The carbonyl group—a carbon double bonded to an oxygen—is probably the most important functional group found in organic compounds. Compounds containing carbonyl groups—called carbonyl compounds—are abundant in nature. Many play important roles in biological processes. Hormones, vitamins, amino acids, drugs, and flavorings are just a few of the carbonyl compounds that affect us daily. An acyl group consists of a carbonyl group attached to an alkyl group or to an aryl group.

The substituents attached to the acyl group strongly affect the reactivity of carbonyl compounds. Carbonyl compounds can be divided into two classes. Class I carbonyl compounds are those in which the acyl group is attached to an atom or a group that can be replaced by another group. Carboxylic acids, acyl halides, acid anhydrides, esters, and amides belong to this class. All of these compounds contain a group (—OH, —Cl, —Br, —O(CO)R, —OR, —NH₂, —NHR, or —NR₂) that can be replaced by a nucleophile. Acyl halides, acid anhydrides, esters, and amides are all called carboxylic acid derivatives because they differ from a carboxylic acid only in the nature of the group that has replaced the OH group of the carboxylic acid.
Class II carbonyl compounds are those in which the acyl group is attached to a group that cannot be readily replaced by another group. Aldehydes and ketones belong to this class. The —H and alkyl or aryl (—R or —Ar) groups of aldehydes and ketones cannot be replaced by a nucleophile.

In Chapter 10, we saw that the likelihood of a group’s being replaced by another group depends on the relative basicities of the two groups: The weaker the basicity of a group, the better its leaving ability. Recall from Section 10.3 that weak bases are good leaving groups because weak bases do not share their electrons as well as strong bases do.

The $pK_a$ values of the conjugate acids of the leaving groups of various carbonyl compounds are listed in Table 17.1. Notice that the acyl groups of Class I carbonyl compounds are attached to weaker bases than are the acyl groups of Class II carbonyl compounds. (Remember that the lower the $pK_a$, the stronger the acid and the weaker its conjugate base.) The —H of an aldehyde and the alkyl or aryl (—R or —Ar) group of a ketone are too basic to be replaced by another group.

This chapter discusses the reactions of Class I carbonyl compounds. We will see that these compounds undergo substitution reactions because they have an acyl group attached to a group that can be replaced by a nucleophile. The reactions of aldehydes and ketones will be considered in Chapter 18. Because aldehydes and ketones have an acyl group attached to a group that cannot be replaced by a nucleophile, we can correctly predict that these compounds do not undergo substitution reactions.

### 17.1 Nomenclature

**Carboxylic Acids**

In systematic nomenclature, a carboxylic acid is named by replacing the terminal “e” of the alkane name with “oic acid.” For example, the one-carbon alkane is methane, so the one-carbon carboxylic acid is methanoic acid.
Carboxylic acids containing six or fewer carbons are frequently called by their common names. These names were chosen by early chemists to describe some feature of the compound, usually its origin. For example, formic acid is found in ants, bees, and other stinging insects; its name comes from *formica*, which is Latin for “ant.” Acetic acid—contained in vinegar—got its name from *acetum*, the Latin word for “vinegar.” Propionic acid is the smallest acid that shows some of the characteristics of the larger fatty acids; its name comes from the Greek words *pro* (“the first”) and *pion* (“fat”). Butyric acid is found in rancid butter; the Latin word for “butter” is *butyrum*. Caproic acid is found in goat’s milk, and if you have the occasion to smell both a goat and caproic acid, you will find that they have similar odors. *Caper* is the Latin word for “goat.”

In systematic nomenclature, the position of a substituent is designated by a number. The carbonyl carbon of a carboxylic acid is always the C-1 carbon. In common nomenclature, the position of a substituent is designated by a lowercase Greek letter, and the carbonyl carbon is not given a designation. The carbon adjacent to the carbonyl carbon is the α-carbon, the carbon adjacent to the α-carbon is the β-carbon, and so on.

<table>
<thead>
<tr>
<th>Carbonyl compound</th>
<th>Leaving group</th>
<th>Conjugate acid of the leaving group</th>
<th>pKₐ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{R-CHO} )</td>
<td>( \text{Br}^- )</td>
<td>HBr</td>
<td>−9</td>
</tr>
<tr>
<td>( \text{R-CHO} )</td>
<td>( \text{Cl}^- )</td>
<td>HCl</td>
<td>−7</td>
</tr>
<tr>
<td>( \text{R-COO} )</td>
<td>( \text{R-COO} )</td>
<td>R-COH</td>
<td>~3–5</td>
</tr>
<tr>
<td>( \text{R-COOR'} )</td>
<td>( \text{R'OR} )</td>
<td>R'OH</td>
<td>~15–16</td>
</tr>
<tr>
<td>( \text{R-COOH} )</td>
<td>( \text{OH} )</td>
<td>H₂O</td>
<td>15.7</td>
</tr>
<tr>
<td>( \text{R-CO(NH₂)} )</td>
<td>( \text{NH₂} )</td>
<td>NH₃</td>
<td>36</td>
</tr>
<tr>
<td><strong>Class II</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{R-CHO} )</td>
<td>( \text{H}^- )</td>
<td>H₂</td>
<td>~40</td>
</tr>
<tr>
<td>( \text{R-CHO} )</td>
<td>( \text{R}^- )</td>
<td>RH</td>
<td>~50</td>
</tr>
</tbody>
</table>

Table 17.1 The pKₐ Values of the Conjugate Acids of the Leaving Groups of Carbonyl Compounds
Take a careful look at the following examples to make sure that you understand the difference between systematic (IUPAC) and common nomenclature:

The functional group of a carboxylic acid is called a **carboxyl group**.

Carboxylic acids in which a carboxyl group is attached to a ring are named by adding “carboxylic acid” to the name of the cyclic compound.

**Acyl Halides**

Acyl halides are compounds that have a halogen atom in place of the OH group of a carboxylic acid. The most common acyl halides are acyl chlorides and acyl bromides. Acyl halides are named by using the acid name and replacing “ic acid” with “yl chloride” (or “yl bromide”). For acids ending with “carboxylic acid,” “carboxylic acid” is replaced with “carbonyl chloride” (or “bromide”).

**Acid Anhydrides**

Loss of water from two molecules of a carboxylic acid results in an **acid anhydride**. “Anhydride” means “without water.”

If the two carboxylic acid molecules forming the acid anhydride are the same, the anhydride is a **symmetrical anhydride**. If the two carboxylic acid molecules are different, the anhydride is a **mixed anhydride**. Symmetrical anhydrides are named by using the acid name and replacing “acid” with “anhydride.” Mixed anhydrides are named by stating the names of both acids in alphabetical order, followed by “anhydride.”
Esters

An ester is a compound that has an OR’ group in place of the OH group of a carboxylic acid. In naming an ester, the name of the group (R’) attached to the carboxyl oxygen is stated first, followed by the name of the acid, with “ic acid” replaced by “ate.”

Salts of carboxylic acids are named in the same way. The cation is named first, followed by the name of the acid, again with “ic acid” replaced by “ate.”

Cyclic esters are called lactones. In systematic nomenclature, they are named as “2-oxacycloalkanones.” Their common names are derived from the common name of the carboxylic acid, which designates the length of the carbon chain, and a Greek letter to indicate the carbon to which the carboxyl oxygen is attached. Thus, four-membered ring lactones are β-lactones (the carboxyl oxygen is on the β-carbon), five-membered ring lactones are γ-lactones, and six-membered ring lactones are δ-lactones.

PROBLEM 1

The word “lactone” has its origin in lactic acid, a three-carbon carboxylic acid with an OH group on the α-carbon. Ironically, lactic acid cannot form a lactone. Why not?
Amides
An amide has an NH₂, NHR, or NR₂ group in place of the OH group of a carboxylic acid. Amides are named by using the acid name, replacing "oic acid" or "ic acid" with "amide." For acids ending with "carboxylic acid," "ylic acid" is replaced with "amide."

If a substituent is bonded to the nitrogen, the name of the substituent is stated first (if there is more than one substituent bonded to the nitrogen, they are stated alphabetically), followed by the name of the amide. The name of each substituent is preceded by a capital N to indicate that the substituent is bonded to a nitrogen.

Cyclic amides are called lactams. Their nomenclature is similar to that of lactones. They are named as “2-azacycloalkanones” in systematic nomenclature (“aza” is used to designate the nitrogen atom). In their common names, the length of the carbon chain is indicated by the common name of the carboxylic acid, and a Greek letter indicates the carbon to which the nitrogen is attached.

Nitriles
Nitriles are compounds that contain a C≡N functional group. Nitriles are considered carboxylic acid derivatives because, like all Class I carbonyl compounds, they react with water to form carboxylic acids (Section 17.18). In systematic nomenclature, nitriles are named by adding “nitrile” to the parent alkane name. Notice that the triple-bonded carbon of the nitrile group is counted in the number of carbons in the longest continuous chain. In common nomenclature, nitriles are named by replacing “ic acid” of the carboxylic acid name with “onitrile.” They can also be named as alkyl cyanides—stating the name of the alkyl group that is attached to the C≡N group.
CHAPTER 17  Carbonyl Compounds I

PROBLEM 2

Name the following compounds:

a. CH₃CH₂CH₂C≡N  

b. CH₃CO₂CH₃  
c. CH₃CH₂CO₂⁻K⁺  
d. CH₃CH₂CH₂CH₂Cl  
e. CH₃CH₂COCH₂CH₃  
f. CH₃CH₂CH₂CH₂CN(CH₃)₂  
g. CH₃CN  
h.  
i. 

PROBLEM 3

Write a structure for each of the following compounds:

a. phenyl acetate  
b. γ-caprolactam  
c. butanenitrile  
d. N-benzylethanamide  
e. γ-caproic acid  
f. ethyl 2-chloropentanoate  
g. β-bromobutyramide  
h. propanoic anhydride  
i. cyclohexanecarbonyl chloride

17.2 Structures of Carboxylic Acids  
and Carboxylic Acid Derivatives

The **carbonyl carbon** in carboxylic acids and carboxylic acid derivatives is \( sp^2 \) hybridized. It uses its three \( sp^2 \) orbitals to form \( σ \) bonds to the carbonyl oxygen, the \( α \)-carbon, and a substituent (Y). The three atoms attached to the carbonyl carbon are in the same plane, and their bond angles are each approximately 120°.

![Figure 17.1](https://example.com/fig17.1.png)  
**Figure 17.1**  
Bonding in a carbonyl group.  
The \( π \) bond is formed by side-to-side overlap of a \( p \) orbital of carbon with a \( p \) orbital of oxygen.  
The **carbonyl oxygen** is also \( sp^2 \) hybridized. One of its \( sp^2 \) orbitals forms a \( σ \) bond with the carbonyl carbon, and each of the other two \( sp^2 \) orbitals contains a lone pair. The remaining \( p \) orbital of the carbonyl oxygen overlaps with the remaining \( p \) orbital of the carbonyl carbon to form a \( π \) bond (Figure 17.1).
Esters, carboxylic acids, and amides each have two major resonance contributors. The second resonance contributor for acyl chlorides and acid anhydrides is much less important.

The second resonance contributor (the one on the right) is more important for the amide than it is for the ester or for the carboxylic acid because nitrogen is better than oxygen at sharing its electrons. Nitrogen is less electronegative than oxygen and, therefore, is better able to accommodate a positive charge.

**PROBLEM 4**
Which is longer, the carbon–oxygen single bond in a carboxylic acid or the carbon–oxygen bond in an alcohol? Why?

**PROBLEM 5**
There are three carbon–oxygen bonds in methyl acetate.

a. What are their relative lengths?
b. What are the relative infrared (IR) stretching frequencies of these bonds?

**PROBLEM 6**
Match the compound with the appropriate carbonyl IR absorption band:

- acyl chloride: ~1800 and 1750 cm\(^{-1}\)
- acid anhydride: ~1640 cm\(^{-1}\)
- ester: ~1730 cm\(^{-1}\)
- amide: ~1800 cm\(^{-1}\)

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17.3 Physical Properties of Carbonyl Compounds

The acid properties of carboxylic acids have been discussed previously (Sections 1.18 and 7.10). Recall that carboxylic acids have pK\(_a\) values of approximately 3–5 (Appendix II; see also “Special Topics I” in the Study Guide and Solutions Manual). The acid properties of dicarboxylic acids will be discussed in Section 17.21. The boiling points and other physical properties of carbonyl compounds are listed in Appendix I. Carbonyl compounds have the following relative boiling points:

**relative boiling points**

- amide > carboxylic acid > nitrile >>> ester ~ acyl chloride ~ aldehyde ~ ketone
The boiling points of the ester, acyl chloride, ketone, and aldehyde are lower than the boiling point of the alcohol with a comparable molecular weight because the molecules of those carbonyl compounds are unable to form hydrogen bonds with each other. The boiling points of the carbonyl compounds are higher than the boiling point of the ether because of the polar carbonyl group.

Carboxylic acids have relatively high boiling points because they form intermolecular hydrogen bonds, giving them larger effective molecular weights.

Amides have the highest boiling points, because they have strong dipole–dipole interactions since the resonance contributor with separated charges contributes significantly to the overall structure of the compound (Section 17.2). If the nitrogen of an amide is bonded to a hydrogen, hydrogen bonds will form between the molecules. The boiling point of a nitrile is similar to that of an alcohol because a nitrile has strong dipole–dipole interactions (Section 2.9).

Carboxylic acid derivatives are soluble in solvents such as ethers, chlorinated alkanes, and aromatic hydrocarbons. Like alcohols and ethers, carbonyl compounds with fewer than four carbons are soluble in water. Esters, N,N-disubstituted amides, and nitriles are often used as solvents because they are polar, but do not have reactive hydroxyl or amino groups. We have seen that dimethylformamide (DMF) is a common aprotic polar solvent (Section 10.3).

### Naturally Occurring Carboxylic Acids and Carboxylic Acid Derivatives

Acyl halides and acid anhydrides are much more reactive than carboxylic acids and esters, which, in turn, are more reactive than amides. We will see the reason for this difference in reactivity in Section 17.5.

Because of their high reactivity, acyl halides and acid anhydrides are not found in nature. Carboxylic acids, on the other hand, are less reactive and are found widely in nature. For example, glucose is metabolized to pyruvic acid. (S)-(+) Lactic acid is the
compound responsible for the burning sensation felt in muscles during anaerobic exercise, and it is also found in sour milk. Spinach and other leafy green vegetables are rich in oxalic acid. Succinic acid and citric acid are important intermediates in the citric acid cycle (Section 25.1), a series of reactions that oxidize acetyl-CoA to CO₂ in biological systems. Citrus fruits are rich in citric acid; the concentration is greatest in lemons, less in grapefruits, and still less in oranges. (S)-(-)-Malic acid is responsible for the sharp taste of unripe apples and pears. As the fruit ripens, the amount of malic acid in the fruit decreases and the amount of sugar increases. The inverse relationship between the levels of malic acid and sugar is important for the propagation of the plant: Animals will not eat the fruit until it becomes ripe—at which time its seeds are mature enough to germinate when they are scattered about. Prostaglandins are locally acting hormones that have several different physiological functions (Sections 17.10 and 26.5), such as stimulating inflammation, causing hypertension, and producing pain and swelling.

Esters are also commonly found in nature. Many of the fragrances of flowers and fruits are due to esters. (See Problem 27.)

Carboxylic acids with an amino group on the α-carbon are commonly called amino acids. Amino acids are linked together by amide bonds to form peptides and proteins (Section 23.7). Caffeine, another naturally occurring amide, is found in cocoa and coffee beans. Penicillin G, a compound with two amide bonds (one of which is in a β-lactam ring), was first isolated from a mold in 1928 by Sir Alexander Fleming.


**THE DISCOVERY OF PENICILLIN**

Sir Alexander Fleming (1881–1955) was born in Scotland. He was a professor of bacteriology at University College, London. The story is told that one day Fleming was about to throw away a culture of staphylococcal bacteria that had been contaminated by a rare strain of the mold *Penicillium notatum*. He noticed that the bacteria had disappeared wherever there was a particle of mold. This suggested to him that the mold must have produced an antibacterial substance. Ten years later, Howard Florey and Ernest Chain isolated the active substance—penicillin G (Section 17.16)—but the delay allowed the sulfa drugs to be the first antibiotics. After penicillin G was found to cure bacterial infections in mice, it was used successfully in 1941 on nine cases of human bacterial infections. By 1943, penicillin G was being produced for the military and was first used for war casualties in Sicily and Tunisia. The drug became available to the civilian population in 1944. The pressure of the war made the determination of penicillin G’s structure a priority because once its structure was determined, large quantities of the drug could be produced.

Fleming, Florey, and Chain shared the 1945 Nobel Prize in physiology or medicine. Chain also discovered penicillinase, the enzyme that destroys penicillin (Section 17.16). Although Fleming is generally given credit for the discovery of penicillin, there is clear evidence that the germicidal activity of the mold was recognized in the nineteenth century by Lord Joseph Lister (1827–1912), the English physician renowned for the introduction of aseptic surgery.

Sir Alexander Fleming (1881–1955) was born in Australia and received a medical degree from the University of Adelaide. He went to England as a Rhodes Scholar and studied at both Oxford and Cambridge Universities. He became a professor of pathology at the University of Sheffield in 1931 and then at Oxford in 1935. Knighted in 1944, he was given a peerage in 1965 that made him Baron Florey of Adelaide.

Ernest B. Chain (1906–1979) was born in Germany and received a Ph.D. from Friedrich-Wilhelm University in Berlin. In 1933, he left Germany for England because Hitler had come to power. He studied at Cambridge, and in 1935 Florey invited him to Oxford. In 1948, he became the director of an institute in Rome, but he returned to England in 1961 to become a professor at the University of London.

**DALMATIANS: DON’T TRY TO FOOL MOTHER NATURE**

When amino acids are metabolized, the excess nitrogen is concentrated into uric acid, a compound with five amide bonds. A series of enzyme-catalyzed reactions degrades uric acid to ammonium ion. The extent to which uric acid is degraded in animals depends on the species. Birds, reptiles, and insects excrete excess nitrogen as uric acid. Mammals excrete excess nitrogen as allantoin. Excess nitrogen in aquatic animals is excreted as allantoic acid, urea, or ammonium salts.

![Diagram of the process](image)

Dalmatians, unlike other mammals, excrete high levels of uric acid. The reason for this is that breeders of Dalmatians select dogs that have no white hairs in their black spots, and the gene that causes the white hairs is linked to the gene that causes uric acid to be converted to allantoin. Dalmatians, therefore, are susceptible to gout (painful deposits of uric acid in joints).
17.5 How Class I Carbonyl Compounds React

The reactivity of carbonyl compounds resides in the polarity of the carbonyl group; oxygen is more electronegative than carbon. The carbonyl carbon, therefore, is an electrophile, so we can safely predict that it will be attacked by nucleophiles.

