitals and Organic Chemistry - Pericyclic Reactions - *CC BY-NC-SA 4.0*

- 14.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 14.2: Molecular Orbitals of Conjugated Pi Systems - *CC BY-NC-SA 4.0*
- 14.3: Electrocyclic Reactions - *CC BY-NC-SA 4.0*
- 14.4: Stereochemistry of Thermal Electrocyclic Reactions - *CC BY-NC-SA 4.0*
- 14.5: Photochemical Electrocyclic Reactions - *CC BY-NC-SA 4.0*
- 14.6: Cycloaddition Reactions - *CC BY-NC-SA 4.0*
- 14.7: Stereochemistry of Cycloadditions - *CC BY-NC-SA 4.0*
- 14.8: Sigmatropic Rearrangements - *CC BY-NC-SA 4.0*
- 14.9: Some Examples of Sigmatropic Rearrangements - *CC BY-NC-SA 4.0*
- 14.10: A Summary of Rules for Pericyclic Reactions - *CC BY-NC-SA 4.0*
- 14.11: Chemistry Matters—Vitamin D, the Sunshine Vitamin - *CC BY-NC-SA 4.0*
- 14.12: Key Terms - *CC BY-NC-SA 4.0*
- 14.13: Summary - *CC BY-NC-SA 4.0*
- 14.14: Additional Problems - *CC BY-NC-SA 4.0*

Back Matter - *Undeclared*

- Index - *Undeclared*
- Glossary - *Undeclared*
- Detailed Licensing - *Undeclared*
- Detailed Licensing - *Undeclared*

Detailed Licensing

Overview

Title: Organic Chemistry II

Webpages: 262

Applicable Restrictions: Noncommercial

All licenses found:

- CC BY-NC-SA 4.0: 95.8% (251 pages)
- Undeclared: 3.4% (9 pages)
- CC BY 4.0: 0.4% (1 page)
- Other: 0.4% (1 page)

By Page

- Organic Chemistry II - *CC BY 4.0*
  - Front Matter - *Undeclared*
    - TitlePage - *Undeclared*
    - InfoPage - *Other*
    - Table of Contents - *Undeclared*
    - Licensing - *Undeclared*
  - 1: Structure Determination - Mass Spectrometry and Infrared Spectroscopy - *CC BY-NC-SA 4.0*
    - 1.1: Why This Chapter? - *CC BY-NC-SA 4.0*
    - 1.2: Mass Spectrometry of Small Molecules - Magnetic-Sector Instruments - *CC BY-NC-SA 4.0*
    - 1.3: Interpreting Mass Spectra - *CC BY-NC-SA 4.0*
    - 1.4: Mass Spectrometry of Some Common Functional Groups - *CC BY-NC-SA 4.0*
    - 1.5: Mass Spectrometry in Biological - Time-of-flight (TOF) Instruments - *CC BY-NC-SA 4.0*
    - 1.6: Spectroscopy and the Electromagnetic Spectrum - *CC BY-NC-SA 4.0*
    - 1.7: Infrared Spectroscopy - *CC BY-NC-SA 4.0*
    - 1.8: Interpreting Infrared Spectra - *CC BY-NC-SA 4.0*
    - 1.9: Infrared Spectra of Some Common Functional Groups - *CC BY-NC-SA 4.0*
    - 1.10: Chemistry Matters—X-Ray Crystallography - *CC BY-NC-SA 4.0*
    - 1.11: Key Terms - *CC BY-NC-SA 4.0*
    - 1.12: Summary - *CC BY-NC-SA 4.0*
    - 1.13: Additional Problems - *CC BY-NC-SA 4.0*
  - 2: Structure Determination - Nuclear Magnetic Resonance Spectroscopy - *CC BY-NC-SA 4.0*
    - 2.1: Why This Chapter? - *CC BY-NC-SA 4.0*
    - 2.2: Nuclear Magnetic Resonance Spectroscopy - *CC BY-NC-SA 4.0*
    - 2.3: The Nature of NMR Absorptions - *CC BY-NC-SA 4.0*
    - 2.4: Chemical Shifts - *CC BY-NC-SA 4.0*
    - 2.5: Chemical Shifts in ^{1}H NMR Spectroscopy - *CC BY-NC-SA 4.0*
    - 2.6: Integration of ^{1}H NMR Absorptions- Proton Counting - *CC BY-NC-SA 4.0*
    - 2.7: Spin-Spin Splitting in ^{1}H NMR Spectra - *CC BY-NC-SA 4.0*
    - 2.8: ^{1}H NMR Spectroscopy and Proton Equivalence - *CC BY-NC-SA 4.0*
    - 2.9: More Complex Spin-Spin Splitting Patterns - *CC BY-NC-SA 4.0*
    - 2.10: Uses of ^{1}H NMR Spectroscopy - *CC BY-NC-SA 4.0*
    - 2.11: ^{13}C NMR Spectroscopy - Signal Averaging and FT-NMR - *CC BY-NC-SA 4.0*
    - 2.12: Characteristics of ^{13}C NMR Spectroscopy - *CC BY-NC-SA 4.0*
    - 2.13: DEPT ^{13}C NMR Spectroscopy - *CC BY-NC-SA 4.0*
    - 2.14: Uses of ^{13}C NMR Spectroscopy - *CC BY-NC-SA 4.0*
    - 2.15: Chemistry Matters—Magnetic Resonance Imaging (MRI) - *CC BY-NC-SA 4.0*
    - 2.16: Key Terms - *CC BY-NC-SA 4.0*
    - 2.17: Summary - *CC BY-NC-SA 4.0*
    - 2.18: Additional Problems - *CC BY-NC-SA 4.0*
  - 3: Conjugated Compounds and Ultraviolet Spectroscopy - *CC BY-NC-SA 4.0*
    - 3.1: Why This Chapter? - *CC BY-NC-SA 4.0*
    - 3.2: Stability of Conjugated Dienes- Molecular Orbital Theory - *CC BY-NC-SA 4.0*