When a nucleophile attacks the carbonyl carbon of a carboxylic acid derivative, the carbon–oxygen $\pi$ bond breaks and an intermediate is formed. The intermediate is called a tetrahedral intermediate because the trigonal ($sp^2$) carbon in the reactant has become a tetrahedral ($sp^3$) carbon in the intermediate. Generally, a compound that has an $sp^3$ carbon bonded to an oxygen atom will be unstable if the $sp^3$ carbon is bonded to another electronegative atom. The tetrahedral intermediate, therefore, is unstable because $Y$ and $Z$ are both electronegative atoms. A lone pair on the oxygen reforms the $\pi$ bond, and either $Y^-$ ($k_2$) or $Z^-$ ($k_{-1}$) is expelled with its bonding electrons.

Whether $Y^-$ or $Z^-$ is expelled depends on their relative basicities. The weaker base is expelled preferentially, making this another example of the principle we first saw in Section 10.3: *The weaker the base, the better it is as a leaving group.* Because a weak base does not share its electrons as well as a strong base does, a weaker base forms a weaker bond—one that is easier to break. If $Z^-$ is a much weaker base than $Y^-$, $Z^-$ will be expelled. In such a case, $k_{-1} \gg k_2$, and the reaction can be written as follows:

In this case, no new product is formed. The nucleophile attacks the carbonyl carbon, but the tetrahedral intermediate expels the attacking nucleophile and reforms the reactants.

On the other hand, if $Y^-$ is a much weaker base than $Z^-$, $Y^-$ will be expelled and a new product will be formed. In this case, $k_2 \gg k_{-1}$, and the reaction can be written as follows:

A compound that has an $sp^3$ carbon bonded to an oxygen atom generally will be unstable if the $sp^3$ carbon is bonded to another electronegative atom.

The weaker the base, the better it is as a leaving group.
This reaction is called a **nucleophilic acyl substitution reaction** because a nucleophile \((Z^-)\) has replaced the substituent \((Y^-)\) that was attached to the acyl group in the reactant. It is also called an **acyl transfer reaction** because an acyl group has been transferred from one group \((Y^-)\) to another \((Z^-)\).

If the basicities of \(Y^-\) and \(Z^-\) are similar, the values of \(k_{-1}\) and \(k_2\) will be similar. Therefore, some molecules of the tetrahedral intermediate will expel \(Y^-\) and others will expel \(Z^-\). When the reaction is over, reactant and product will both be present. The relative amounts of each will depend on the relative basicities of \(Y^-\) and \(Z^-\)—that is, the relative values of \(k_2\) and \(k_{-1}\)—as well as the relative nucleophilicities of \(Y^-\) and \(Z^-\)—that is, the relative values of \(k_1\) and \(k_{-2}\).

These three cases are illustrated by the reaction coordinate diagrams shown in Figure 17.2.

1. If the new group in the tetrahedral intermediate is a weaker base than the group that was attached to the acyl group in the reactant, the easier pathway—the lower energy hill—is for the tetrahedral intermediate (TI) to expel the newly added group and reform the reactants, so no reaction takes place (Figure 17.2a).

2. If the new group in the tetrahedral intermediate is a stronger base than the group that was attached to the acyl group in the reactant, the easier pathway is for the tetrahedral intermediate to expel the group that was attached to the acyl group in the reactant and form a substitution product (Figure 17.2b).

3. If both groups in the tetrahedral intermediate have similar basicities, the tetrahedral intermediate can expel either group with similar ease. A mixture of reactant and substitution product will result (Figure 17.2c).

We can make the following general statement about the reactions of carboxylic acid derivatives: **A carboxylic acid derivative will undergo a nucleophilic acyl substitution reaction, provided that the newly added group in the tetrahedral intermediate is not a much weaker base than the group that was attached to the acyl group in the reactant.**

For a carboxylic acid derivative to undergo a nucleophilic acyl substitution reaction, the incoming nucleophile must not be a much weaker base than the group that is to be replaced.
Let's now look at a molecular orbital description of how carbonyl compounds react. In Section 1.6, which first introduced you to molecular orbital theory, you saw that because oxygen is more electronegative than carbon, the 2\(p\) orbital of oxygen contributes more to the \(\pi\) bonding molecular orbital—it is closer to it in energy—and the 2\(p\) orbital of carbon contributes more to the \(\pi^*\) antibonding molecular orbital. (See Figure 1.8.) This means that the \(\pi^*\) antibonding orbital is largest at the carbon atom, so that is where the nucleophile's nonbonding orbital—in which the lone pair resides—overlaps. This allows the greatest amount of orbital overlap, and greater overlap means greater stability. When a filled orbital and an empty orbital overlap, the result is a molecular orbital—that is more stable than either of the overlapping orbitals (Figure 17.3).

**Figure 17.3**
The filled nonbonding orbital containing the nucleophile's lone pair overlaps the empty \(\pi^*\) antibonding molecular orbital of the carbonyl group, forming the new \(\sigma\) bond in the tetrahedral intermediate.

**PROBLEM 7**
Using the \(pK_a\) values in Table 17.1, predict the products of the following reactions:

a. \(\text{CH}_3\text{C}=\text{O} \cdot \text{OCH}_3 + \text{NaCl} \rightarrow \)

b. \(\text{CH}_3\text{C}=\text{O} \cdot \text{Cl} + \text{NaOH} \rightarrow \)

c. \(\text{CH}_3\text{C}=\text{O} \cdot \text{Cl} + \text{CH}_3\text{CO}^+\text{Na}^- \rightarrow \)

d. \(\text{CH}_3\text{C}=\text{O} \cdot \text{OCH}_3 + \text{NaCl} \rightarrow \)

**PROBLEM 8**
Is the following statement true or false?

If the newly added group in the tetrahedral intermediate is a stronger base than the group attached to the acyl group in the reactant, formation of the tetrahedral intermediate is the rate-limiting step of a nucleophilic acyl substitution reaction.

17.6 **Relative Reactivities of Carboxylic Acids and Carboxylic Acid Derivatives**

We have just seen that there are two steps in a nucleophilic acyl substitution reaction: formation of a tetrahedral intermediate and collapse of the tetrahedral intermediate. The weaker the base attached to the acyl group, the easier it is for both steps of the
reaction to take place. In other words, the reactivity of a carboxylic acid derivative depends on the basicity of the substituent attached to the acyl group: the less basic the substituent, the more reactive the carboxylic acid derivative.

**relative basicities of the leaving groups**

![Diagram showing relative basicities of the leaving groups: Cl\(^-\) < OCR < OR < OH < NH\(_2\)\(^-\)](image)

**relative reactivities of carboxylic acid derivatives**

![Diagram showing relative reactivities of carboxylic acid derivatives: acyl chloride > acid anhydride > ester > carboxylic acid > amide](image)

How does having a weak base attached to the acyl group make the first step of the nucleophilic substitution reaction easier? First of all, a weaker base is a more electronegative base; that is, it is better able to accommodate its negative charge (Section 1.18). Thus, weaker bases are better at withdrawing electrons inductively from the carbonyl carbon (Section 1.18); electron withdrawal increases the carbonyl carbon’s susceptibility to nucleophilic attack.

![Diagram showing inductive electron withdrawal by Y increases the electrophilicity of the carbonyl carbon](image)

Second, the weaker the basicity of Y, the smaller is the contribution from the resonance contributor with a positive charge on Y (Section 17.2); the less the carboxylic acid derivative is stabilized by electron delocalization, the more reactive it will be.

![Diagram showing resonance contributors of a carboxylic acid or carboxylic acid derivative](image)

A weak base attached to the acyl group will also make the second step of the nucleophilic acyl substitution reaction easier because weak bases are easier to eliminate when the tetrahedral intermediate collapses.

![Diagram showing the weaker the base, the easier it is to eliminate](image)

In Section 17.4 we saw that in a nucleophilic acyl substitution reaction, the nucleophile that forms the tetrahedral intermediate must be a stronger base than the base that is already there. This means that a carboxylic acid derivative can be converted into a less reactive carboxylic acid derivative, but not into one that is more reactive. For example, an acyl chloride can be converted into an anhydride because a carboxylate ion is a stronger base than a chloride ion.
Section 17.7 General Mechanism for Nucleophilic Acyl Substitution Reactions

All carboxylic acid derivatives undergo nucleophilic acyl substitution reactions by the same mechanism. If the nucleophile is negatively charged, the mechanism discussed in Section 17.5 is followed: The nucleophile attacks the carbonyl carbon, forming a tetrahedral intermediate. When the tetrahedral intermediate collapses, the weaker base is eliminated.

If the nucleophile is neutral, the mechanism has an additional step. A proton is lost from the tetrahedral intermediate formed in the first step, resulting in a tetrahedral intermediate equivalent to the one formed by negatively charged nucleophiles. This tetrahedral intermediate expels the weaker of the two bases—the newly added group after it has lost a proton or the group that was attached to the acyl group in the reactant. (HB represents any species in the solution that is capable of donating a proton, and \( \cdot B \) represents any species in the solution that is capable of removing a proton.)

The remaining sections of this chapter cover specific examples of these general principles. Keep in mind that all the reactions follow the same mechanism. Therefore, you can always determine the outcome of the reactions of carboxylic acids and carboxylic acid derivatives presented in this chapter by examining the tetrahedral intermediate and remembering that the weaker base is preferentially eliminated (Section 17.5).
PROBLEM 9+

What will be the product of a nucleophilic acyl substitution reaction—a new carboxylic acid derivative, a mixture of two carboxylic acid derivatives, or no reaction—if the new group in the tetrahedral intermediate is the following?

a. a stronger base than the group that was already there
b. a weaker base than the group that was already there
c. similar in basicity to the group that was already there

17.8 Reactions of Acyl Halides

Acyl halides react with carboxylate ions to form anhydrides, with alcohols to form esters, with water to form carboxylic acids, and with amines to form amides because in each case the incoming nucleophile is a stronger base than the departing halide ion (Table 17.1). Notice that both alcohols and phenols can be used to prepare esters.

$$\text{acetyl chloride} + \text{CH}_3\text{CO}^- \rightarrow \text{acetic anhydride} + \text{Cl}^-$$

$$\text{benzoyl chloride} + \text{CH}_3\text{OH} \rightarrow \text{methyl benzoate} + \text{H}^+ + \text{Cl}^-$$

$$\text{propionyl chloride} + \text{PhOH} \rightarrow \text{phenyl propionate} + \text{H}^+ + \text{Cl}^-$$

$$\text{butyryl chloride} + \text{H}_2\text{O} \rightarrow \text{butyric acid} + \text{H}^+ + \text{Cl}^-$$

$$\text{cyclohexanecarbonyl chloride} + 2\text{CH}_3\text{NH}_2 \rightarrow \text{N-methylcyclohexanecarboxamide} + \text{CH}_3\text{NH}_3\text{Cl}^-$$

All the reactions follow the general mechanism described in Section 17.7. In the conversion of an acyl chloride into an acid anhydride, the nucleophilic carboxylate ion attacks the carbonyl carbon of the acyl chloride. Because the resulting tetrahedral intermediate is unstable, the double bond is immediately reformed, expelling chloride ion because it is a weaker base than the carboxylate ion. The final product is an anhydride.
Section 17.8  Reactions of Acyl Halides

In the conversion of an acyl chloride into an ester, the nucleophilic alcohol attacks the carbonyl carbon of the acyl chloride. Because the protonated ether group is a strong acid (Section 1.17), the tetrahedral intermediate loses a proton. Chloride ion is expelled from the deprotonated tetrahedral intermediate because chloride ion is a weaker base than the alkoxide ion.

The reaction of an acyl chloride with ammonia or with a primary or secondary amine forms an amide and HCl. The acid generated in the reaction will protonate unreacted ammonia or unreacted amine; because they are not nucleophiles, the protonated amines cannot react with the acyl chloride. The reaction, therefore, must be carried out with twice as much ammonia or amine as acyl chloride so that there will be enough amine to react with all the acyl halide.

Because tertiary amines cannot form amides, an equivalent of a tertiary amine such as triethylamine or pyridine can be used instead of excess amine.
PROBLEM 10 SOLVED

a. Two amides are obtained from the reaction of acetyl chloride with a mixture of ethylamine and propylamine. Identify the amides.
b. Only one amide is obtained from the reaction of acetyl chloride with a mixture of ethylamine and pyridine. Why is only one amide obtained?

SOLUTION TO 10a Either of the amines can react with acetyl chloride, so both N-ethylacetamide and N-propylacetamide are formed.

\[
\begin{align*}
\text{CH}_3\text{Cl} + \text{CH}_3\text{CH}_2\text{NH}_2 + \text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2 & \rightarrow \text{CH}_3\text{C} = \text{O} - \text{NHCH}_2\text{CH}_3 + \text{CH}_3\text{C} = \text{O} - \text{NHCH}_2\text{CH}_2\text{CH}_3 \\
& \quad + \text{CH}_3\text{CH}_2\text{NH}_3\text{Cl}^- + \text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_3\text{Cl}^-
\end{align*}
\]

SOLUTION TO 10b Initially two amides are formed. However, the amide formed by pyridine (a tertiary amine) is very reactive because it has a positively charged nitrogen atom, which makes it an excellent leaving group. Therefore, it will react immediately with unreacted ethylamine, causing N-ethylacetamide to be the only amide formed in the reaction.

PROBLEM 11
Although excess amine is necessary in the reaction of an acyl chloride with an amine, explain why it is not necessary to use excess alcohol in the reaction of an acyl chloride with an alcohol.

PROBLEM 12
Write the mechanism for the following reactions:
a. the reaction of acetyl chloride with water to form acetic acid
b. the reaction of acetyl bromide with methylamine to form N-methylacetamide

PROBLEM 13◆
Starting with acetyl chloride, what nucleophile would you use to make each of the following compounds?

a. CH₃COCH₂CH₂CH₃      c. CH₃CN(CH₃)₂      e. CH₃COCCH₃
b. CH₃CNHCH₂CH₃      d. CH₃COH      f. CH₃COC₆H₄NO₂
Acid anhydrides do not react with sodium chloride or with sodium bromide because the incoming halide ion is a weaker base than the departing carboxylate ion (Table 17.1).

\[
\text{CH}_3\text{C}O\backslash\text{C}O\backslash\text{CH}_3 + \text{Cl}^- \rightarrow \text{no reaction}
\]

Because the incoming halide ion is the weaker base, it will be the substituent expelled from the tetrahedral intermediate.

An acid anhydride reacts with an alcohol to form an ester and a carboxylic acid, with water to form two equivalents of a carboxylic acid, and with an amine to form an amide and a carboxylate ion. In each case, the incoming nucleophile—after it loses a proton—is a stronger base than the departing carboxylate ion. In the reaction of an amine with an anhydride, two equivalents of the amine or one equivalent of the amine plus one equivalent of a tertiary amine such as pyridine must be used so that sufficient amine is present to react with the proton produced in the reaction.

All the reactions follow the general mechanism described in Section 17.7. For example, compare the following mechanism for conversion of an acid anhydride into an ester with the mechanism for conversion of an acyl chloride into an ester presented on p. 687.
CHAPTER 17 Carbonyl Compounds I

PROBLEM 14

a. Propose a mechanism for the reaction of acetic anhydride with water.
b. How does this mechanism differ from the mechanism for the reaction of acetic anhydride with an alcohol?

PROBLEM 15

We have seen that acid anhydrides react with alcohols, water, and amines. In which one of these three reactions does the tetrahedral intermediate not have to lose a proton before it eliminates the carboxylate ion? Explain.

17.10 Reactions of Esters

Esters do not react with halide ions or with carboxylate ions because these nucleophiles are much weaker bases than the RO\(^{-}\) leaving group of the ester (Table 17.1).

An ester reacts with water to form a carboxylic acid and an alcohol. This is an example of a hydrolysis reaction—a reaction with water that converts one compound into two compounds (\(\text{lysis}\) is Greek for “breaking down”).

**a hydrolysis reaction**

\[
\text{CH}_3\text{C}(\text{O})\text{OCH}_3 + \text{H}_2\text{O} \xrightarrow{\text{HCl}} \text{CH}_3\text{C}(\text{O})\text{OH} + \text{CH}_3\text{OH}
\]

An ester reacts with an alcohol to form a new ester and a new alcohol. This is an example of an alcoholysis reaction. This particular alcoholysis reaction is also called a transesterification reaction because one ester is converted to another ester.

**a transesterification reaction**

\[
\text{C}_6\text{H}_5\text{C}(\text{O})\text{OCH}_3 + \text{CH}_3\text{CH}_2\text{OH} \xrightarrow{\text{HCl}} \text{C}_6\text{H}_5\text{C}(\text{O})\text{OCH}_2\text{CH}_3 + \text{CH}_3\text{OH}
\]

Both the hydrolysis and the alcoholysis of an ester are very slow reactions because water and alcohols are poor nucleophiles and esters have very basic leaving groups. These reactions, therefore, are always catalyzed when carried out in the laboratory. Both hydrolysis and alcoholysis of an ester can be catalyzed by acids. (See Section 17.11.) The rate of hydrolysis can also be increased by hydroxide ion, and the rate of alcoholysis can be increased by the conjugate base (RO\(^{-}\)) of the reactant alcohol (Section 17.12).

Esters also react with amines to form amides. A reaction with an amine that converts one compound into two compounds is called aminolysis. Notice that the aminolysis of an ester requires only one equivalent of amine, unlike the aminolysis of an acyl halide or an acid anhydride, which requires two equivalents (Sections 17.8 and 17.9). This is because the leaving group of an ester (RO\(^{-}\)) is more basic than the amine, so the alkoxide ion—rather than unreacted amine—picks up the proton generated in the reaction.

**an aminolysis reaction**

\[
\text{CH}_3\text{CH}_2\text{C}(\text{O})\text{OCH}_2\text{CH}_3 + \text{CH}_3\text{NH}_2 \rightarrow \text{CH}_3\text{CH}_2\text{C}(\text{O})\text{NHCH}_3 + \text{CH}_3\text{CH}_2\text{OH}
\]
The reaction of an ester with an amine is not as slow as the reaction of an ester with water or an alcohol, because an amine is a better nucleophile. This is fortunate, because the rate of the reaction of an ester with an amine cannot be increased by acid or by HO⁻ or RO⁻ (Problem 20). The aminolysis of an ester can be driven to completion by using excess amine or by distilling off the alcohol as it is formed.

\[
\begin{align*}
\text{CH}_3\text{CO}_2\text{H} + \text{CH}_3\text{CH}_2\text{NH}_2 & \rightarrow \text{CH}_3\text{CO}\text{NH}(\text{CH}_2)_2\text{CH}_3 + \text{CH}_3\text{OH} \\
\text{excess} & \\
\end{align*}
\]

In Section 7.10, we saw that phenols are stronger acids than alcohols. Therefore, phenoxide ions (ArO⁻) are weaker bases than alkoxide ions (RO⁻), which means that phenyl esters are more reactive than alkyl esters.

\[
\begin{align*}
\text{pK}_a &= 10.0 \\
\text{CH}_3\text{OH} & \text{pK}_a = 15.5
\end{align*}
\]

**ASPIRIN**

A transesterification reaction that blocks prostaglandin synthesis is responsible for aspirin’s activity as an anti-inflammatory agent. Prostaglandins have several different biological functions, one of which is to stimulate inflammation. The enzyme prostaglandin synthase catalyzes the conversion of arachidonic acid into PGH₂, a precursor of prostaglandins and the related thromboxanes (Section 26.5).

Prostaglandin synthase is composed of two enzymes. One of the enzymes—cyclooxygenase—has a CH₂OH group (called a serine hydroxyl group because it is part of the amino acid called serine) that is necessary for enzyme activity. The CH₂OH group reacts with aspirin (acetylsalicylic acid) in a transesterification reaction and becomes acetylated. This inactivates the enzyme. Prostaglandin therefore cannot be synthesized, and inflammation is suppressed.

\[
\begin{align*}
\text{arachidonic acid} & \xrightarrow{\text{prostaglandin synthase}} \text{PGH}_2 \\
\text{PGH}_2 & \xrightarrow{\text{thromboxanes}} \\
\end{align*}
\]

Thromboxanes stimulate platelet aggregation. Because aspirin inhibits the formation of PGH₂, it inhibits thromboxane production and, therefore, platelet aggregation. Presumably, this is why low levels of aspirin have been reported to reduce the incidence of strokes and heart attacks that result from blood clot formation. Aspirin’s activity as an anticoagulant is why doctors caution patients not to take aspirin for several days before surgery.
PROBLEM 16

Write a mechanism for the following reactions:

a. the noncatalyzed hydrolysis of methyl propionate
b. the aminolysis of phenyl formate, using methylamine

PROBLEM 17

a. State three factors that contribute to the fact that the noncatalyzed hydrolysis of an ester is a slow reaction.
b. Which is faster, hydrolysis of an ester or aminolysis of the same ester?

PROBLEM 18 SOLVED

a. List the following esters in order of decreasing reactivity toward hydrolysis:

\[
\begin{align*}
\text{CH}_3\text{C} & \text{O} - \text{\text{C}}\text{H}_3 \\
\text{CH}_3\text{C}\text{O} & - \text{\text{C}}\text{H}_3\text{O} - \text{\text{N}}\text{O}_2 \\
\text{CH}_3\text{C} & \text{O} - \text{\text{C}}\text{H}_3\text{O} - \text{\text{O}}\text{CH}_3
\end{align*}
\]

b. How would the rate of hydrolysis of the para-methylphenyl ester compare with the rate of hydrolysis of these three esters?

SOLUTION TO 18a Because the nitro group withdraws electrons from the benzene ring and the methoxy group donates electrons into the benzene ring, the nitro-substituted ester will be the most susceptible, and the methoxy-substituted ester the least susceptible, to nucleophilic attack. We know that electron withdrawal increases acidity and electron donation decreases acidity, so para-nitrophenol is a stronger acid than phenol, which is a stronger acid than para-methoxyphenol. Therefore, the para-nitrophenoxide ion is the weakest base and the best leaving group of the three, whereas the para-methoxyphenoxide ion is the strongest base and the worst leaving group. Thus, both relatively slow steps of the hydrolysis reaction are fastest for the ester with the electron-withdrawing nitro substituent and slowest for the ester with the electron-donating methoxy substituent.

\[
\begin{align*}
\text{CH}_3\text{C} & \text{O} - \text{\text{C}}\text{H}_3\text{O} - \text{\text{N}}\text{O}_2 > \text{CH}_3\text{C} & \text{O} - \text{\text{C}}\text{H}_3\text{O} - \text{\text{O}}\text{CH}_3 \\
\text{CH}_3\text{C} & \text{O} - \text{\text{C}}\text{H}_3\text{O} - \text{\text{O}}\text{CH}_3
\end{align*}
\]

SOLUTION TO 18b The methyl substituent donates electrons inductively into the benzene ring, but donates electrons to a lesser extent than does the resonance-donating methoxy substituent. Therefore, the rate of hydrolysis of the methyl-substituted ester is slower than the rate of hydrolysis of the unsubstituted ester, but faster than the rate of hydrolysis of the methoxy-substituted ester.

\[
\begin{align*}
\text{CH}_3\text{C} & \text{O} - \text{\text{C}}\text{H}_3 > \text{CH}_3\text{C} & \text{O} - \text{\text{C}}\text{H}_3\text{O} - \text{\text{O}}\text{CH}_3 \\
\text{CH}_3\text{C} & \text{O} - \text{\text{C}}\text{H}_3\text{O} - \text{\text{O}}\text{CH}_3
\end{align*}
\]

17.11 Acid-Catalyzed Ester Hydrolysis

We have seen that esters hydrolyze slowly because water is a poor nucleophile and esters have very basic leaving groups. The rate of hydrolysis can be increased by either acid or HO\(^-\). When you examine the following mechanisms, notice a feature that holds for all organic reactions:

1. In an acid-catalyzed reaction, all organic intermediates and products are positively charged or neutral; \textit{negatively charged organic intermediates and products are not formed in acidic solutions}.

2. In a reaction in which HO\(^-\) is used to increase the rate of the reaction, all organic intermediates and products are negatively charged or neutral; \textit{positively charged organic intermediates and products are not formed in basic solutions}.
Normal Ester Hydrolysis

The first step in the mechanism for acid-catalyzed ester hydrolysis is protonation of the carbonyl oxygen by the acid. Recall that $H\text{B}^+$ represents any species in the solution that is capable of donating a proton and $B^-$ represents any species in the solution that is capable of removing a proton.

The carbonyl oxygen is protonated because it is the atom with the greatest electron density, as shown by the resonance contributors.

In the second step of the mechanism, the nucleophile (H$_2$O) attacks the protonated carbonyl group. The resulting protonated tetrahedral intermediate (tetrahedral intermediate I) is in equilibrium with its nonprotonated form (tetrahedral intermediate II). Either the OH or the OR group of tetrahedral intermediate II (in this case, OR = OCH$_3$) can be protonated. Because the OH and OR groups have approximately the same basicity, both tetrahedral intermediate I (OH is protonated) and tetrahedral intermediate III (OR is protonated) are formed. (From Section 1.20, we know that the relative amounts of the three tetrahedral intermediates depend on the pH of the solution and the pK$_a$ values of the protonated intermediates.) When tetrahedral intermediate I collapses, it expels H$_2$O in preference to CH$_3$O$^-$ because H$_2$O is a weaker base, thereby reforming the ester. When tetrahedral intermediate III collapses, it expels CH$_3$OH rather than HO$^-$ because CH$_3$OH is a weaker base, thereby forming the carboxylic acid. (Tetrahedral intermediate II is less likely to collapse, because both HO$^-$ and CH$_3$O$^-$ are strong bases.) Acid-catalyzed ester hydrolysis is discussed in greater detail in Section 24.3.
Because \( \text{H}_2\text{O} \) and \( \text{CH}_3\text{OH} \) have approximately the same basicity, it will be as likely for tetrahedral intermediate I to collapse to reform the ester as it will for tetrahedral intermediate III to collapse to form the carboxylic acid. Consequently, when the reaction has reached equilibrium, both ester and carboxylic acid will be present in approximately equal amounts.

Excess water will force the equilibrium to the right (Le Châtelier’s principle; Section 10.4). Or, if the boiling point of the product alcohol is significantly lower than the boiling points of the other components of the reaction, the reaction can be driven to the right by distilling off the product alcohol as it is formed.

The mechanism for the acid-catalyzed reaction of a carboxylic acid and an alcohol to form an ester and water is the exact reverse of the mechanism for the acid-catalyzed hydrolysis of an ester to form a carboxylic acid and an alcohol. If the ester is the desired product, the reaction should be carried out under conditions that will drive the equilibrium to the left—using excess alcohol or removing water as it is formed (Section 17.14).

**PROBLEM 19**

Referring to the mechanism for the acid-catalyzed hydrolysis of methyl acetate:

a. What species could be represented by \( \text{HB}^+ \)?

b. What species could be represented by \( \cdot \text{B}^- \)?

c. What species is \( \text{HB}^+ \) most likely to be in a hydrolysis reaction?

d. What species is \( \text{HB}^+ \) most likely to be in the reverse reaction?

**PROBLEM 20**

Referring to the mechanism for the acid-catalyzed hydrolysis of methyl acetate, write the mechanism—showing all the curved arrows—for the acid-catalyzed reaction of acetic acid and methanol to form methyl acetate. Use \( \text{HB}^+ \) and \( \cdot \text{B}^- \) to represent proton-donating and proton-removing species, respectively.

Now let’s see how the acid increases the rate of ester hydrolysis. The acid is a catalyst. Recall that catalyst is a substance that increases the rate of a reaction without being consumed or changed in the overall reaction (Section 4.5). For a catalyst to increase the rate of a reaction, it must increase the rate of the slow step of the reaction. Changing the rate of a fast step will not affect the rate of the overall reaction. Four of the six steps in the mechanism for acid-catalyzed ester hydrolysis are proton transfer steps. Proton transfer to or from an electronegative atom such as oxygen or nitrogen is a fast step. So there are two relatively slow steps in the mechanism: formation of a
tetrahedral intermediate and collapse of a tetrahedral intermediate. The acid increases the rates of both of these steps.

The acid increases the rate of formation of the tetrahedral intermediate by protonating the carbonyl oxygen. Protonated carbonyl groups are more susceptible than nonprotonated carbonyl groups to nucleophilic attack because a positively charged oxygen is more electron withdrawing than a neutral oxygen. Increased electron withdrawal by the oxygen increases the electron deficiency of the carbonyl carbon, which increases its attractiveness to nucleophiles.

\[
\text{protonation of the carbonyl oxygen increases the susceptibility of the carbonyl carbon to nucleophilic attack}
\]

The acid increases the rate of collapse of the tetrahedral intermediate by decreasing the basicity of the leaving group, which makes it easier to eliminate. In the acid-catalyzed hydrolysis of an ester, the leaving group is ROH, a weaker base than the leaving group (RO\(^-\)) in the uncatalyzed reaction.

\[
\text{An acid catalyst increases the electrophilicity of the carbonyl carbon atom and decreases the basicity of the leaving group.}
\]

### Hydrolysis of Esters with Tertiary Alkyl Groups

Esters with tertiary alkyl groups undergo hydrolysis much more rapidly than do other esters because they hydrolyze by a completely different mechanism—one that does not involve formation of a tetrahedral intermediate. The hydrolysis of an ester with a tertiary alkyl group is an \(S_N1\) reaction because when the carboxylic acid leaves, it leaves behind a relatively stable tertiary carbocation.

\[
\text{departure of the leaving group to form a tertiary carbocation}
\]

\[
\text{reaction of the carbocation with a nucleophile}
\]

### Transesterification

Transesterification—the reaction of an ester with an alcohol—is also catalyzed by acid. The mechanism for transesterification is identical to the mechanism for normal ester hydrolysis, except that the nucleophile is ROH rather than \(\text{H}_2\text{O}\). As in hydrolysis,
the leaving groups in the tetrahedral intermediate formed in transesterification have approximately the same basicity. Consequently, an excess of the reactant alcohol must be used to produce more of the desired product.

\[
\text{CH}_3\text{C(O\text{CH}_3)} + \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} \xrightarrow{\text{HCl}} \text{CH}_3\text{C(O\text{CH}_3\text{CH}_2\text{CH}_3)} + \text{CH}_3\text{OH}
\]

**PROBLEM 21**

Write the mechanism for the acid-catalyzed transesterification reaction of methyl acetate with ethanol.

### 17.12 Hydroxide-Ion-Promoted Ester Hydrolysis

The rate of hydrolysis of an ester can be increased by carrying out the reaction in a basic solution. Like an acid, hydroxide ion increases the rates of both slow steps of the reaction.

Hydroxide ion increases the rate of formation of the tetrahedral intermediate because \(\text{HO}^-\) is a better nucleophile than \(\text{H}_2\text{O}\), so \(\text{HO}^-\) more readily attacks the carbonyl carbon. Hydroxide ion increases the rate of collapse of the tetrahedral intermediate because a smaller fraction of the negatively charged tetrahedral intermediate becomes protonated in a basic solution. A negatively charged oxygen can more readily expel the very basic leaving group (\(\text{RO}^-\)) because the oxygen does not develop a partial positive charge in the transition state.

**mechanism for hydroxide-ion-promoted hydrolysis of an ester**

\[
\begin{align*}
\text{CH}_3\text{C(O\text{CH}_3)} + \text{HO}^- & \rightarrow \text{CH}_3\text{C(O\text{CH}_3\text{OH})} \\
\text{HO}^- + \text{H}_2\text{O} & \rightarrow \text{HO}^- \text{H}_2\text{O} \\
\text{CH}_3\text{C(O\text{CH}_3\text{OH})} & \rightarrow \text{CH}_3\text{C(O\text{CH}_3\text{O})^-} + \text{CH}_3\text{OH}
\end{align*}
\]

Notice that when \(\text{CH}_3\text{O}^-\) is expelled, the final products are not the carboxylic acid and methoxide ion because if only one species is protonated, it will be the more basic one. The final products are the carboxylate ion and methanol because \(\text{CH}_3\text{O}^-\) is more basic than \(\text{CH}_3\text{COO}^-\). Since carboxylate ions are negatively charged, they are not attacked by nucleophiles.

\[
\text{CH}_3\text{C(O\text{O}^-)} + \text{Nu} \rightarrow \text{X}
\]

Therefore, the hydroxide-ion-promoted hydrolysis of an ester, unlike the acid-catalyzed hydrolysis of an ester, is *not* a reversible reaction.
This reaction is called a hydroxide-ion-promoted reaction rather than a base-catalyzed reaction because hydroxide ion increases the rate of the first step of the reaction by being a better nucleophile than water—not by being a stronger base than water—and because hydroxide ion is consumed in the overall reaction. To be a catalyst, a species must not be changed by or consumed in the reaction (Section 17.11). So hydroxide ion is actually a reagent rather than a catalyst. Therefore, it is more accurate to call the reaction a hydroxide-ion-promoted reaction than a hydroxide-ion-catalyzed reaction.

Hydroxide ion promotes only hydrolysis reactions, not transesterification reactions or aminolysis reactions. Hydroxide ion cannot promote reactions of carboxylic acid derivatives with alcohols or with amines because one function of hydroxide ion is to provide a strong nucleophile for the first step of the reaction. Thus, when the nucleophile is supposed to be an alcohol or an amine, nucleophilic attack by hydroxide ion would form a product different from the product that would be formed from nucleophilic attack by an alcohol or amine. Hydroxide can be used to promote a hydrolysis reaction because the same product is formed, regardless of whether the attacking nucleophile is or .

Reactions in which the nucleophile is an alcohol can be promoted by the conjugate base of the alcohol. The function of the alkoxide ion is to provide a strong nucleophile for the reaction, so only reactions in which the nucleophile is an alcohol can be promoted by its conjugate base.

**PROBLEM 22**

a. What species other than an acid can be used to increase the rate of a transesterification reaction that converts methyl acetate to propyl acetate?

b. Explain why the rate of aminolysis of an ester cannot be increased by H⁺, HO⁻, or RO⁻.

You have seen that nucleophilic acyl substitution reactions take place by a mechanism in which a tetrahedral intermediate is formed and subsequently collapses. The tetrahedral intermediate, however, is too unstable to be isolated. How, then, do we know that it is formed? How do we know that the reaction doesn’t take place by a one-step direct-displacement mechanism (similar to the mechanism of an SN₂ reaction) in which the incoming nucleophile attacks the carbonyl carbon and displaces the leaving group—a mechanism that would not form a tetrahedral intermediate?
To answer this question, Myron Bender investigated the hydroxide-ion-promoted hydrolysis of ethyl benzoate, with the carbonyl oxygen of ethyl benzoate labeled with $^{18}$O. When he isolated ethyl benzoate from an incomplete reaction mixture, he found that some of the ester was no longer labeled. If the reaction had taken place by a one-step direct-displacement mechanism, all the isolated ester would have remained labeled because the carbonyl group would not have participated in the reaction. On the other hand, if the mechanism involved a tetrahedral intermediate, some of the isolated ester would no longer be labeled because some of the label would have been transferred to the hydroxide ion. By this experiment, Bender provided evidence for the reversible formation of a tetrahedral intermediate.

Myron L. Bender (1924–1988) was born in St. Louis. He was a professor of chemistry at the Illinois Institute of Technology and at Northwestern University.

**PROBLEM 23**

If butanoic acid and $^{18}$O-labeled methanol are allowed to react under acidic conditions, what compounds will be labeled when the reaction has reached equilibrium?

**PROBLEM 24**

D. N. Kursanov, a Russian chemist, proved that the bond that is broken in the hydroxide-ion-promoted hydrolysis of an ester is the acyl $\text{C}$$\equiv\text{O}$ bond, rather than the alkyl $\text{C}$$\equiv\text{O}$ bond, by studying the reaction of the following ester with $\text{HO}^-$/H$_2$O:
Section 17.12 Hydroxide-Ion-Promoted Ester Hydrolysis

PROBLEM 25 SOLVED

Early chemists could envision several possible mechanisms for hydroxide-ion-promoted ester hydrolysis:

1. a nucleophilic acyl substitution reaction

\[
\begin{array}{c}
\text{R}^+ \text{C} = \text{O} + \text{HO}^- \rightarrow \text{R}^- \text{C} = \text{O}^- + \text{R}^+\text{OH}
\end{array}
\]

2. an \( \text{S}_\text{N}2 \) reaction

\[
\begin{array}{c}
\text{R} \text{C} = \text{O} + \text{HO}^- \rightarrow \text{R}^- \text{C} = \text{O}^- + \text{R}^+\text{OH}
\end{array}
\]

3. an \( \text{S}_\text{N}1 \) reaction

\[
\begin{array}{c}
\text{R} \text{C} = \text{O} \rightarrow \text{R}^- \text{C} = \text{O}^- + \text{R}^+ \rightarrow \text{R}^+\text{OH}
\end{array}
\]

Devise an experiment that would distinguish among these three reactions.

SOLUTION Start with a single stereoisomer of an alcohol whose OH group is bonded to an asymmetric carbon, and determine the specific rotation of the alcohol. Then convert the alcohol into an ester, using a method that does not break any bonds to the asymmetric carbon. Next, hydrolyze the ester, isolate the alcohol obtained from hydrolysis, and determine its specific rotation.

If the reaction is a nucleophilic acyl substitution reaction, the product alcohol will have the same specific rotation as the reactant alcohol because no bonds to the asymmetric carbon are broken (Section 5.12).

If the reaction is an \( \text{S}_\text{N}2 \) reaction, the product alcohol and the reactant alcohol will have opposite specific rotations because the mechanism requires back-side attack on the asymmetric carbon (Section 10.2).

If the reaction is an \( \text{S}_\text{N}1 \) reaction, the product alcohol will have a small (or zero) specific rotation because the mechanism requires carbocation formation, which leads to racemization of the alcohol (Section 10.7).
17.13 Soaps, Detergents, and Micelles

**Fats** and **oils** are triesters of glycerol. Glycerol contains three alcohol groups and therefore can form three ester groups. When the ester groups are hydrolyzed in a basic solution, glycerol and carboxylate ions are formed. The carboxylic acids that are bonded to glycerol in fats and oils have long, unbranched R groups. Because they are obtained from fats, long-chain unbranched carboxylic acids are called **fatty acids**. In Section 26.3, we will see that the difference between a fat and an oil resides in the structure of the fatty acids.