- 3.3: Electrophilic Additions to Conjugated Dienes- Allylic Carbocations - *CC BY-NC-SA 4.0*
- 3.4: Kinetic vs. Thermodynamic Control of Reactions - *CC BY-NC-SA 4.0*
- 3.5: The Diels-Alder Cycloaddition Reaction - *CC BY-NC-SA 4.0*
- 3.6: Characteristics of the Diels-Alder Reaction - *CC BY-NC-SA 4.0*
- 3.7: Diene Polymers - Natural and Synthetic Rubbers - *CC BY-NC-SA 4.0*
- 3.8: Ultraviolet Spectroscopy - *CC BY-NC-SA 4.0*
- 3.9: Interpreting Ultraviolet Spectra- The Effect of Conjugation - *CC BY-NC-SA 4.0*
- 3.10: Conjugation, Color, and the Chemistry of Vision - *CC BY-NC-SA 4.0*
- 3.11: Chemistry Matters—Photolithography - *CC BY-NC-SA 4.0*
- 3.12: Key Terms - *CC BY-NC-SA 4.0*
- 3.13: Summary - *CC BY-NC-SA 4.0*
- 3.14: Summary of Reactions - *CC BY-NC-SA 4.0*
- 3.15: Additional Problems - *CC BY-NC-SA 4.0*

4: Benzene and Aromaticity - *CC BY-NC-SA 4.0*

- 4.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 4.2: Naming Aromatic Compounds - *CC BY-NC-SA 4.0*
- 4.3: Structure and Stability of Benzene - *CC BY-NC-SA 4.0*
- 4.4: Aromaticity and the Hückel 4n + 2 Rule - *CC BY-NC-SA 4.0*
- 4.5: Aromatic Ions - *CC BY-NC-SA 4.0*
- 4.6: Aromatic Heterocycles - Pyridine and Pyrrole - *CC BY-NC-SA 4.0*
- 4.7: Polycyclic Aromatic Compounds - *CC BY-NC-SA 4.0*
- 4.8: Spectroscopy of Aromatic Compounds - *CC BY-NC-SA 4.0*
- 4.9: Chemistry Matters—Aspirin, NSAIDs, and COX-2 Inhibitors - *CC BY-NC-SA 4.0*
- 4.10: Key Terms - *CC BY-NC-SA 4.0*
- 4.11: Summary - *CC BY-NC-SA 4.0*
- 4.12: Additional Problems - *CC BY-NC-SA 4.0*

5: Chemistry of Benzene - Electrophilic Aromatic Substitution - *CC BY-NC-SA 4.0*