Soaps are sodium or potassium salts of fatty acids. Thus, soaps are obtained when fats or oils are hydrolyzed under basic conditions. The hydrolysis of an ester in a basic solution is called **saponification**—the Latin word for “soap” is *sapo*. The following compounds are three of the most common soaps:

![3-D Molecules: Sodium stearate; Sodium oleate; Sodium linoleate](image)

**PROBLEM 26 SOLVED**

An oil obtained from coconuts is unusual in that all three fatty acid components are identical. The molecular formula of the oil is C_{45}H_{86}O_{6}. What is the molecular formula of the carboxylate ion obtained when the oil is saponified?

**SOLUTION** When the oil is saponified, it forms glycerol and three equivalents of carboxylate ion. In losing glycerol, the fat loses three carbons and five hydrogens. Thus, the three equivalents of carboxylate ion have a combined molecular formula of C_{32}H_{81}O_{6}. Dividing by three gives a molecular formula of C_{14}H_{27}O_{2} for the carboxylate ion.

Long-chain carboxylate ions do not exist as individual ions in aqueous solution. Instead, they arrange themselves in spherical clusters called **micelles**, as shown in Figure 17.4. Each micelle contains 50 to 100 long-chain carboxylate ions. A micelle resembles a large ball, with the polar head of each carboxylate ion and its counterion on the outside of the ball because of their attraction for water and the nonpolar tail buried in the interior of the ball to minimize its contact with water. The attractive forces of hydrocarbon chains for each other in water are called **hydrophobic interactions** (Section 23.14). Soap has cleansing ability because nonpolar oil molecules, which carry dirt, dissolve in the nonpolar interior of the micelle and are carried away with the soap during rinsing.
In aqueous solution, soap forms micelles, with the polar heads (carboxylate groups) on the surface and the nonpolar tails (fatty acid R groups) in the interior.

Because the surface of the micelle is negatively charged, the individual micelles repel each other instead of clustering to form larger aggregates. As river water flows over and around rocks, it leaches out calcium and magnesium ions. The concentration of calcium and magnesium ions in water is described by its “hardness.” Hard water contains high concentrations of these ions; soft water contains few, if any, calcium and magnesium ions. While micelles with sodium and potassium cations are dispersed in water, micelles with calcium and magnesium cations form aggregates. In hard water, therefore, soaps form a precipitate that we know as “bathtub ring” or “soap scum.”

The formation of soap scum in hard water led to a search for synthetic materials that would have the cleansing properties of soap, but would not form scum when they encountered calcium and magnesium ions. The synthetic “soaps” that were developed, known as detergents, are salts of benzene sulfonic acids. Calcium and magnesium sulfonate salts do not form aggregates. “Detergent” comes from the Latin detergere,
which means “to wipe off.” After the initial introduction of detergents into the marketplace, it was discovered that straight-chain alkyl groups are biodegradable, whereas branched-chain alkyl groups are not. To prevent nonbiodegradable detergents from polluting rivers and lakes, detergents should have straight-chain alkyl groups.

Compounds that lower the surface tension of water are called **surfactants**. Surfactants have a polar head group and a long-chain nonpolar tail. Soaps and detergents are surfactants—that is why soap and detergent solutions feel slippery. Lowering the surface tension enables the soap or detergent to penetrate the fibers of a fabric, thus enhancing its cleaning ability. Because the polar head of a soap or a detergent is negatively charged, it is called an **anionic** surfactant. **Cationic** surfactants are used widely as fabric softeners and hair conditioners.

### 17.14 Reactions of Carboxylic Acids

Carboxylic acids can undergo nucleophilic acyl substitution reactions only when they are in their acidic forms. The basic form of a carboxylic acid does not undergo nucleophilic acyl substitution reactions because the negatively charged carboxylate ion is resistant to nucleophilic attack (Section 17.12). Thus, carboxylate ions are even less reactive toward nucleophilic acyl substitution reactions than are amides.

Carboxylic acids have approximately the same reactivity as esters—the HO⁻ leaving group of a carboxylic acid has approximately the same basicity as the RO⁻ leaving group of an ester. Therefore, like esters, carboxylic acids do not react with halide ions or with carboxylate ions.

Carboxylic acids react with alcohols to form esters. The reaction must be carried out in an acidic solution, not only to catalyze the reaction but also to keep the carboxylic acid in its acid form so that it will react with the nucleophile. Because the tetrahedral intermediate formed in this reaction has two potential leaving groups of approximately the same basicity, the reaction must be carried out with excess alcohol to drive it toward products. Emil Fischer (Section 5.5) was the first to discover that an ester could be prepared by treating a carboxylic acid with excess alcohol in the presence of an acid catalyst, so the reaction is called a **Fischer esterification**.

Carboxylic acids do not undergo nucleophilic acyl substitution reactions with amines. Because a carboxylic acid has a lower pKₐ than a protonated amine, the carboxylic
acid immediately donates a proton to the amine when the two compounds are mixed. The ammonium carboxylate salt is the final product of the reaction; the carboxylate ion is unreactive and the protonated amine is not a nucleophile.

\[
\begin{align*}
\text{CH}_3\text{OH} + \text{CH}_3\text{CH}_2\text{NH}_2 & \rightarrow \text{CH}_3\text{O}^+\text{H}_3\text{NCH}_2\text{CH}_3 \\
\text{CH}_3\text{CH}_2\text{O} + \text{NH}_3 & \rightarrow \text{CH}_3\text{CH}_2\text{O}^+\text{NH}_4
\end{align*}
\]

**PROBLEM 27**

Using an alcohol for one method and an alkyl halide for the other, show two ways to make each of the following esters:

- a. methyl butyrate (odor of apples)
- b. propyl acetate (odor of pears)
- c. ethyl butyrate (odor of pineapple)
- d. octyl acetate (odor of oranges)
- e. isopentyl acetate (odor of bananas)
- f. methyl phenylethanoate (odor of honey)

**PROBLEM-SOLVING STRATEGY**

Propose a mechanism for the following reaction:

When you are asked to propose a mechanism, look carefully at the reagents to determine the first step of the mechanism. One of the reagents has two functional groups: a carboxyl group and a carbon–carbon double bond. The other reagent, Br₂, does not react with carboxylic acids, but does react with alkenes (Section 4.7). One side of the alkene is sterically hindered by the carboxyl group. Therefore, Br₂ will add to the other side of the double bond, forming a bromonium ion. We know that in the second step of the addition reaction, a nucleophile will attack the bromonium ion. Of the two nucleophiles present, the carbonyl oxygen is positioned to attack the back side of the bromonium ion, resulting in a compound with the observed configuration. Loss of a proton gives the final product of the reaction.

Now continue on to Problem 28.

**PROBLEM 28**

Propose a mechanism for the following reaction. *(Hint: Number the carbons to help you see where they end up in the product.)*

\[
\begin{align*}
\text{CH}_2=\text{CHCH}_2\text{CH}=\text{CCH}_3 + \text{CH}_3\text{COH} & \xrightarrow{\text{H}_2\text{SO}_4} \text{H}_3\text{CCH}_3\text{O} \xrightarrow{\text{CH}_3} \text{O}\text{CH}_3
\end{align*}
\]
Amides are very unreactive compounds, which is comforting, since proteins are composed of amino acids linked together by amide bonds (Section 23.11). Amides do not react with halide ions, carboxylate ions, alcohols, or water because, in each case, the incoming nucleophile is a weaker base than the leaving group of the amide (Table 17.1).

Amides do, however, react with water and alcohols if the reaction mixture is heated in the presence of an acid. The reason for this will be explained in Section 17.16.

Molecular orbital theory can explain why amides are unreactive. In Section 17.3, we saw that amides have an important resonance contributor in which nitrogen shares its lone pair with the carbonyl carbon—the orbital that contains the lone pair overlaps the empty \( \pi^* \) orbital of the carbonyl group (Figure 17.3). This overlap lowers the energy of the lone pair—it is neither basic nor nucleophilic—and it raises the energy of the \( \pi^* \) orbital of the carbonyl group, making it less reactive to nucleophiles (Figure 17.5).

An amide with an \( \text{NH}_2 \) group can be dehydrated to a nitrile. Dehydrating reagents commonly employed for this purpose are \( \text{P}_2\text{O}_5 \), \( \text{POCl}_3 \), and \( \text{SOCl}_2 \).
**PROBLEM 29**

a. Which of the following reactions would lead to the formation of an amide?

1. \[ R'\text{CO} + \text{CH}_3\text{NH}_2 \]
2. \[ R\text{C}O\text{CH}_3 + \text{CH}_3\text{NH}_2 \]
3. \[ R\text{C}O\text{CH}_3 + \text{CH}_3\text{NH}_2 \]
4. \[ R'\text{CO} + \text{CH}_3\text{NH}_2 \]
5. \[ R'\text{C}C\text{Cl} + \text{CH}_3\text{NH}_2 \]
6. \[ R\text{C}O\text{CH}_3 + \text{CH}_3\text{NH}_2 \]

b. For those reactions that do form amides, what could you do to improve either the rate of amide formation or the yield of the amide product?

**PROBLEM 30**

Propose a mechanism for the reaction of an amide with thionyl chloride to form a nitrile. (Hint: In the first step of the reaction, the amide is the nucleophile and thionyl chloride is the electrophile.)

**NATURE’S SLEEPING PILL**

Melatonin, a naturally occurring amide, is a hormone that is synthesized by the pineal gland from the amino acid tryptophan. Melatonin regulates the dark–light clock that governs such things as the sleep–wake cycle, body temperature, and hormone production.

Melatonin levels increase from evening to night and then decrease as morning approaches. People with high levels of melatonin sleep longer and more soundly than those with low levels. The concentration of the hormone in the blood varies with age—6-year-olds have more than five times the concentration that 80-year-olds have—which is one of the reasons why young people have less trouble sleeping than older people. Melatonin supplements are used to treat insomnia, jet lag, and seasonal affective disorder.
17.16 Acid-Catalyzed Hydrolysis of Amides

When an amide is hydrolyzed under acidic conditions, the acid protonates the carbonyl oxygen, increasing the susceptibility of the carbonyl carbon to nucleophilic attack. Nucleophilic attack by water on the carbonyl carbon leads to tetrahedral intermediate I, which is in equilibrium with its nonprotonated form, tetrahedral intermediate II. Reprotonation can occur either on oxygen to reform tetrahedral intermediate I or on nitrogen to form tetrahedral intermediate III. Protonation on nitrogen is favored because the NH$_2$ group is a stronger base than the OH group. Of the two possible leaving groups in tetrahedral intermediate III (OH$^-$ and NH$_3$), NH$_3$ is the weaker base, so it is expelled, forming the carboxylic acid as the final product. Since the reaction is carried out in an acidic solution, NH$_3$ will be protonated after it is expelled from the tetrahedral intermediate. This prevents the reverse reaction from occurring.

Let's take a minute to see why an amide cannot be hydrolyzed without a catalyst. In the uncatalyzed reaction, the amide is not protonated. Therefore, water, a very poor nucleophile, must attack a neutral amide that is much less susceptible to nucleophilic attack than a protonated amide would be. In addition, the NH$_2$ group of the tetrahedral intermediate is not protonated in the uncatalyzed reaction. Therefore, HO$^-$ is the group expelled from the tetrahedral intermediate—because HO$^-$ is a weaker base than NH$_2$—which reforms the amide.

An amide reacts with an alcohol in the presence of acid for the same reason that it reacts with water in the presence of acid.
Section 17.16  Acid-Catalyzed Hydrolysis of Amides

PENICILLIN AND DRUG RESISTANCE

Penicillin contains a strained $\beta$-lactam ring. The strain in the four-membered ring increases the amide’s reactivity. It is thought that the antibiotic activity of penicillin results from its ability to acylate (put an acyl group on) a $\text{CH}_2\text{OH}$ group of an enzyme that is involved in the synthesis of bacterial cell walls. Acylation inactivates the enzyme, and actively growing bacteria die because they are unable to produce functional cell walls. Penicillin has no effect on mammalian cells because mammalian cells are not enclosed by cell walls. To minimize hydrolysis of the $\beta$-lactam ring during storage, penicillins are refrigerated.

Bacteria that are resistant to penicillin secrete penicillinase, an enzyme that catalyzes the hydrolysis of the $\beta$-lactam ring of penicillin. The ring-opened product has no antibacterial activity.

PENICILLINS IN CLINICAL USE

More than 10 different penicillins are currently in clinical use. They differ only in the group (R) attached to the carbonyl group. Some of these penicillins are shown here. In addition to their structural differences, the penicillins differ in the organisms against which they are most effective. They also differ in their resistance to penicillinase. For example, ampicillin, a synthetic penicillin, is clinically effective against bacteria that are resistant to penicillin G, a naturally occurring penicillin. Almost 19% of humans are allergic to penicillin G.

Penicillin V is a semisynthetic penicillin that is in clinical use. It is not a naturally occurring penicillin; nor is it a true synthetic penicillin because chemists don’t synthesize it. The *Penicillum* mold synthesizes it after the mold is fed 2-phenoxyethanol, the compound it needs for the side chain.
PROBLEM 31

List the following amides in order of decreasing reactivity toward acid-catalyzed hydrolysis:

- A
- B
- C
- D

17.17 Hydrolysis of an Imide: The Gabriel Synthesis

An **imide** is a compound with two acyl groups bonded to a nitrogen. The **Gabriel synthesis**, which converts alkyl halides into primary amines, involves the hydrolysis of an imide.

\[ \text{RCH}_2\text{Br} \xrightarrow{\text{Gabriel synthesis}} \text{RCH}_2\text{NH}_2 \]

In the first step of the reaction, a base removes a proton from the nitrogen of phthalimide. The resulting nucleophile reacts with an alkyl halide. Because this is an \( S_N 2 \) reaction, it works best with primary alkyl halides (Section 10.2). Hydrolysis of the \( N \)-substituted phthalimide is catalyzed by acid. Because the solution is acidic, the final products are a primary alkyl ammonium ion and phthalic acid. Neutralization of the ammonium ion with base forms the primary amine. Notice that the alkyl group of the primary amine is identical to the alkyl group of the alkyl halide.

Only one alkyl group can be placed on the nitrogen because there is only one hydrogen bonded to the nitrogen of phthalimide. This means that the Gabriel synthesis can be used only for the preparation of primary amines.

PROBLEM 32

What alkyl bromide would you use in a Gabriel synthesis to prepare each of the following amines?

a. pentyamine
b. isoheptylamine
c. benzylamine
d. cyclohexylamine
17.18 Hydrolysis of Nitriles

Nitriles are even harder to hydrolyze than amides. Nitriles are slowly hydrolyzed to carboxylic acids when heated with water and an acid.

\[
\text{CH}_3\text{CH}_2\text{C}==\text{N} + \text{H}_2\text{O} \xrightarrow{\Delta} \text{CH}_3\text{CH}_2\text{OH} + \text{H}^+\text{NH}_4^+ + \text{H}_2\text{O}
\]

In the first step of the acid-catalyzed hydrolysis of a nitrile, the acid protonates the nitrogen of the cyano group, making it easier for water to attack the carbon of the cyano group in the next step. Attack on the cyano group by water is analogous to attack on a carbonyl group by water. Because nitrogen is a stronger base than oxygen, oxygen loses a proton and nitrogen gains a proton, resulting in a product that is a protonated amide (whose two resonance contributors are shown). The amide is immediately hydrolyzed to a carboxylic acid—because an amide is easier to hydrolyze than a nitrile—following the acid-catalyzed mechanism shown in Section 17.15.

**mechanism for acid-catalyzed hydrolysis of a nitrile**

![Mechanism Diagram](image)

Because nitriles can be prepared from the reaction of an alkyl halide with cyanide ion (Section 10.4), you now know how to convert an alkyl halide into a carboxylic acid. Notice that the carboxylic acid has one more carbon than the alkyl halide.

\[
\text{CH}_3\text{CH}_2\text{Br} \quad \xrightarrow{\text{DMF}} \quad \text{CH}_3\text{CH}_2\text{C}==\text{N} \quad \xrightarrow{\Delta \text{HCl}, \text{H}_2\text{O}} \quad \text{CH}_3\text{CH}_2\text{OH}
\]

---

PROBLEM 33

Primary amines can also be prepared by the reaction of an alkyl halide with azide ion, followed by catalytic hydrogenation. What advantage do this method and the Gabriel synthesis have over the synthesis of a primary amine using an alkyl halide and ammonia?

\[\text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \rightarrow_{\text{N}_3} \text{CH}_3\text{CH}_2\text{CH}_2\text{N}==\text{N} \rightarrow_{\text{H}_2, \text{Pt}} \text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2 + \text{N}_2\]

---

PROBLEM 34

Which alkyl halides form the following carboxylic acids after reacting with sodium cyanide and the product heated in an acidic aqueous solution?

- a. butyric acid
- b. isovaleric acid
- c. cyclohexanecarboxylic acid
17.19 Designing a Synthesis IV: The Synthesis of Cyclic Compounds

Most of the reactions we have studied are intermolecular reactions: The two reacting groups are in different molecules. Cyclic compounds are formed from intramolecular reactions: The two reacting groups are in the same molecule. We have seen that intramolecular reactions are particularly favorable if the reaction forms a compound with a five- or a six-membered ring (Section 11.11).

In designing the synthesis of a cyclic compound, we must examine the target molecule to determine what kinds of reactive groups will be necessary for a successful synthesis. For example, we know that an ester is formed from the acid-catalyzed reaction of a carboxylic acid with an alcohol. Therefore, a cyclic ester (lactone) can be prepared from a reactant that has both a carboxylic acid group and an alcohol group in the same molecule. The size of the lactone ring will be determined by the number of carbon atoms between the carboxylic acid group and the alcohol group.

A compound with a ketone group attached to a benzene ring can be prepared using a Friedel–Crafts acylation reaction (Section 15.13). Therefore, a cyclic ketone will result if a Lewis acid (AlCl₃) is added to a compound that contains both a benzene ring and an acyl chloride group separated by the appropriate number of carbon atoms.

A cyclic ether can be prepared by an intramolecular Williamson ether synthesis (Section 11.9).
A cyclic ether can also be prepared by an intramolecular electrophilic addition reaction.

\[
\text{CH}_2\text{CHCH}_2\text{CH}_3 + \text{HCl} \xrightarrow{\Delta} \text{CH}_3\text{CHCH}_2\text{CH}_2\text{CHCl} \xrightarrow{\text{NBS}} \text{CH}_3\text{OCH}_2\text{CH}_3 \xrightarrow{\text{Br}} \text{CH}_3\text{OCH}_2\text{CH}_3 + \text{H}^+
\]

The product obtained from the intramolecular reaction can undergo further reactions allowing for the synthesis of many different compounds. For example, the alkyl bromide could undergo an elimination reaction, could undergo substitution with a wide variety of nucleophiles, or could be converted into a Grignard reagent that could react with many different electrophiles.

**Problem 35**

Design a synthesis for each of the following compounds, using an intramolecular reaction:

- a. 
- b. 
- c. 
- d. 
- e. 
- f. 

---

**Section 17.20 Synthesis of Carboxylic Acid Derivatives**

Of the various classes of carbonyl compounds discussed in this chapter—acyl halides, acid anhydrides, esters, carboxylic acids, and amides—carboxylic acids are the most commonly available both in the laboratory and in biological systems. This means that carboxylic acids are the reagents most likely to be available when a chemist or a cell needs to synthesize a carboxylic acid derivative. However, we have seen that carboxylic acids are relatively unreactive toward nucleophilic acyl substitution reactions because the OH group of a carboxylic acid is a strong base and therefore a poor leaving group. In neutral solutions (physiological pH = 7.3), a carboxylic acid is even more resistant to nucleophilic acyl substitution reactions because it exists predominantly in its unreactive negatively charged basic form (Sections 1.20 and 17.14). Therefore, both organic chemists and cells need a way to activate carboxylic acids so that they can readily undergo nucleophilic acyl substitution reactions.

**Activation of Carboxylic Acids for Nucleophilic Acyl Substitution Reactions in the Laboratory**

Because acyl halides are the most reactive of the carboxylic acid derivatives, the easiest way to synthesize any other carboxylic acid derivative is to add the appropriate nucleophile to an acyl halide. Consequently, organic chemists activate carboxylic acids by converting them into acyl halides.
A carboxylic acid can be converted into an acyl chloride by heating it either with thionyl chloride (SOCl₂) or with phosphorus trichloride (PCl₃). Acyl bromides can be synthesized by using phosphorus tribromide (PBr₃).

\[
\begin{align*}
\text{Acetic acid} & \quad \text{Thionyl chloride} & \quad \text{Acetyl chloride} \\
\text{Butanoic acid} & \quad \text{Phosphorus trichloride} & \quad \text{Butanoyl chloride} \\
\text{Benzoic acid} & \quad \text{Phosphorus tribromide} & \quad \text{Benzoyl bromide} \\
\end{align*}
\]

All these reagents convert the OH group of a carboxylic acid into a better leaving group than the halide ion.

Therefore, when the halide ion subsequently attacks the carbonyl carbon and forms a tetrahedral intermediate, the halide ion is not the group that is eliminated.

Notice that the reagents that cause the OH group of a carboxylic acid to be replaced by a halogen are the same reagents that cause the OH group of an alcohol to be replaced by a halogen (Section 12.3).

Once the acyl halide has been prepared, a wide variety of carboxylic acid derivatives can be synthesized by adding the appropriate nucleophile (Section 17.8).
Carboxylic acids can also be activated for nucleophilic acyl substitution reactions by being converted into anhydrides. Treating a carboxylic acid with a strong dehydrating agent such as $P_2O_5$ yields an anhydride.

\[
\begin{align*}
\text{2 HCO}_2\text{H} & \xrightarrow{P_2O_5} \text{HCO}_2\text{O} \cdot \text{O} \cdot \text{HCO}_2\text{H} \\
\end{align*}
\]

Carboxylic acids and carboxylic acid derivatives can also be prepared by methods other than nucleophilic acyl substitution reactions. A summary of the methods used to synthesize these compounds is given in Appendix IV.

**Activation of Carboxylate Ions for Nucleophilic Acyl Substitution Reactions in Biological Systems**

The synthesis of compounds by biological organisms is called **biosynthesis**. Acyl halides and acid anhydrides are too reactive to be used as reagents in biological systems. Cells live in a predominantly aqueous environment, and acyl halides and acid anhydrides are rapidly hydrolyzed in water. So living organisms must activate carboxylic acids in a different way.

One way living organisms activate carboxylic acids is to convert them into acyl phosphates, acyl pyrophosphates, and acyl adenylates.

An **acyl phosphate** is a mixed anhydride of a carboxylic acid and phosphoric acid; an **acyl pyrophosphate** is a mixed anhydride of a carboxylic acid and pyrophosphoric acid; an **acyl adenylate** is a mixed anhydride of a carboxylic acid and adenosine monophosphate (AMP).

The structure of adenosine triphosphate (ATP) is shown below with “Ad” in place of the adenosyl group; adenosine monophosphate has two fewer phosphate groups.

Acyl phosphates are formed by nucleophilic attack of a carboxylate ion on the $\gamma$-phosphorus (the terminal phosphorus) of ATP. Attack of a nucleophile on the $P=O$
group breaks a phosphoanhydride bond (rather than the \( \pi \) bond), so an intermediate is not formed. Essentially, it is an S_N2 reaction with an adenosine pyrophosphate leaving group. This reaction and the ones that follow will be discussed in greater detail in Sections 27.3 and 27.4.

Acyl pyrophosphates are formed by nucleophilic attack of a carboxylate ion on the \( \beta \)-phosphorus of ATP.

Acyl adenylates are formed by nucleophilic attack of a carboxylate ion on the \( \alpha \)-phosphorus of ATP.

Because these mixed anhydrides are negatively charged, they are not readily approached by nucleophiles. Thus, they are used only in enzyme-catalyzed reactions. One of the functions of enzymes that catalyze biological nucleophilic acyl substitution reactions is to neutralize the negative charges of the mixed anhydride (Section 27.5). Another function of the enzyme is to exclude water from the site where the reaction takes place. Otherwise hydrolysis of the mixed anhydride would compete with the desired nucleophilic acyl substitution reaction.

A thioester is an ester with a sulfur atom in place of the oxygen atom between the acyl and alkyl groups.

Thioesters are the most common forms of activated carboxylic acids in a cell. Although thioesters hydrolyze at about the same rate as oxygen esters, they are much more reactive than oxygen esters toward attack by nitrogen and carbon nucleophiles. This allows a thioester to survive in the aqueous environment of the cell—without being hydrolyzed—waiting to be a substrate in a nucleophilic acyl substitution reaction.
The carbonyl carbon of a thioester is more susceptible to nucleophilic attack than is the carbonyl carbon of an oxygen ester because there is less electron delocalization onto the carbonyl oxygen when \( Y \) is S than when \( Y \) is O. There is less electron delocalization because there is less overlap between the \( 3p \) orbital of sulfur and the \( 2p \) orbital of carbon, compared with the amount of overlap between the \( 2p \) orbital of oxygen and the \( 2p \) orbital of carbon (Section 17.2). In addition, a thiolate ion is a weaker base and therefore a better leaving group than an alkoxide ion.

\[
\begin{align*}
\text{RC} \equiv O & \quad \leftrightarrow \quad \text{RC} \equiv O^- \\
\text{CH}_3\text{CH}_2\text{SH} & \quad \text{CH}_3\text{CH}_2\text{OH} \\
\text{pK}_a = 10.5 & \quad \text{pK}_a = 15.9
\end{align*}
\]

The thiol used in biological systems for the formation of thioesters is coenzyme A. The compound is written “CoASH” to emphasize that the thiol group is the reactive part of the molecule.

Coenzyme A was discovered by Fritz A. Lipmann (1899–1986). He also was the first to recognize its importance in intermediary metabolism. Lipmann was born in Germany. To escape the Nazis, he moved to Denmark in 1932 and to the United States in 1939, becoming a U.S. citizen in 1944. For his work on coenzyme A, he received the Nobel Prize in physiology or medicine in 1953, sharing it with Hans Krebs.

The first step in converting a carboxylic acid into a thioester is to convert the carboxylic acid into an acyl adenylate. The acyl adenylate then reacts with CoASH to form the thioester. The most common thioester in cells is acetyl-CoA.

\[
\begin{align*}
\text{CH}_3\text{C} & + \text{ATP} \quad \text{enzyme} \quad \text{CH}_3\text{C} & + \text{CoASH} \quad \text{AMP} \\
\text{O} & \quad \text{O} + \text{pyrophosphate} \\
\text{O} & \quad \text{O}
\end{align*}
\]

Acetylcholine, an ester, is one example of a carboxylic acid derivative that cells synthesize using acetyl-CoA. Acetylcholine is a neurotransmitter—a compound that transmits nerve impulses across the synapses between nerve cells.

\[
\begin{align*}
\text{CH}_3\text{C} \quad + \quad \text{HOCH}_2\text{CH}_2\text{NCH}_3 \quad \text{enzyme} \quad \text{CH}_3\text{C} \quad + \quad \text{CoASH} \\
\text{SCoA} & \quad \text{choline} & \quad \text{SCoA} & \quad \text{acetylcholine}
\end{align*}
\]

It is believed that one way genes are activated is by amide formation between acetyl-CoA and a lysine residue (an amine) of a DNA-bound protein.

\[
\begin{align*}
\text{CH}_3\text{C} \quad + \quad \text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2 \quad \text{enzyme} \quad \text{CH}_3\text{C} \quad + \quad \text{CoASH} \\
\text{SCoA} & \quad \text{a lysine residue} & \quad \text{SCoA} & \quad \text{an amide}
\end{align*}
\]
NERVE IMPULSES, PARALYSIS, AND INSECTICIDES

After a nerve impulse is transmitted between cells, acetylcholine must be rapidly hydrolyzed to enable the recipient cell to receive another impulse.

\[
\text{CH}_3 \text{OCH}_2 \text{CH}_2 \text{NCH}_3 + \text{H}_2\text{O} \xrightarrow{\text{acetylcholinesterase}} \text{CH}_3 \text{CO} - + \text{HOCH}_2 \text{CH}_2 \text{NCH}_3
\]

Acetylcholinesterase, the enzyme that catalyzes this hydrolysis, has a CH$_2$OH group that is necessary for its catalytic activity. Diisopropyl fluorophosphate (DFP), a military nerve gas, inhibits acetylcholinesterase by reacting with the CH$_2$OH group.

When the enzyme is inhibited, paralysis occurs because the nerve impulses cannot be transmitted properly. DFP is extremely toxic: Its LD$_{50}$ (the lethal dose for 50% of the test animals) is only 0.5 mg/kg of body weight.

Malathion and parathion, compounds related to DFP, are used as insecticides. The LD$_{50}$ of malathion is 2800 mg/kg. Parathion is more toxic, with an LD$_{50}$ of 2 mg/kg.

17.21 Dicarboxylic Acids and Their Derivatives

The structures of some common dicarboxylic acids and their pK$_a$ values are shown in Table 17.2. Although the two carboxyl groups of a dicarboxylic acid are identical, the two pK$_a$ values are different because the protons are lost one at a time and therefore leave from different species. The first proton is lost from a neutral molecule, whereas the second proton is lost from a negatively charged ion.

\[
\begin{align*}
\text{HO} & \text{C} \text{COOH} & \text{pK}_{a1} = 2.86 \\
\text{HO} & \text{C} \text{COCH}_2 & \text{pK}_{a2} = 5.70 \\
& + \text{H}^+ & + \text{H}^+
\end{align*}
\]

A COOH group withdraws electrons (more strongly than does an H) and therefore increases the stability of the conjugate base that is formed when the first COOH group loses a proton—thereby increasing its acidity. The pK$_a$ values of the dicarboxylic acids
show that the acid-strengthening effect of the COOH group decreases as the separation between the two carboxyl groups increases.

Dicarboxylic acids readily lose water when heated if they can form a cyclic anhydride with a five- or a six-membered ring.

Cyclic anhydrides are more easily prepared if the dicarboxylic acid is heated in the presence of acetyl chloride or acetic anhydride or if it is treated with a strong dehydrating agent such as $P_2O_5$.
PROBLEM 36

a. Propose a mechanism for the formation of succinic anhydride in the presence of acetic anhydride.

b. How does acetic anhydride help in the formation of succinic anhydride?

Carbonic acid—a compound with two OH groups bonded to the carbonyl carbon—is unstable, readily breaking down to CO₂ and H₂O. The reaction is reversible, so carbonic acid is formed when CO₂ is bubbled into water (Section 1.20).

SYNTHETIC POLYMERS

Synthetic polymers play important roles in our daily lives. Polymers are compounds that are made by linking together many small molecules called monomers. In many synthetic polymers, the monomers are held together by ester and amide bonds. For example, Dacron® is a polyester and nylon is a polyamide.

Synthetic polymers have taken the place of metals, fabrics, glass, ceramics, wood, and paper, allowing us to have a greater variety and larger quantities of materials than nature could have provided. New polymers are continually being designed to fit human needs. For example, Kevlar® has a tensile strength greater than steel. It is used for high-performance skis and bulletproof vests. Lexan® is a strong and transparent polymer used for such things as traffic light lenses and compact disks.

These and other synthetic polymers are discussed in detail in Chapter 28.
We have seen that the OH group of a carboxylic acid can be substituted to give a variety of carboxylic acid derivatives. Similarly, the OH groups of carboxylic acids can be substituted by other groups.

\[
\begin{align*}
\text{Cl}_2\text{C} & \quad \text{Cl} \\
\text{CH}_3\text{O} & \quad \text{OCH}_3 \\
\text{H}_2\text{N} & \quad \text{NH}_2 \\
\text{H}_2\text{N} & \quad \text{OH} \\
\text{H}_2\text{N} & \quad \text{OCH}_3
\end{align*}
\]

**PROBLEM 37**

What products would you expect to obtain from the following reactions?

- a. phosgene + excess diethylamine
- b. malonic acid + 2 acetyl chloride
- c. methyl carbamate + methylamine
- d. urea + water
- e. urea + water + H^+
- f. \(\beta\)-ethylglutaric acid + acetyl chloride + \(\Delta\)

**Summary**

A **carbonyl group** is a carbon double-bonded to an oxygen; an **acyl group** is a carbonyl group attached to an alkyl or aryl group. **Acyl halides, acid anhydrides, esters**, and **amides** are called **carboxylic acid derivatives** because they differ from a carboxylic acid only in the nature of the group that has replaced the OH group of the carboxylic acid. Cyclic esters are called **lactones**; cyclic amides are **lactams**. There are **symmetrical anhydrides** and **mixed anhydrides**.

**Carbonyl compounds** can be placed in one of two classes. Class I carbonyl compounds contain a group that can be replaced by another group; carboxylic acids and carboxylic acid derivatives belong to this class. Class II carbonyl compounds do not contain a group that can be replaced by another group; aldehydes and ketones belong to this class.

The reactivity of carbonyl compounds resides in the polarity of the carbonyl group; the carbonyl carbon has a partial positive charge that is attractive to nucleophiles. Class I carbonyl compounds undergo **nucleophilic acyl substitution reactions**: a nucleophile replaces the substituent that was attached to the acyl group in the reactant. All Class I carbonyl compounds react with nucleophiles in the same way: the nucleophile attacks the carbonyl carbon, forming an unstable tetrahedral intermediate. (Generally, a compound with an \(sp^3\) carbon bonded to an oxygen is unstable if the \(sp^3\) carbon is bonded to another electronegative atom.) The tetrahedral intermediate reforms a carbonyl compound by eliminating the weakest base.

A carboxylic acid derivative will undergo a nucleophilic acyl substitution reaction provided that the newly added group in the tetrahedral intermediate is not a much weaker base than the group that was attached to the acyl group in the reactant. The weaker the base attached to the acyl group, the easier it is for both steps of the nucleophilic acyl substitution reaction to take place. The relative reactivities toward nucleophilic acyl substitution: acyl halides > acid anhydrides > carboxylic acids and esters > amides > carboxylate ions.

**Hydrolysis**, **alcoholysis**, and **aminolysis** are reactions in which water, alcohols, and amines, respectively, convert one compound into two compounds. A **transesterification reaction** converts one ester to another ester. Treating a carboxylic acid with excess alcohol and an acid catalyst is called a **Fischer esterification**. An ester with a tertiary alkyl group hydrolyzes via an \(S_n1\) reaction.

The rate of hydrolysis can be increased by either acid or \(\text{HO}^-\); the rate of alcoholysis can be increased by either acid or \(\text{RO}^-\). An acid increases the rate of formation of the tetrahedral intermediate by protonating the carbonyl oxygen, which increases the electrophilicity of the carbonyl group, and by decreasing the basicity of the leaving group, which makes it easier to eliminate. Hydroxide (or alkoxide) ion increases the rate of formation of the tetrahedral intermediate—it is a better nucleophile than water (or an alcohol)—and increases the rate of collapse of the tetrahedral intermediate. Hydroxide ion promotes only hydrolysis reactions; alkoxide ion promotes only alcoholysis reactions. In an acid-catalyzed reaction, all organic reactants, intermediates, and products are positively charged or neutral; in hydroxide-ion- or alkoxide-ion-promoted reactions, all organic reactants, intermediates, and products are negatively charged or neutral.

**Fats** and **oils** are triesters of glycerol. Hydrolyzing the ester groups in a basic solution (**saponification**) forms glycerol and fatty acid salts (soaps). Long-chain carboxylate ions arrange themselves in spherical clusters called **micelles**. The attractive forces of hydrocarbon chains for each other in water are called **hydrophobic interactions**.

Amides are unreactive compounds but do react with water and alcohols if the reaction mixture is heated in the presence of an acid. Nitriles are harder to hydrolyze than amides. The **Gabriel synthesis**, which converts alkyl halides into primary amines, involves the hydrolysis of an **imide**.