- 5.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 5.2: Electrophilic Aromatic Substitution Reactions - Bromination - *CC BY-NC-SA 4.0*
- 5.3: Other Aromatic Substitutions - *CC BY-NC-SA 4.0*
- 5.4: Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction - *CC BY-NC-SA 4.0*
- 5.5: Substituent Effects in Electrophilic Substitutions - *CC BY-NC-SA 4.0*
- 5.6: Trisubstituted Benzenes- Additivity of Effects - *CC BY-NC-SA 4.0*
- 5.7: Nucleophilic Aromatic Substitution - *CC BY-NC-SA 4.0*
- 5.8: Benzyne - *CC BY-NC-SA 4.0*
- 5.9: Oxidation of Aromatic Compounds - *CC BY-NC-SA 4.0*
- 5.10: Reduction of Aromatic Compounds - *CC BY-NC-SA 4.0*
- 5.11: Synthesis of Polysubstituted Benzenes - *CC BY-NC-SA 4.0*
- 5.12: Chemistry Matters—Combinatorial Chemistry - *CC BY-NC-SA 4.0*
- 5.13: Key Terms - *CC BY-NC-SA 4.0*
- 5.14: Summary - *CC BY-NC-SA 4.0*
- 5.15: Summary of Reactions - *CC BY-NC-SA 4.0*
- 5.16: Additional Problems - *CC BY-NC-SA 4.0*

6: Alcohols and Phenols - *CC BY-NC-SA 4.0*

- 6.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 6.2: Naming Alcohols and Phenols - *CC BY-NC-SA 4.0*
- 6.3: Properties of Alcohols and Phenols - *CC BY-NC-SA 4.0*
- 6.4: Preparation of Alcohols- A Review - *CC BY-NC-SA 4.0*
- 6.5: Alcohols from Carbonyl Compounds - Reduction - *CC BY-NC-SA 4.0*
- 6.6: Alcohols from Carbonyl Compounds - Grignard Reagents - *CC BY-NC-SA 4.0*
- 6.7: Reactions of Alcohols - *CC BY-NC-SA 4.0*
- 6.8: Oxidation of Alcohols - *CC BY-NC-SA 4.0*
- 6.9: Protection of Alcohols - *CC BY-NC-SA 4.0*
- 6.10: Phenols and Their Uses - *CC BY-NC-SA 4.0*
- 6.11: Reactions of Phenols - *CC BY-NC-SA 4.0*
- 6.12: Spectroscopy of Alcohols and Phenols - *CC BY-NC-SA 4.0*
- 6.13: Chemistry Matters—Ethanol- Chemical, Drug, and Poison - *CC BY-NC-SA 4.0*
- 6.14: Key Terms - *CC BY-NC-SA 4.0*
- 6.15: Summary - *CC BY-NC-SA 4.0*
- 6.16: Summary of Reactions - *CC BY-NC-SA 4.0*
- 6.17: Additional Problems - *CC BY-NC-SA 4.0*

7: Ethers and Epoxides; Thiols and Sulfides - *CC BY-NC-SA 4.0*

- 7.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 7.2: Names and Properties of Ethers - *CC BY-NC-SA 4.0*

- 7.3: Preparing Ethers - *CC BY-NC-SA 4.0*
- 7.4: Reactions of Ethers - Acidic Cleavage - *CC BY-NC-SA 4.0*
- 7.5: Cyclic Ethers - Epoxides - *CC BY-NC-SA 4.0*
- 7.6: Reactions of Epoxides - Ring-opening - *CC BY-NC-SA 4.0*
- 7.7: Crown Ethers - *CC BY-NC-SA 4.0*
- 7.8: Thiols and Sulfides - *CC BY-NC-SA 4.0*
- 7.9: Spectroscopy of Ethers - *CC BY-NC-SA 4.0*
- 7.10: Chemistry Matters—Epoxy Resins and Adhesives - *CC BY-NC-SA 4.0*
- 7.11: Key Terms - *CC BY-NC-SA 4.0*
- 7.12: Summary - *CC BY-NC-SA 4.0*
- 7.13: Summary of Reactions - *CC BY-NC-SA 4.0*
- 7.14: Additional Problems - *CC BY-NC-SA 4.0*
- 7.15: Preview of Carbonyl Chemistry - *CC BY-NC-SA 4.0*