Organic chemists activate carboxylic acids by converting them into acyl halides or acid anhydrides. Cells activate carboxylic acids by converting them into **acyl phosphates**, **acyl pyrophosphates**, **acyl adenylates**, and **thioesters**.
Summary of Reactions

1. Reactions of acyl halides (Section 17.8)

\[ RCOCl + CH_3O^- \rightarrow RCOOCH_3 + Cl^- \]
\[ RCOCl + CH_3OH \rightarrow RCOOCH_3 + HCl \]
\[ RCOCl + H_2O \rightarrow RCOOH + HCl \]
\[ RCOCl + 2CH_3NH_2 \rightarrow RCONHCH_3 + CH_3NH_3Cl^- \]

2. Reactions of acid anhydrides (Section 17.9)

\[ R(O)OCR + CH_3OH \rightarrow RCOOCH_3 + RCOH \]
\[ R(O)OCR + H_2O \rightarrow 2RCOH \]
\[ R(O)OCR + 2CH_3NH_2 \rightarrow RCONHCH_3 + RCO^+CH_3NCH_3 \]

3. Reactions of esters (Sections 17.10–17.13)

\[ RCOOR + CH_3OH \overset{HCl}{\rightarrow} RCOOCH_3 + ROH \]
\[ RCOOR + H_2O \overset{HCl}{\rightarrow} RCOOH + ROH \]
\[ RCOOR + H_2O \overset{HO^-}{\rightarrow} RCOO^- + ROH \]
\[ RCOOR + CH_3NH_2 \rightarrow RCONHCH_3 + ROH \]
4. Reactions of carboxylic acids (Section 17.14)

\[
\text{RCOOH} + \text{CH}_3\text{OH} \xrightleftharpoons{\text{HCl}} \text{RCOCH}_3 + \text{H}_2\text{O}
\]

\[
\text{RCOOH} + \text{CH}_3\text{NH}_2 \rightarrow \text{RCO}^-\text{H}_3\text{NCH}_3^+
\]

5. Reactions of amides (Sections 17.15 and 17.16)

\[
\text{RCONH}_2 + \text{H}_2\text{O} \xrightarrow{\text{HCl}} \text{RCOOH} + \text{NH}_4^+
\]

\[
\text{RCONH}_2 \xrightarrow{\text{P}_2\text{O}_5} \text{RC}≡\text{N}
\]

6. Gabriel synthesis of primary amines (Section 17.17)

\[
\text{RCH}_2\text{Br} \xrightarrow{1. \text{phthalimide, } \text{H}^+} \text{RCH}_2\text{NH}_2
\]

7. Hydrolysis of nitriles (Section 17.18)

\[
\text{RC}≡\text{N} + \text{H}_2\text{O} \xrightarrow{\Delta} \text{RCOOH} + \text{NH}_4^+
\]

8. Activation of carboxylic acids by chemists (Section 17.20)

\[
\text{RCOOH} + \text{SOCl}_2 \xrightarrow{\Delta} \text{RCOCl} + \text{SO}_2 + \text{HCl}
\]

\[
\text{RCOOH} + \text{PCl}_3 \xrightarrow{\Delta} 3\text{RCOCl} + \text{H}_3\text{PO}_3
\]

9. Activation of carboxylic acids by cells (Section 17.20)

\[
\text{RCOO}^- + \text{PO}_4^3- \xrightarrow{\text{enzyme}} \text{RCPO}_4^- + \text{PO}_4^3-
\]

\[
\text{RCOO}^- + \text{PO}_4^3- \xrightarrow{\text{enzyme}} \text{RCPO}_4^- + \text{PO}_4^3-\text{Ad}
\]
10. Dehydration of dicarboxylic acids (Section 17.21)

Key Terms

- acid anhydride (p. 673)
- acyl adenylate (p. 713)
- acyl group (p. 670)
- acyl halide (p. 673)
- acyl phosphate (p. 713)
- acyl pyrophosphate (p. 713)
- acyl transfer reaction (p. 682)
- alcoholysis (p. 690)
- α-carbon (p. 672)
- amide (p. 675)
- amino acid (p. 679)
- aminolysis (p. 690)
- biosynthesis (p. 713)
- carbonyl carbon (p. 676)
- carbonyl compound (p. 670)
- carbonyl group (p. 670)
- carbonyl oxygen (p. 676)
- carboxyl group (p. 673)
- carboxylic acid (p. 671)
- carboxylic acid derivative (p. 670)
- carboxyl oxygen (p. 674)
- catalyst (p. 694)
- detergent (p. 701)
- ester (p. 674)
- fatty acid (p. 700)
- fats (p. 700)
- Fischer esterification (p. 702)
- Gabriel synthesis (p. 708)
- hydrolysis (p. 690)
- hydrophobic interactions (p. 700)
- imide (p. 708)
- lactam (p. 675)
- lactone (p. 674)
- micelle (p. 700)
- mixed anhydride (p. 673)
- neurotransmitter (p. 715)
- nitriles (p. 675)
- nucleophilic acyl substitution reaction (p. 682)
- oils (p. 700)
- phosphoanhydride bond (p. 714)
- ritter reaction (p. 728)
- saponification (p. 700)
- soap (p. 700)
- symmetrical anhydride (p. 673)
- tetrahedral intermediate (p. 681)
- thioester (p. 714)
- transesterification reaction (p. 690)

Problems

38. Write a structure for each of the following compounds:
   a. N,N-dimethylhexanamide
   b. 3,3-dimethylhexanamide
   c. cyclohexanecarbonyl chloride
   d. propanenitrile
   e. propionyl bromide
   f. sodium acetate
   g. benzoic anhydride
   h. β-valerolactone
   i. 3-methylbutanenitrile
   j. cycloheptanecarboxylic acid
39. Name the following compounds:

- a. CH₃CH₂CH₂CH₂CH₂COH
- b. CH₃CH₂COCH₂CH₂CH₃
- c. CH₃CH₂CH₂CH₂C≡N
- d. CH₃CH₂COCH₂CH₃
- e. CH₃CH₂CH₂CN(CH₃)₂
- f. CH₃CH₂CH₂CH₂Cl
- g. \(\text{O-O} \quad \text{O}\)
- h. CH₂=CHCH₂CNHCH₃
- i. CH₃CH₂CH₂COOH
- j. CH₃CH₂CH₂CH₂CN

40. What products would be formed from the reaction of benzoyl chloride with the following reagents?

- a. sodium acetate
- b. water
- c. dimethylamine
- d. aqueous HCl
- e. aqueous NaOH
- f. cyclohexanol
- g. benzylamine
- h. 4-chlorophenol
- i. isopropyl alcohol
- j. aniline

41. a. List the following esters in order of decreasing reactivity in the first step of a nucleophilic acyl substitution reaction (formation of the tetrahedral intermediate):

- A
- B
- C
- D

b. List the same esters in order of decreasing reactivity in the second step of a nucleophilic acyl substitution reaction (collapse of the tetrahedral intermediate).

42. a. Which compound would you expect to have a higher dipole moment, methyl acetate or butanone?

- CH₃COCH₂CH₃ (methyl acetate)
- CH₃C(CH₃)₂CH₂CH₂O (butanone)

b. Which would you expect to have a higher boiling point?

43. How could you use \(^1\text{H NMR}\) spectroscopy to distinguish among the following esters?

- A
- B
- C
- D

44. If propionyl chloride is added to one equivalent of methylamine, only a 50% yield of N-methylpropanamide is obtained. If, however, the acyl chloride is added to two equivalents of methylamine, the yield of N-methylpropanamide is almost 100%. Explain these observations.

45. a. When a carboxylic acid is dissolved in isotopically labeled water (H₂O\(^{18}\)), the label is incorporated into both oxygens of the acid. Propose a mechanism to account for this.

- CH₃COOH + H₂O\(^{18}\) \(\rightarrow\) CH₃COOH + H₂O

b. If a carboxylic acid is dissolved in isotopically labeled methanol (CH₃\(^{18}\)OH) and an acid catalyst is added, where will the label reside in the product?

46. What reagents would you use to convert methyl propanoate into the following compounds?

- a. isopropyl propanoate
- b. sodium propanoate
- c. N-ethylpropanamide
- d. propanoic acid
47. A compound with molecular formula C₆H₁₀O₂ gives the following IR spectrum. When it undergoes acid-catalyzed hydrolysis, the compound with the following ¹H NMR spectrum is formed. Identify the compounds.

![IR Spectrum]

![NMR Spectrum]

48. Aspartame, the sweetener used in the commercial products NutraSweet® and Equal®, is 160 times sweeter than sucrose. What products would be obtained if aspartame were hydrolyzed completely in an aqueous solution of HCl?

![Aspartame Structure]

49. a. Which of the following reactions will not give the carbonyl product shown?

1. CH₃COH + CH₃CO⁻ → CH₃COCCCH₃
2. CH₃CCl + CH₃CO⁻ → CH₃COCCH₃
3. CH₃CNH₂ + Cl⁻ → CH₃CCl
4. CH₃COH + CH₃NH₂ → CH₃CNHCH₃
5. CH₃COCH₃ + CH₃NH₂ → CH₃COCCH₃
6. CH₃COCH₃ + Cl⁻ → CH₃CCl
7. \[ \text{CH}_3\text{CNHCH}_3 + \text{CH}_3\text{CO}^- \rightarrow \text{CH}_3\text{OCCH}_3 \]

8. \[ \text{CH}_3\text{Cl} + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{COH} \]

9. \[ \text{CH}_3\text{CNHCH}_3 + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{COH} \]

10. \[ \text{CH}_3\text{COCH}_3 + \text{CH}_3\text{OH} \rightarrow \text{CH}_3\text{COCH}_3 \]

b. Which of the reactions that do not occur can be made to occur if an acid catalyst is added to the reaction mixture?

50. 1,4-Diazabicyclo[2.2.2]octane (abbreviated DABCO) is a tertiary amine that catalyzes transesterification reactions. Propose a mechanism to show how it does this.

51. Identify the major and minor products of the following reaction:

52. Two products, A and B, are obtained from the reaction of 1-bromobutane with \( \text{NH}_3 \). Compound A reacts with acetyl chloride to form C, and B reacts with acetyl chloride to form D. The IR spectra of C and D are shown. Identify A, B, C, and D.

53. Phosgene (\( \text{COCl}_2 \)) was used as a poison gas in World War I. Give the product that would be formed from the reaction of phosgene with each of the following reagents:
   1. one equivalent of methanol
   2. excess methanol
   3. excess propylamine
   4. one equivalent of ethanol followed by one equivalent of methylamine

54. When Ethyl Ester treated butanedioic acid with thionyl chloride, she was surprised to find that the product she obtained was an anhydride rather than an acyl chloride. Propose a mechanism to explain why she obtained an anhydride.
55. Give the products of the following reactions:

a. \(\text{CH}_3\text{CCl}_2 + \text{KF} \rightarrow\)

b. \(\text{H}_2\text{O} + \text{HCl}\)

c. \(\text{ClCCl}_2 + \text{OH}_2\text{OH}\)

d. \(\text{H}_2\text{O} \rightarrow\)

e. \(\text{HCl} + \text{OH}_2\text{OH}\)

f. \(\text{H}_2\text{O} + \text{HCl}\)

g. \(\text{CH}_3\text{CH}_2\text{OH} + \text{CH}_3\text{OH} \rightarrow\)

h. \(\text{CH}_3\text{COH} + \text{NH}_3 \rightarrow\)

i. \(\text{CH}_3\text{COH} + \text{CH}_3\text{OH} \rightarrow\)

j. \(\text{CH}_3\text{COH} + \text{CH}_3\text{OH} \rightarrow\)

56. When treated with an equivalent of methanol, compound A, with molecular formula \(\text{C}_4\text{H}_6\text{Cl}_2\text{O}\), forms the compound whose \(^1\text{H}\) NMR spectrum is shown below. Identify compound A.

![NMR spectrum]

57. a. Identify the two products obtained from the following reaction:

\[\text{CH}_3\text{COCCH}_3 + \text{CH}_3\text{CHCH}_2\text{CH}_2\text{OH} \rightarrow\]

b. Eddie Amine carried out the preceding reaction, but stopped it before it was half over, whereupon he isolated the major product. He was surprised to find that the product he isolated was neither of the products obtained when the reaction was allowed to go to completion. What product did he isolate?

58. An aqueous solution of a primary or secondary amine reacts with an acyl chloride to form an amide as the major product. However, if the amine is tertiary, an amide is not formed. What product is formed? Explain.

59. a. Ann Hydride did not obtain any ester when she added 2,4,6-trimethylbenzoic acid to an acidic solution of methanol. Why? (Hint: Build models.)

b. Would Ann have encountered the same problem if she had tried to synthesize the methyl ester of \(p\)-methylbenzoic acid in the same way?

c. How could she prepare the methyl ester of 2,4,6-trimethylbenzoic acid? (Hint: See Section 16.12.)
60. When a compound with molecular formula C_{11}H_{14}O_{2} undergoes acid-catalyzed hydrolysis, one of the products that is isolated gives the following $^1$H NMR spectrum. Identify the compound.

61. List the following compounds in order of decreasing frequency of the carbon–oxygen double-bond stretch:

- CH$_3$COCH$_3$
- CH$_3$CCl
- CH$_3$CH
- CH$_3$CNH$_2$

62. a. If the equilibrium constant for the reaction of acetic acid and ethanol to form ethyl acetate is 4.02, what will be the concentration of ethyl acetate at equilibrium if the reaction is carried out with equal amounts of acetic acid and ethanol?

b. What will be the concentration of ethyl acetate at equilibrium if the reaction is carried out with 10 times more ethanol than acetic acid? *Hint: Recall the quadratic equation: For $ax^2 + bx + c = 0$, $x = -b \pm (b^2 - 4ac)^{1/2} / 2a$*

c. What will be the concentration of ethyl acetate at equilibrium if the reaction is carried out with 100 times more ethanol than acetic acid?

63. The $^1$H NMR spectra for two esters with molecular formula C$_8$H$_8$O$_2$ are shown below. If each of the esters is added to an aqueous solution with a pH of 10, which of the esters will be hydrolyzed more completely when the hydrolysis reactions have reached equilibrium?
64. Show how the following compounds could be prepared from the given starting materials. You can use any necessary organic or inorganic reagents.
   
   a. $\text{CH}_3\text{CH}_2\text{CNH}_2 \rightarrow \text{CH}_3\text{CH}_2\text{CCl}$
   
   b. $\text{CH}_3\text{CH}_2\text{CH}_2\text{OH} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{COH}$
   
   c. $\text{CH}_3(\text{CH}_2)_{10}\text{COH} \rightarrow \text{CH}_3(\text{CH}_2)_{11}\text{C}_6\text{H}_4\text{SO}_3^- \text{Na}^+$
   
   a detergent
   
   d. $\text{CH}_3\text{C}_6\text{H}_5 \rightarrow \text{CH}_3\text{C}_6\text{H}_5\text{CNHCH}_3$
   
   e. $\text{C}_6\text{H}_5\text{NH}_2 \rightarrow \text{C}_6\text{H}_5\text{C}_6\text{H}_4\text{CO}$
   
   f. $\text{CH}_3\text{C}_6\text{H}_5 \rightarrow \text{CH}_3\text{C}_6\text{H}_5\text{COH}$

65. Is the acid-catalyzed hydrolysis of acetamide a reversible or an irreversible reaction? Explain.

66. The reaction of a nitrile with an alcohol in the presence of a strong acid forms a secondary amide. This reaction is known as the Ritter reaction. The Ritter reaction does not work with primary alcohols.

   \[
   \text{RC}≡\text{N} + \text{R′OH} \xrightleftharpoons{\text{H}^+} \text{RCNHR}′
   \]

   a. Propose a mechanism for the Ritter reaction.
   b. Why does the Ritter reaction not work with primary alcohols?
   c. How does the Ritter reaction differ from the acid-catalyzed hydrolysis of a nitrile to form a primary amide?

67. The intermediate shown here is formed during the hydroxide-ion-promoted hydrolysis of the ester group. Propose a mechanism for the reaction.

68. What product would you expect to obtain from each of the following reactions?

   a. $\text{CH}_3\text{CH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2\text{COH} + \text{HCl} \rightarrow \text{CH}_3\text{CH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2\text{COH}$
   
   b. $\text{CH}_2\text{COCH}_2\text{CH}_3 + \text{HCl} \rightarrow \text{CH}_2\text{COCH}_2\text{CH}_3$
   
   c. $\text{CH}_3\text{C}_6\text{H}_5 \xrightarrow{1. \text{SOCl}_2 \ 2. \text{AlCl}_3 \ 3. \text{H}_2\text{O}} \text{CH}_3\text{C}_6\text{H}_5\text{COH}$
69. Sulfonamides, the first antibiotics, were introduced clinically in 1934 (Sections 25.8 and 30.4). Show how a sulfonamide can be prepared from benzene.

\[
\text{H}_2\text{N}-\text{C}_6\text{H}_4\text{SNHR} \quad \text{a sulfonamide}
\]

70. a. How could aspirin be synthesized, starting with benzene?

b. Ibuprofen is the active ingredient in pain relievers such as Advil\textsuperscript{®}, Motrin\textsuperscript{®}, and Nuprin\textsuperscript{®}. How could ibuprofen be synthesized, starting with benzene?

\[
\begin{align*}
\text{Aspirin} & : \text{C}_6\text{H}_5\text{COOH} \\
\text{Ibuprofen} & : \text{CH}_3\text{CHCH}_2-\text{C}_6\text{H}_4-\text{CHCOH}
\end{align*}
\]

71. The following compound has been found to be an inhibitor of penicillinase. The enzyme can be reactivated by hydroxylamine (NH\textsubscript{2}OH). Propose a mechanism to account for the inhibition and for the reactivation.

\[
\text{Inhibitor}
\]

72. For each of the following reactions, propose a mechanism that will account for the formation of the product:

a. 

b. 

73. Show how Novocain\textsuperscript{®}, a painkiller used frequently by dentists (Section 30.3), can be prepared from benzene.

\[
\text{Novocain}\textsuperscript{®}
\]

74. Catalytic antibodies catalyze a reaction by binding to the transition state, thereby stabilizing it. As a result, the energy of activation is lowered and the reaction goes faster. The synthesis of the antibody is carried out in the presence of a transition state analog—a
stable molecule that structurally resembles the transition state. This causes an antibody to be generated that will recognize and bind to the transition state. For example, the following transition state analog has been used to generate a catalytic antibody that catalyzes the hydrolysis of the structurally similar ester:

\[
\begin{array}{c}
\text{HO-} \quad \text{O-} \quad \text{P-} \quad \text{NO}_2 \\
\text{transition state analog}
\end{array}
\]

\[
\begin{array}{c}
\text{HO-} \quad \text{O-} \quad \text{P-} \quad \text{NO}_2 \quad \text{H}_2\text{O} \\
\text{HO-} \quad \text{O-} \quad \text{P-} \quad \text{NO}_2 \quad \text{OH} \quad \text{+} \quad \text{HO-} \quad \text{O-} \quad \text{P-} \quad \text{NO}_2
\end{array}
\]

a. Draw the transition state for the hydrolysis reaction.
b. The following transition state analog is used to generate a catalytic antibody for the catalysis of ester hydrolysis. Give the structure of an ester whose rate of hydrolysis would be increased by this catalytic antibody.

c. Design a transition state analog that would catalyze amide hydrolysis at the amide group indicated.

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75. Saccharin, an artificial sweetener, is about 300 times sweeter than sucrose. Describe how saccharin could be prepared, using benzene as the starting material.

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76. Information about the mechanism of reaction of a series of substituted benzenes can be obtained by plotting the logarithm of the observed rate constant obtained at a particular pH against the Hammett substituent constant (\(\sigma\)) for the particular substituent. The \(\sigma\) value for hydrogen is 0. Electron-donating substituents have negative \(\sigma\) values; electron-withdrawing substituents have positive \(\sigma\) values. The more strongly electron donating the substituent, the more negative its \(\sigma\) value will be; the more strongly electron withdrawing the substituent, the more positive value its \(\sigma\) value will be. The slope of a plot of the logarithm of the rate constant versus \(\sigma\) is called the \(\rho\) (rho) value. The \(\rho\) value for the hydroxide-ion-promoted hydrolysis of a series of meta- and para-substituted ethyl benzoates is +2.46; the \(\rho\) value for amide formation for the reaction of a series of meta- and para-substituted anilines with benzoyl chloride is \(-2.78\).

a. Why does one set of experiments give a positive \(\rho\) value while the other set of experiments gives a negative \(\rho\) value?
b. Why do you think that ortho-substituted compounds were not included in the experiment?
c. What would you predict the sign of the \(\rho\) value to be for the ionization of a series of meta- and para-substituted benzoic acids?
In Section 17.0, we saw that carbonyl compounds—compounds that possess a carbonyl group (C=O)—can be divided into two classes: Class I carbonyl compounds, which have a group that can be replaced by a nucleophile, and Class II carbonyl compounds, which comprise aldehydes and ketones. Unlike Class I carbonyl compounds, Class II carbonyl compounds do not have a group that can be replaced by a nucleophile.

The carbonyl carbon of the simplest aldehyde, formaldehyde, is bonded to two hydrogens. The carbonyl carbon in all other aldehydes is bonded to a hydrogen and to an alkyl (or an aryl) group. The carbonyl carbon of a ketone is bonded to two alkyl (or aryl) groups. Aldehydes and ketones do not have a group that can be replaced by another group, because hydride ions (H⁻) and carbanions (R⁻) and are too basic to be displaced by nucleophiles under normal conditions.

The physical properties of aldehydes and ketones are discussed in Section 17.3 (see also Appendix I), and the methods used to prepare aldehydes and ketones are summarized in Appendix IV.

Many compounds found in nature have aldehyde or ketone functional groups. Aldehydes have pungent odors, whereas ketones tend to smell sweet. Vanillin and cinnamaldehyde are examples of naturally occurring aldehydes. A whiff of vanilla extract will allow you to appreciate the pungent odor of vanilla. The ketones carvone and camphor are responsible for the characteristic sweet odors of spearmint leaves, caraway seeds, and the camphor tree.
In ketosis, a pathological condition that can occur in people with diabetes, the body produces more acetoacetate than can be metabolized. The excess acetoacetate breaks down to acetone—a ketone—and CO₂. Ketosis can be recognized by the smell of acetone on a person’s breath.

Two ketones that are of biological importance illustrate how a small difference in structure can be responsible for a large difference in biological activity: Progesterone is a female sex hormone synthesized primarily in the ovaries, whereas testosterone is a male sex hormone synthesized primarily in the testes.

18.1 Nomenclature

Aldehydes

The systematic name of an aldehyde is obtained by replacing the terminal “e” from the name of the parent hydrocarbon with “al.” For example, a one-carbon aldehyde is methanal; a two-carbon aldehyde is ethanal. The position of the carbonyl carbon does not have to be designated, because it is always at the end of the parent hydrocarbon and therefore always has the 1-position.

The common name of an aldehyde is the same as the common name of the corresponding carboxylic acid (Section 17.1), except that “aldehyde” is substituted for “ic acid” (or “oic acid”). When common names are used, the position of a substituent is designated by a lowercase Greek letter. The carbonyl carbon is not designated; the carbon adjacent to the carbonyl carbon is the α-carbon.
Notice that the terminal “e” is not removed in hexanedial; the “e” is removed only to avoid two successive vowels.

If the aldehyde group is attached to a ring, the aldehyde is named by adding “carbaldehyde” to the name of the cyclic compound.

In Section 8.1, we saw that a carbonyl group has a higher nomenclature priority than an alcohol or an amine group. However, all carbonyl compounds do not have the same priority. The nomenclature priorities of the various carbonyl groups are shown in Table 18.1.

If a compound has two functional groups, the one with the lower priority is indicated by its prefix. The prefix of an aldehyde oxygen that is part of the parent hydrocarbon is “oxo.” The prefix of a one-carbon aldehyde group that is not part of the parent hydrocarbon is “formyl.”

<table>
<thead>
<tr>
<th>Class</th>
<th>Suffix Name</th>
<th>Prefix Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxylic acid</td>
<td>-oic acid</td>
<td>Carboxy</td>
</tr>
<tr>
<td>Ester</td>
<td>-oate</td>
<td>Alkoxycarboxyl</td>
</tr>
<tr>
<td>Amide</td>
<td>-amide</td>
<td>Amido</td>
</tr>
<tr>
<td>Nitrile</td>
<td>-nitrile</td>
<td>Cyano</td>
</tr>
<tr>
<td>Aldehyde</td>
<td>-al</td>
<td>Oxo (==O)</td>
</tr>
<tr>
<td>Aldehyde</td>
<td>-al</td>
<td>Formyl (==CH==O)</td>
</tr>
<tr>
<td>Ketone</td>
<td>-one</td>
<td>Oxo (==O)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>-ol</td>
<td>Hydroxy</td>
</tr>
<tr>
<td>Amine</td>
<td>-amine</td>
<td>Amino</td>
</tr>
<tr>
<td>Alkene</td>
<td>-ene</td>
<td>Alkenyl</td>
</tr>
<tr>
<td>Alkyne</td>
<td>-yne</td>
<td>Alkynyl</td>
</tr>
<tr>
<td>Alkane</td>
<td>-ane</td>
<td>Alkyl</td>
</tr>
<tr>
<td>Ether</td>
<td>—</td>
<td>Alkoxy</td>
</tr>
<tr>
<td>Alkyl halide</td>
<td>—</td>
<td>Halo</td>
</tr>
</tbody>
</table>
If the compound has both an alkene and an aldehyde functional group, the alkene is cited first, with the “e” ending omitted to avoid two successive vowels (Section 8.1).

**Ketones**

The systematic name of a ketone is obtained by removing the “e” from the name of the parent hydrocarbon and adding “one.” The chain is numbered in the direction that gives the carbonyl carbon the smaller number. In the case of cyclic ketones, a number is not necessary because the carbonyl carbon is assumed to be at the 1-position. Frequently, derived names are used for ketones—the substituents attached to the carbonyl group are cited in alphabetical order, followed by “ketone.”

![Chemical structures of various ketones](image)

Only a few ketones have common names. The smallest ketone, propanone, is usually referred to by its common name, acetone. Acetone is a common laboratory solvent. Common names are also used for some phenyl-substituted ketones; the number of carbons (other than those of the phenyl group) is indicated by the common name of the corresponding carboxylic acid, substituting “ophenone” for “ic acid.”

![Chemical structures of various ketones](image)

If the ketone has a second functional group of higher naming priority, the ketone oxygen is indicated by the prefix “oxo.”

![Chemical structures of various ketones](image)
Section 18.2 Relative Reactivities of Carbonyl Compounds

BUTANEDIONE: AN UNPLEASANT COMPOUND

Fresh perspiration is odorless. Bacteria that are always present on our skin produce lactic acid, thereby creating an acidic environment that allows other bacteria to break down the components of perspiration, producing compounds with the unappealing odors we associate with armpits and sweaty feet. One such compound is butanedione.

PROBLEM 1

Why are numbers not used to designate the positions of the functional groups in propanone and butanedione?

PROBLEM 2

Give two names for each of the following compounds:

a. CH₂CH₃CHCH₂CH₃
   b. CH₃CH₂CH₂CH₂CH₃
   c. CH₃CH₂CH₂CCH₂CH₂CH₃
   d. CH₂CH₂CH₂CH₂CH₂CH₃
   e. CH₃CH₂CHCH₂CH₂CH₃
   f. CH₂=CHCCH₂CH₂CH₂CH₃

PROBLEM 3

Name the following compounds:

a. CH₂CH₂CH₂CH₂CH₂CH₂CH₃
   b. CH₂CH₂CH₂CH₂CH₂CH₂CNH₂
   c. CH₂CH₂CH₂CH₂CH₂CH₂NH₂

18.2 Relative Reactivities of Carbonyl Compounds

We have seen that the carbonyl group is polar because oxygen, being more electronegative than carbon, has a greater share of the electrons of the double bond (Section 17.5). The partial positive charge on the carbonyl carbon causes carbonyl compounds to be attacked by nucleophiles. The electron deficiency of the carbonyl carbon is indicated by the blue areas in the electrostatic potential maps.

An aldehyde has a greater partial positive charge on its carbonyl carbon than does a ketone because a hydrogen is electron withdrawing compared with an alkyl group (Section 4.2). An aldehyde, therefore, is less stable than a ketone, which makes it more reactive toward nucleophilic attack.
Steric factors also contribute to the greater reactivity of an aldehyde. The carbonyl carbon of an aldehyde is more accessible to the nucleophile than is the carbonyl carbon of a ketone because the hydrogen attached to the carbonyl carbon of an aldehyde is smaller than the alkyl group attached to the carbonyl carbon of a ketone. Steric factors also become important in the tetrahedral transition state because the bond angles are 109.5°; therefore, the alkyl groups are closer to one another than they are in the carbonyl compound, in which the bond angles are 120°. Ketones have greater steric crowding in their transition states, so they have less stable transition states than aldehydes have.

For the same reason, ketones with small alkyl groups bonded to the carbonyl carbon are more reactive than ketones with large alkyl groups.

PROBLEM 4

Which ketone is more reactive?

a. 2-heptanone or 4-heptanone
b. p-nitroacetophenone or p-methoxyacetophenone

Aldehydes and ketones are less reactive than acyl chlorides and acid anhydrides, but more reactive than esters and amides.
Consequently, aldehydes and ketones are not as reactive as carbonyl compounds in which $Y^-$ is a very weak base (acyl halides and acid anhydrides), but are more reactive than carbonyl compounds in which $Y^-$ is a relatively strong base (carboxylic acids, esters, and amides). A molecular orbital explanation of why resonance electron donation decreases the reactivity of the carbonyl group is given in Section 17.15.

18.3 How Aldehydes and Ketones React

In Section 17.5, we saw that the carbonyl group of a carboxylic acid or a carboxylic acid derivative is attached to a group that can be replaced by another group. These compounds therefore react with nucleophiles to form substitution products.

$$
\text{R}^\text{Y} \text{C} - \text{Z} \xrightarrow{\text{HZ}} \text{R}^\text{Y} \text{C} - \text{Z} + \text{Y}^-
$$

In contrast, the carbonyl group of an aldehyde or a ketone is attached to a group that is too strong a base ($\text{H}^-$ or $\text{R}^-$) to be eliminated under normal conditions, so it cannot be replaced by another group. Consequently, aldehydes and ketones react with nucleophiles to form addition products, not substitution products. Thus, aldehydes and ketones undergo **nucleophilic addition** reactions, whereas carboxylic acid derivatives undergo **nucleophilic acyl substitution** reactions.

When a nucleophile adds to a carbonyl group, the hybridization of the carbonyl carbon changes from $sp^2$ in the carbonyl compound to $sp^3$ in the addition product. In Section 17.5, we saw that a compound that has an $sp^3$ carbon bonded to an oxygen atom generally will be unstable if the $sp^3$ carbon is also bonded to another electronegative atom. Therefore, if the nucleophile that adds to the aldehyde or ketone is one in which $Z$ is not electronegative ($Z$ is an $\text{H}$ or a $\text{C}$ nucleophile), the tetrahedral addition product will be stable. It will be an alkoxide ion that can be protonated either by the solvent or by added acid. ($\text{HB}^+$ is any species that provides a proton; $:\text{B}$ is any species that removes a proton.)

$$
\text{R}^\text{Y} \text{C} - \text{Z} \xrightarrow{\text{HZ}} \text{R}^\text{Y} \text{C} - \text{Z} + \text{Y}^-
$$

If, on the other hand, the nucleophile that adds to the aldehyde or ketone is one in which $Z$ is electronegative ($Z$ is an $\text{O}$ or an $\text{N}$ nucleophile), the tetrahedral addition product

$$
\text{R}^\text{Y} \text{C} - \text{Z} \xrightarrow{\text{HZ}} \text{R}^\text{Y} \text{C} - \text{Z} + \text{Y}^-
$$

Consequently, aldehydes and ketones are not as reactive as carbonyl compounds in which $Y^-$ is a very weak base (acyl halides and acid anhydrides), but are more reactive than carbonyl compounds in which $Y^-$ is a relatively strong base (carboxylic acids, esters, and amides). A molecular orbital explanation of why resonance electron donation decreases the reactivity of the carbonyl group is given in Section 17.15.

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$$
\text{R}^\text{Y} \text{C} - \text{Z} \xrightarrow{\text{HZ}} \text{R}^\text{Y} \text{C} - \text{Z} + \text{Y}^-
$$

If, on the other hand, the nucleophile that adds to the aldehyde or ketone is one in which $Z$ is electronegative ($Z$ is an $\text{O}$ or an $\text{N}$ nucleophile), the tetrahedral addition product

$$
\text{R}^\text{Y} \text{C} - \text{Z} \xrightarrow{\text{HZ}} \text{R}^\text{Y} \text{C} - \text{Z} + \text{Y}^-
$$
product will not be stable. Water will be eliminated from the addition product. This is called a **nucleophilic addition–elimination reaction**. We will see that the fate of the dehydrated product depends on the identity of $Z$.

\[
\begin{array}{c}
\text{OH} \\
R - C - R' \\
\vdots \\
Z
\end{array} \quad \xrightarrow{\text{HB}^+} \quad \begin{array}{c}
\text{+OH} \\
\text{R - C - R'} \\
\vdots \\
Z
\end{array} \quad \xrightarrow{\text{H}_2\text{O}} \quad \begin{array}{c}
\text{R}^- \\
\text{R'} \\
\vdots \\
+Z
\end{array} + \text{H}_2\text{O}
\]

**18.4 Reactions of Carbonyl Compounds with Carbon Nucleophiles**

Few reactions in organic chemistry result in the formation of new C—C bonds. Consequently, those reactions that do are very important to synthetic organic chemists when they need to synthesize larger organic molecules from smaller molecules. The addition of a carbon nucleophile to a carbonyl compound is an example of a reaction that forms a new C—C bond and therefore forms a product with more carbon atoms than the starting material.

**Reaction with Grignard Reagents**

Addition of a Grignard reagent to a carbonyl compound is a versatile reaction that leads to the formation of a new C—C bond. The reaction can produce compounds with a variety of structures because both the structure of the carbonyl compound and the structure of the Grignard reagent can be varied. In Section 12.11, we saw that a Grignard reagent can be prepared by adding an alkyl halide to magnesium shavings in diethyl ether. We also saw that a Grignard reagent reacts as if it were a carbanion.

\[
\text{CH}_3\text{CH}_2\text{Br} \xrightarrow{\text{Et}_2\text{O}} \text{CH}_3\text{CH}_2\text{MgBr}
\]

\[
\text{CH}_3\text{CH}_2\text{MgBr} \quad \text{reacts as if it were} \quad \text{CH}_3\text{CH}_2^+ \cdot \text{MgBr}^-
\]

Attack of a Grignard reagent on a carbonyl carbon forms an alkoxide ion that is complexed with magnesium ion. Addition of water or dilute acid breaks up the complex. When a Grignard reagent reacts with formaldehyde, the addition product is a primary alcohol.

\[
\begin{array}{c}
\text{CH}_3\text{CH}_2\text{H} \\
\text{C} \quad \text{H}
\end{array} + \begin{array}{c}
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{MgBr}
\end{array} \quad \xrightarrow{\text{H}_2\text{O}^+} \quad \begin{array}{c}
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{H}^+
\end{array}
\]

When a Grignard reagent reacts with an aldehyde other than formaldehyde, the addition product is a secondary alcohol.

\[
\begin{array}{c}
\text{CH}_3\text{CH}_2\text{H} \\
\text{C} \quad \text{H}
\end{array} + \begin{array}{c}
\text{CH}_3\text{CH}_2\text{H} \\
\text{C} \quad \text{H}
\end{array} + \begin{array}{c}
\text{CH}_3\text{CH}_2\text{MgBr}
\end{array} \quad \xrightarrow{\text{H}_2\text{O}^+} \quad \begin{array}{c}
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{H}^+
\end{array}
\]

**Aldehydes and ketones undergo nucleophilic addition–elimination reactions with oxygen and nitrogen nucleophiles.**
When a Grignard reagent reacts with a ketone, the addition product is a tertiary alcohol.

\[
\begin{align*}
\text{CH}_3\text{C-CH}_2\text{CH}_2\text{CH}_3 & \quad \text{2-pentanone} \\
+ & \quad \text{ethylmagnesium bromide} \\
\text{CH}_3\text{C-CCH}_2\text{CH}_2\text{CH}_3 & \quad \text{3-methyl-3-hexanol} \\
\text{a tertiary alcohol}
\end{align*}
\]

In the following reactions, numbers are used with the reagents to indicate that the acid is not added until the reaction with the Grignard reagent is complete:

\[
\begin{align*}
\text{CH}_3\text{C-CH}_2\text{CH}_2\text{CH}_3 & \quad \text{3-pentanone} \\
\text{1. CH}_3\text{MgBr} & \quad \text{3-methyl-3-pentanol} \\
\text{2. H}_3\text{O}^+ & \\
\text{CH}_3\text{C-CH}_2\text{CH}_2\text{CH}_3 & \quad \text{butanal} \\
\text{1. } & \quad \text{1-phenyl-1-butanol} \\
\text{MgBr} & \quad \text{carbon dioxide} \\
\text{butanoic acid}
\end{align*}
\]

A Grignard reagent can also react with carbon dioxide. The product of the reaction is a carboxylic acid with one more carbon atom than the Grignard reagent has.

\[
\begin{align*}
\text{O} & \quad \text{carbon dioxide} \\
+ & \quad \text{propylmagnesium bromide} \\
\text{CH}_3\text{CH}_2\text{CH}_2\text{MgBr} & \quad \text{butanoic acid}
\end{align*}
\]

**PROBLEM 5**

a. How many isomers are obtained from the reaction of 2-pentanone with ethylmagnesium bromide followed by treatment with aqueous acid?

b. How many isomers are obtained from the reaction of 2-pentanone with methylmagnesium bromide followed by treatment with aqueous acid?

**PROBLEM 6**

We saw that 3-methyl-3-hexanol can be synthesized from the reaction of 2-pentanone with ethylmagnesium bromide. What two other combinations of ketone and Grignard reagent could be used to prepare the same tertiary alcohol?

In addition to reacting with aldehydes and ketones—Class II carbonyl compounds—Grignard reagents react with Class I carbonyl compounds—carbonyl compounds that have groups that can be replaced by another group.

Class I carbonyl compounds undergo two successive reactions with the Grignard reagent. For example, when an ester reacts with a Grignard reagent, the first reaction is a **nucleophilic acyl substitution reaction** because an ester, unlike an aldehyde or a ketone, has a group that can be replaced by the Grignard reagent. The product of the reaction is a ketone. The reaction does not stop at the ketone stage, however, because ketones are more reactive than esters toward nucleophilic attack (Section 18.2). Reaction of the ketone with a second molecule of the Grignard reagent forms a tertiary alcohol. Because the tertiary alcohol is formed as a result of two successive reactions with a Grignard reagent, the alcohol has two identical groups bonded to the tertiary carbon.
Tertiary alcohols are also formed from the reaction of two equivalents of a Grignard reagent with an acyl halide.

In theory, we should be able to stop this reaction at the ketone stage because a ketone is less reactive than an acyl halide. However, the Grignard reagent is so reactive that it can be prevented from reacting with the ketone only under very carefully controlled conditions. There are better ways to synthesize ketones (Appendix IV).

**PROBLEM 7**

What product would be obtained from the reaction of one equivalent of a carboxylic acid with one equivalent of a Grignard reagent?

**PROBLEM 8 SOLVED**

a. Which of the following tertiary alcohols cannot be prepared from the reaction of an ester with excess Grignard reagent?