8: Aldehydes and Ketones- Nucleophilic Addition Reactions - *CC BY-NC-SA 4.0*

- 8.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 8.2: Naming Aldehydes and Ketones - *CC BY-NC-SA 4.0*
- 8.3: Preparing Aldehydes and Ketones - *CC BY-NC-SA 4.0*
- 8.4: Oxidation of Aldehydes and Ketones - *CC BY-NC-SA 4.0*
- 8.5: Nucleophilic Addition Reactions of Aldehydes and Ketones - *CC BY-NC-SA 4.0*
- 8.6: Nucleophilic Addition of Water- Hydration - *CC BY-NC-SA 4.0*
- 8.7: Nucleophilic Addition of HCN - Cyanohydrin Formation - *CC BY-NC-SA 4.0*
- 8.8: Nucleophilic Addition of Hydride and Grignard Reagents- Alcohol Formation - *CC BY-NC-SA 4.0*
- 8.9: Nucleophilic Addition of Amines- Imine and Enamine Formation - *CC BY-NC-SA 4.0*
- 8.10: Nucleophilic Addition of Hydrazine - The Wolff-Kishner Reaction - *CC BY-NC-SA 4.0*
- 8.11: Nucleophilic Addition of Alcohols - Acetal Formation - *CC BY-NC-SA 4.0*
- 8.12: Nucleophilic Addition of Phosphorus Ylides- The Wittig Reaction - *CC BY-NC-SA 4.0*
- 8.13: Biological Reductions - *CC BY-NC-SA 4.0*
  - 8.13.1: Amines and Heterocycles - *CC BY-NC-SA 4.0*
    - 8.13.1.1: Why This Chapter? - *CC BY-NC-SA 4.0*
    - 8.13.1.2: Naming Amines - *CC BY-NC-SA 4.0*
    - 8.13.1.3: Structure and Properties of Amines - *CC BY-NC-SA 4.0*
    - 8.13.1.4: Basicity of Amines - *CC BY-NC-SA 4.0*
    - 8.13.1.5: Basicity of Arylamines - *CC BY-NC-SA 4.0*
    - 8.13.1.6: Biological Amines and the Henderson-Hasselbalch Equation - *CC BY-NC-SA 4.0*
    - 8.13.1.7: Synthesis of Amines - *CC BY-NC-SA 4.0*
    - 8.13.1.8: Reactions of Amines - *CC BY-NC-SA 4.0*
    - 8.13.1.9: Reactions of Arylamines - *CC BY-NC-SA 4.0*
    - 8.13.1.10: Heterocyclic Amines - *CC BY-NC-SA 4.0*
    - 8.13.1.11: Spectroscopy of Amines - *CC BY-NC-SA 4.0*
    - 8.13.1.12: Chemistry Matters - Green Chemistry II- Ionic Liquids - *CC BY-NC-SA 4.0*
    - 8.13.1.13: Key Terms - *CC BY-NC-SA 4.0*
    - 8.13.1.14: Summary - *CC BY-NC-SA 4.0*
    - 8.13.1.15: Summary of Reactions - *CC BY-NC-SA 4.0*
    - 8.13.1.16: Additional Problems - *CC BY-NC-SA 4.0*
- 8.14: Conjugate Nucleophilic Addition to α,β-Unsaturated Aldehydes and Ketones - *CC BY-NC-SA 4.0*
- 8.15: Spectroscopy of Aldehydes and Ketones - *CC BY-NC-SA 4.0*
- 8.16: Chemistry Matters—Enantioselective Synthesis - *CC BY-NC-SA 4.0*
- 8.17: Key Terms - *CC BY-NC-SA 4.0*
- 8.18: Summary - *CC BY-NC-SA 4.0*
- 8.19: Summary of Reactions - *CC BY-NC-SA 4.0*
- 8.20: Additional Problems - *CC BY-NC-SA 4.0*
- 8.21: Carbonyl Condensation Reactions - *CC BY-NC-SA 4.0*

9: Carboxylic Acids and Nitriles - *CC BY-NC-SA 4.0*

- 9.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 9.2: Naming Carboxylic Acids and Nitriles - *CC BY-NC-SA 4.0*
- 9.3: Structure and Properties of Carboxylic Acids - *CC BY-NC-SA 4.0*
- 9.4: Biological Acids and the Henderson-Hasselbalch Equation - *CC BY-NC-SA 4.0*

- 9.5: Substituent Effects on Acidity - *CC BY-NC-SA 4.0*
- 9.6: Preparing Carboxylic Acids - *CC BY-NC-SA 4.0*
- 9.7: Reactions of Carboxylic Acids - An Overview - *CC BY-NC-SA 4.0*
- 9.8: Chemistry of Nitriles - *CC BY-NC-SA 4.0*
- 9.9: Spectroscopy of Carboxylic Acids and Nitriles - *CC BY-NC-SA 4.0*
- 9.10: Chemistry Matters—Vitamin C - *CC BY-NC-SA 4.0*
- 9.11: Key Terms - *CC BY-NC-SA 4.0*
- 9.12: Summary - *CC BY-NC-SA 4.0*
- 9.13: Summary of Reactions - *CC BY-NC-SA 4.0*
- 9.14: Additional Problems - *CC BY-NC-SA 4.0*

10: Carboxylic Acid Derivatives- Nucleophilic Acyl Substitution Reactions - *CC BY-NC-SA 4.0*

- 10.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 10.2: Naming Carboxylic Acid Derivatives - *CC BY-NC-SA 4.0*
- 10.3: Nucleophilic Acyl Substitution Reactions - *CC BY-NC-SA 4.0*
- 10.4: Reactions of Carboxylic Acids - *CC BY-NC-SA 4.0*
- 10.5: Chemistry of Acid Halides - *CC BY-NC-SA 4.0*
- 10.6: Chemistry of Acid Anhydrides - *CC BY-NC-SA 4.0*
- 10.7: Chemistry of Esters - *CC BY-NC-SA 4.0*
- 10.8: Chemistry of Amides - *CC BY-NC-SA 4.0*
- 10.9: Chemistry of Thioesters and Acyl Phosphates - Biological Carboxylic Acid Derivatives - *CC BY-NC-SA 4.0*
- 10.10: Polyamides and Polyesters - Step-Growth Polymers - *CC BY-NC-SA 4.0*
- 10.11: Spectroscopy of Carboxylic Acid Derivatives - *CC BY-NC-SA 4.0*
- 10.12: Chemistry Matters—β-Lactam Antibiotics - *CC BY-NC-SA 4.0*
- 10.13: Key Terms - *CC BY-NC-SA 4.0*
- 10.14: Summary - *CC BY-NC-SA 4.0*
- 10.15: Summary of Reactions - *CC BY-NC-SA 4.0*
- 10.16: Additional Problems - *CC BY-NC-SA 4.0*
- 10.17: Carbonyl Condensation Reactions - *CC BY-NC-SA 4.0*

11: Carbonyl Alpha-Substitution Reactions - *CC BY-NC-SA 4.0*

- 11.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 11.2: Keto-Enol Tautomerism - *CC BY-NC-SA 4.0*
- 11.3: Reactivity of Enols- α-Substitution Reactions - *CC BY-NC-SA 4.0*
- 11.4: Alpha Halogenation of Aldehydes and Ketones - *CC BY-NC-SA 4.0*
- 11.5: Alpha Bromination of Carboxylic Acids - *CC BY-NC-SA 4.0*
- 11.6: Acidity of Alpha Hydrogen Atoms- Enolate Ion Formation - *CC BY-NC-SA 4.0*
- 11.7: Reactivity of Enolate Ions - *CC BY-NC-SA 4.0*
- 11.8: Alkylation of Enolate Ions - *CC BY-NC-SA 4.0*
- 11.9: Chemistry Matters—Barbiturates - *CC BY-NC-SA 4.0*
- 11.10: Key Terms - *CC BY-NC-SA 4.0*
- 11.11: Summary - *CC BY-NC-SA 4.0*
- 11.12: Summary of Reactions - *CC BY-NC-SA 4.0*
- 11.13: Additional Problems - *CC BY-NC-SA 4.0*

12: Carbonyl Condensation Reactions - *CC BY-NC-SA 4.0*

- 12.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 12.2: Carbonyl Condensations - The Aldol Reaction - *CC BY-NC-SA 4.0*
- 12.3: Carbonyl Condensations versus Alpha Substitutions - *CC BY-NC-SA 4.0*
- 12.4: Dehydration of Aldol Products - Synthesis of Enones - *CC BY-NC-SA 4.0*
- 12.5: Using Aldol Reactions in Synthesis - *CC BY-NC-SA 4.0*
- 12.6: Mixed Aldol Reactions - *CC BY-NC-SA 4.0*
- 12.7: Intramolecular Aldol Reactions - *CC BY-NC-SA 4.0*
- 12.8: The Claisen Condensation Reaction - *CC BY-NC-SA 4.0*
- 12.9: Mixed Claisen Condensations - *CC BY-NC-SA 4.0*
- 12.10: Intramolecular Claisen Condensations - The Dieckmann Cyclization - *CC BY-NC-SA 4.0*
- 12.11: Conjugate Carbonyl Additions - The Michael Reaction - *CC BY-NC-SA 4.0*
- 12.12: Carbonyl Condensations with Enamines - The Stork Enamine Reaction - *CC BY-NC-SA 4.0*
- 12.13: The Robinson Annulation Reaction - *CC BY-NC-SA 4.0*
- 12.14: Some Biological Carbonyl Condensation Reactions - *CC BY-NC-SA 4.0*
- 12.15: Chemistry Matters - A Prologue to Metabolism - *CC BY-NC-SA 4.0*
- 12.16: Key Terms - *CC BY-NC-SA 4.0*
- 12.17: Summary - *CC BY-NC-SA 4.0*
- 12.18: Summary of Reactions - *CC BY-NC-SA 4.0*
- 12.19: Additional Problems - *CC BY-NC-SA 4.0*

13: Amines and Heterocycles - *CC BY-NC-SA 4.0*

- 13.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 13.2: Naming Amines - *CC BY-NC-SA 4.0*
- 13.3: Structure and Properties of Amines - *CC BY-NC-SA 4.0*
- 13.4: Basicity of Amines - *CC BY-NC-SA 4.0*
- 13.5: Basicity of Arylamines - *CC BY-NC-SA 4.0*
- 13.6: Biological Amines and the Henderson-Hasselbalch Equation - *CC BY-NC-SA 4.0*
- 13.7: Synthesis of Amines - *CC BY-NC-SA 4.0*
- 13.8: Reactions of Amines - *CC BY-NC-SA 4.0*
- 13.9: Reactions of Arylamines - *CC BY-NC-SA 4.0*
- 13.10: Heterocyclic Amines - *CC BY-NC-SA 4.0*
- 13.11: Spectroscopy of Amines - *CC BY-NC-SA 4.0*
- 13.12: Chemistry Matters - Green Chemistry II- Ionic Liquids - *CC BY-NC-SA 4.0*
- 13.13: Key Terms - *CC BY-NC-SA 4.0*
- 13.14: Summary - *CC BY-NC-SA 4.0*
- 13.15: Summary of Reactions - *CC BY-NC-SA 4.0*
- 13.16: Additional Problems - *CC BY-NC-SA 4.0*

14: Orbitals and Organic Chemistry - Pericyclic Reactions - *CC BY-NC-SA 4.0*

- 14.1: Why This Chapter? - *CC BY-NC-SA 4.0*
- 14.2: Molecular Orbitals of Conjugated Pi Systems - *CC BY-NC-SA 4.0*
- 14.3: Electrocyclic Reactions - *CC BY-NC-SA 4.0*
- 14.4: Stereochemistry of Thermal Electrocyclic Reactions - *CC BY-NC-SA 4.0*
- 14.5: Photochemical Electrocyclic Reactions - *CC BY-NC-SA 4.0*
- 14.6: Cycloaddition Reactions - *CC BY-NC-SA 4.0*
- 14.7: Stereochemistry of Cycloadditions - *CC BY-NC-SA 4.0*
- 14.8: Sigmatropic Rearrangements - *CC BY-NC-SA 4.0*
- 14.9: Some Examples of Sigmatropic Rearrangements - *CC BY-NC-SA 4.0*
- 14.10: A Summary of Rules for Pericyclic Reactions - *CC BY-NC-SA 4.0*
- 14.11: Chemistry Matters—Vitamin D, the Sunshine Vitamin - *CC BY-NC-SA 4.0*
- 14.12: Key Terms - *CC BY-NC-SA 4.0*
- 14.13: Summary - *CC BY-NC-SA 4.0*
- 14.14: Additional Problems - *CC BY-NC-SA 4.0*

Back Matter - *Undeclared*

- Index - *Undeclared*
- Glossary - *Undeclared*
- Detailed Licensing - *Undeclared*
- Detailed Licensing - *Undeclared*