1. \( \text{CH}_3\text{CH}_2\text{MgBr} \)

2. \( \text{CH}_3\text{CH}_2\text{CH}_2 \text{CH}_2 \text{OH} \)

3. \( \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \)

4. \( \text{CH}_3\text{CH}_2\text{CCH}_2\text{CH}_3 \)

5. \( \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \)

b. For those alcohols that can be prepared by the reaction of an ester with excess Grignard reagent, what ester and what Grignard reagent should be used?

**SOLUTION TO 8a**

A tertiary alcohol is obtained from the reaction of an ester with two equivalents of a Grignard reagent. Therefore, tertiary alcohols prepared in this way must have two identical substituents on the carbon to which the \( \text{OH} \) is bonded, because two
substituents come from the Grignard reagent. Alcohols (3) and (5) cannot be prepared in this way because they do not have two identical substituents.

**SOLUTION TO 8b(2)** Methyl propanoate and excess methylmagnesium bromide.

**PROBLEM 9**
Which of the following secondary alcohols can be prepared from the reaction of methyl formate with excess Grignard reagent?

<table>
<thead>
<tr>
<th>Alcohol Structure</th>
<th>Reaction Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃CH₂CHCH₃OH</td>
<td>CH₃CH₂CHCH₂CH₃</td>
</tr>
<tr>
<td>CH₃CHCH₃OH</td>
<td>CH₃CH₂CHCH₂CH₃</td>
</tr>
<tr>
<td>CH₃CHCH₂CH₂CH₃OH</td>
<td>CH₃CH₂CHCH₂CH₂CH₃</td>
</tr>
</tbody>
</table>

**Reaction with Acetylide Ions**
We have seen that a terminal alkyne can be converted into an acetylide ion by a strong base (Section 6.9).

![Acetylide ion reaction](image)

An acetylide ion is another example of a carbon nucleophile that reacts with carbonyl compounds. When the reaction is over, a weak acid (one that will not react with the triple bond, such as pyridinium ion), is added to the reaction mixture to protonate the alkoxide ion.

**PROBLEM 10**
Show how the following compounds could be prepared, using ethyne as one of the starting materials. Explain why ethyne should be alkylated before, rather than after, nucleophilic addition.

- a. 1-pentyn-3-ol
- b. 1-phenyl-2-butyn-1-ol
- c. 2-methyl-3-hexyn-2-ol

**Reaction with Hydrogen Cyanide**
Hydrogen cyanide adds to aldehydes and ketones to form cyanohydrins. This reaction forms a product with one more carbon atom than the reactant. In the first step of the reaction, the cyanide ion attacks the carbonyl carbon. The alkoxide ion then accepts a proton from an undissociated molecule of hydrogen cyanide.

![Reaction with hydrogen cyanide](image)

Because hydrogen cyanide is a toxic gas, the best way to carry out this reaction is to generate hydrogen cyanide during the reaction by adding HCl to a mixture of the aldehyde or ketone and excess sodium cyanide. Excess sodium cyanide is used in order to make sure that some cyanide ion is available to act as a nucleophile.
Compared with other carbon nucleophiles, cyanide ion is a relatively weak base (the $pK_a$ of $\text{HC}≡\text{N}$ is 9.14, the $pK_a$ of $\text{HC}≡\text{CH}$ is 25, the $pK_a$ of $\text{CH}_3\text{CH}_3$ is 50), which means that the cyano group is the most easily eliminated of the carbon nucleophiles from the addition product. Cyanohydrins, however, are stable because the OH group will not eliminate the cyano group; the transition state for the elimination reaction would be relatively unstable since the oxygen atom would bear a partial positive charge. If the OH group loses its proton, however, the cyano group will be eliminated because the oxygen atom would have a partial negative charge instead of a partial positive charge in the transition state of the elimination reaction. Therefore, in basic solutions, a cyanohydrin is converted back to the carbonyl compound.

Cyanide ion does not react with esters because the cyanide ion is a weaker base than an alkoxide ion, so the cyanide ion would be eliminated from the tetrahedral intermediate.

The addition of hydrogen cyanide to aldehydes and ketones is a synthetically useful reaction because of the subsequent reactions that can be carried out on the cyanohydrin. For example, the acid-catalyzed hydrolysis of a cyanohydrin forms an $\alpha$-hydroxycarboxylic acid (Section 17.18).

The catalytic addition of hydrogen to a cyanohydrin produces a primary amine with an OH group on the $\beta$-carbon.

**Problem 11**
Can a cyanohydrin be prepared by treating a ketone with sodium cyanide?

**Problem 12**
Explain why aldehydes and ketones react with a weak acid such as hydrogen cyanide in the presence of $\text{CN}^-$, but do not react with strong acids such as $\text{HCl}$ or $\text{H}_2\text{SO}_4$ in the presence of $\text{Cl}^-$ or $\text{HSO}_4^-$. 

**Problem 13 SOLVED**
How can the following compounds be prepared, starting with a carbonyl compound with one fewer carbon atoms than the desired product?

a. $\text{HOCH}_2\text{CH}_2\text{NH}_2$

b. $\text{CH}_3\text{CHCOH}$
**SOLUTION TO 13a** The starting material for the synthesis of the two-carbon compound must be formaldehyde. Addition of hydrogen cyanide followed by addition of H₂ to the triple bond of the cyanohydrin forms the desired compound.

\[
\text{HCHO} \xrightarrow{\text{NaC}≡\text{N}} \text{HOCCH}_{2}≡\text{N} \xrightarrow{\text{H}_{2}} \text{HOCH}_{2}\text{CH}_{2}\text{NH}_{2}
\]

**SOLUTION TO 13b** The starting material for the synthesis of the three-carbon α-hydroxycarboxylic acid must be ethanal. Addition of hydrogen cyanide, followed by hydrolysis of the cyanohydrin, forms the target molecule.

\[
\text{CH}_{3}\text{CH} \xrightarrow{\text{NaC}≡\text{N}} \text{CH}_{3}\text{CHC}≡\text{N} \xrightarrow{\text{HCl, H}_2\text{O}} \text{CH}_{3}\text{CHCOH}
\]

### 18.5 Reactions of Carbonyl Compounds with Hydride Ion

Addition of hydride ion to an aldehyde or ketone forms an alkoxide ion. Subsequent protonation by an acid produces an alcohol. The overall reaction adds H₂ to the carbonyl group. Recall that the addition of hydrogen to an organic compound is a **reduction reaction** (Section 4.8).

\[
\begin{align*}
\text{R}^-' \text{C} & \xrightarrow{\text{H}^-} \text{R}^- \text{C}^- \text{R}' \xrightarrow{\text{H}^+} \text{R}^- \text{C}^+ \text{R}' \\
\end{align*}
\]

Aldehydes and ketones are generally reduced using sodium borohydride (NaBH₄) as the source of hydride ion. Aldehydes are reduced to primary alcohols, and ketones are reduced to secondary alcohols. Notice that the acid is not added to the reaction mixture until the reaction with the hydride donor is complete.

**PROBLEM 14**

What alcohols are obtained from the reduction of the following compounds with sodium borohydride?

a. 2-methylpropanal
d. acetophenone
b. cyclohexanone
c. benzaldehyde

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{C} & \xrightarrow{1. \text{NaBH}_4} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} \\
\text{CH}_3\text{CH}_2\text{CH}_2\text{C} & \xrightarrow{1. \text{NaBH}_4} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}
\end{align*}
\]
The reaction of a Class I carbonyl compound (i.e., a carbonyl compound with a group that can be replaced by another group) with hydride ion involves two successive reactions with the nucleophile. (Recall that Class I carbonyl compounds also undergo two successive reactions with a Grignard reagent; see Section 18.4.) Sodium borohydride (NaBH₄) is not a sufficiently strong hydride donor to react with the less reactive (compared with aldehydes and ketones) esters, carboxylic acids, and amides, so esters, carboxylic acids, and amides must be reduced with lithium aluminum hydride (LiAlH₄), a more reactive hydride donor.

Because lithium aluminum hydride is more reactive than sodium borohydride, it is not as safe or as easy to use. Since it reacts violently with protic solvents, lithium aluminum hydride must be used in a dry, aprotic solvent.

The reaction of an ester with LiAlH₄ produces two alcohols, one corresponding to the acyl portion of the ester and one corresponding to the alkyl portion.

When an ester reacts with hydride ion, the first reaction is a nucleophilic acyl substitution reaction because an ester has a group that can be substituted by hydride ion. The product of this reaction is an aldehyde. The aldehyde then undergoes a nucleophilic addition reaction with a second equivalent of hydride ion, forming an alkoxide ion, which when protonated gives a primary alcohol. The reaction cannot be stopped at the aldehyde stage because an aldehyde is more reactive than an ester toward nucleophilic attack.

Chemists have found that if diisobutylaluminum hydride (DIBALH) is used as the hydride donor at a low temperature, the reaction can be stopped after the addition of one equivalent of hydride ion. This reagent, therefore, makes it possible to convert esters into aldehydes, which is initially surprising, since aldehydes are more reactive than esters toward hydride ion.
The reaction is carried out at $-78^\circ$C (the temperature of a dry ice-acetone bath). At this cold temperature, the initially formed tetrahedral intermediate is stable, so it does not eliminate the alkoxide ion. All of the unreacted hydride donor is removed from the solution before the solution warms up. Therefore, when the tetrahedral intermediate eliminates the alkoxide ion, there is no reducing agent to react with the aldehyde. If, however, the reaction is carried out at room temperature, a primary alcohol is obtained—the same product obtained when an ester reacts with LiAlH$_4$.

The reaction of a carboxylic acid with LiAlH$_4$ forms a single primary alcohol.

![Diagram of the mechanism for the reaction of a carboxylic acid with hydride ion]

In the first step of the reaction, a hydride ion reacts with the acidic hydrogen of the carboxylic acid, forming H$_2$ and a carboxylate ion. We have seen that nucleophiles do not react with carboxylate ions because of their negative charge. However, in this case, an electrophile (AlH$_3$) is present that accepts a pair of electrons from the carboxylate ion and forms a new hydride donor. Then, analogous to the reduction of an ester by LiAlH$_4$, two successive additions of hydride ion take place, with an aldehyde being formed as an intermediate on the way to the primary alcohol.

Acyl chlorides, like esters and carboxylic acids, undergo two successive additions of hydride ion when treated with LiAlH$_4$.

Amides also undergo two successive additions of hydride ion when they react with LiAlH$_4$. The product of the reaction is an amine. Primary, secondary, or tertiary amines can be formed, depending on the number of substituents bonded to the nitrogen.
of the amide. Overall, the reaction converts a carbonyl group into a methylene group. (Notice that H₂O rather than H₂O⁺ is used in the second step of the reaction. The product, therefore, is an amine rather than an ammonium ion.)

The mechanism of the reaction shows why the product of the reaction is an amine. Take a minute to note the similarities between the mechanisms for the reaction of hydride ion with an \(N\)-substituted amide and with a carboxylic acid.

The mechanisms for the reaction of LiAlH₄ with unsubstituted and \(N,N\)-disubstituted amines are somewhat different, but have the same result: the conversion of a carbonyl group into a methylene group.

**PROBLEM 15**
What amides would you treat with LiAlH₄ in order to prepare the following amines?

a. benzylmethylamine  
c. diethylamine  
b. ethylamine  
d. triethylamine

**PROBLEM 16**
Starting with \(N\)-benzylbenzamide, how would you make the following compounds?

a. dibenzylamine  
c. benzaldehyde  
b. benzoic acid  
d. benzyl alcohol
Aldehydes and ketones react with a primary amine (RNH₂) to form an imine. An **imine** is a compound with a carbon–nitrogen double bond. The imine obtained from the reaction of a carbonyl compound and a primary amine is often called a **Schiff base**.

The orbital model of a C= N group (Figure 18.1) is similar to the orbital model of a C= O group (Figure 17.1 on p. 676). The imine nitrogen is sp² hybridized. One of its sp² orbitals forms a σ bond with the imine carbon, one forms a σ bond with a substituent, and the third contains a lone pair. The p orbital of nitrogen and the p orbital of carbon overlap to form a π bond.

Aldehydes and ketones react with a secondary amine to form an enamine (pronounced “ENE-amine”). An **enamine** is an α,β-unsaturated tertiary amine—a tertiary amine with a double bond in the α,β-position relative to the nitrogen atom. Notice that the double bond is in the part of the molecule that comes from the aldehyde or ketone. The name “enamine” comes from “ene” + “amine,” with the “e” omitted in order to avoid two successive vowels.

When you first look at the products of imine and enamine formation, they appear to be quite different. However, when you look at the mechanisms for the reactions, you will see that the mechanisms are exactly the same except for the site from which a proton is lost in the last step of the reaction.

### Addition of Primary Amines
Aldehydes and ketones react with primary amines to form imines. The reaction requires a catalytic (small) amount of acid—we will see that the pH of the reaction mixture must be carefully controlled.
represents any species in the solution that is capable of donating a proton, and \( \text{HB}^+ \) represents any species in the solution that is capable of removing a proton.

In the first step of the mechanism for imine formation, the amine attacks the carbonyl carbon. Gain of a proton by the alkoxide ion and loss of a proton by the ammonium ion forms a neutral tetrahedral intermediate. The neutral tetrahedral intermediate, called a carbinolamine, is in equilibrium with two protonated forms. Protonation can take place on either the nitrogen or the oxygen atom. Elimination of water from the oxygen-protonated intermediate forms a protonated imine that loses a proton to yield the imine.

\[
\text{benzaldehyde} \quad \text{an aldehyde} \quad \text{ethylamine} \quad \text{a primary amine} \quad \text{an imine}
\]

\[
\text{CH}_3\text{CH}_2\text{C}=\text{O} + \text{H}_2\text{NCH}_2\text{C}_\text{H}_3 \xrightleftharpoons{\text{catalytic \ H}^+} \text{CH}_3\text{CH}_2\text{CH}(_\text{2})\text{NCH}_2\text{C}_\text{H}_3 + \text{H}_2\text{O}
\]

\[
\text{CH}_3\text{CH}_2\text{C}=\text{O} + \text{H}_2\text{NCH}_2\text{C}_\text{H}_3 \xrightleftharpoons{\text{catalytic \ H}^+} \text{CH}_3\text{CH}_2\text{CH}(_\text{2})\text{NCH}_2\text{C}_\text{H}_3 + \text{H}_2\text{O}
\]

**mechanism for imine formation**

The equilibrium favors the nitrogen-protonated tetrahedral intermediate because nitrogen is more basic than oxygen. The equilibrium can be forced toward the imine by removing water as it is formed or by precipitation of the imine product.

Overall, the addition of a nitrogen nucleophile to an aldehyde or a ketone is a nucleophilic addition–elimination reaction: nucleophilic addition of an amine to form an unstable tetrahedral intermediate, followed by elimination of water. The tetrahedral intermediates are unstable because the newly formed \( sp^3 \) carbon is bonded to an oxygen and to a nitrogen—another electronegative atom. Water is eliminated, and loss of a proton from the resulting protonated imine forms a stable imine.

In contrast, the reaction of an aldehyde or a ketone with a carbon or hydrogen nucleophile forms a stable tetrahedral compound because the newly formed \( sp^3 \) carbon is not bonded to a second electronegative atom. Thus, aldehydes and ketones undergo nucleophilic addition reactions with carbon and hydrogen nucleophiles, whereas they undergo nucleophilic addition–elimination reactions with nitrogen nucleophiles.

The pH at which imine formation is carried out must be carefully controlled. There must be sufficient acid present to protonate the tetrahedral intermediate so that \( \text{H}_2\text{O} \) rather than the much more basic \( \text{HO}^- \) is the leaving group. However, if too much acid

A compound with an \( sp^3 \) carbon bonded to an oxygen and to another electronegative atom is unstable.
1.5
1.0
0.5
3
2
1
4
5
6
7

Figure 18.2 Dependence of the rate of the reaction of acetone with hydroxylamine on the pH of the reaction mixture.

Section 18.6 Reactions of Aldehydes and Ketones with Nitrogen Nucleophiles

Aldehydes and ketones react with primary amines to form imines. Protonated amines are not nucleophiles, so they cannot react with carbonyl groups. Therefore, unlike the acid-catalyzed reactions we have seen previously (Section 17.11), there is not sufficient acid present to protonate the carbonyl group in the first step of the reaction (see Problem 17).

A plot of the observed rate constant for the reaction of acetone with hydroxylamine as a function of the pH of the reaction mixture is shown in Figure 18.2. This type of plot is called a pH-rate profile. The pH-rate profile in the figure is a bell-shaped curve with the maximum rate occurring at about pH 4.5, 1.5 pH units below the $pK_a$ of hydroxylamine ($pK_a = 6.0$). As the acidity increases below pH 4.5, the rate of the reaction decreases because more and more of the amine becomes protonated. As a result, less and less of the amine is present in the nucleophilic nonprotonated form. As the acidity decreases above pH 4.5, the rate decreases because less and less of the tetrahedral intermediate is present in the reactive protonated form.

Imine formation is reversible: In acidic aqueous solutions, imines are hydrolyzed back to the carbonyl compound and amine.

\[
\text{CH}_2\text{NCH}_2\text{CH}_3 + \text{H}_2\text{O} \xrightleftharpoons{\text{HCl}} \text{CH}=\text{O} + \text{CH}_3\text{CH}_2\text{NH}_3^+ 
\]

In an acidic solution, the amine is protonated and, therefore, is unable to react with the carbonyl compound to reform the imine.

Imine formation and hydrolysis are important reactions in biological systems (Sections 19.21, 24.9, and 25.6). Imine hydrolysis is the reason DNA contains A, G, C, and T nucleotides, whereas RNA contains A, G, C, and U nucleotides (Section 27.14).

### PROBLEM 17

The $pK_a$ of protonated acetone is about $-7.5$ and the $pK_a$ of protonated hydroxylamine is 6.0.

a. In its reaction with hydroxylamine at pH = 4.5 (Figure 18.2), what fraction of acetone will be present in its acidic, protonated form? *(Hint: See Section 1.20.)*

b. In its reaction with hydroxylamine at pH = 1.5, what fraction of acetone will be present in its acidic, protonated form?

c. In its reaction with acetone at pH = 1.5 (Figure 18.2), what fraction of hydroxylamine will be present in its reactive basic form?

### PROBLEM 18

A ketone can be prepared from the reaction of a nitrile with a Grignard reagent. Describe the intermediate that is formed in this reaction, and explain how it can be converted to a ketone.

### Addition of Secondary Amines

Aldehydes and ketones react with secondary amines to form enamines. Like imine formation, the reaction requires a trace amount of an acid catalyst.

3-D Molecule: N,N-Diethyl-1-cyclopentenamine
The mechanism for enamine formation is exactly the same as that for imine formation, until the last step of the reaction. When a primary amine reacts with an aldehyde or a ketone, the protonated imine loses a proton from nitrogen in the last step of the reaction, forming a neutral imine. However, when the amine is secondary, the positively charged nitrogen is not bonded to a hydrogen. A stable neutral molecule is obtained by removing a proton from the α-carbon of the compound derived from the carbonyl compound. An enamine is the result.

In aqueous acidic solutions, an enamine is hydrolyzed back to the carbonyl compound and secondary amine, a reaction that is similar to the acid-catalyzed hydrolysis of an imine back to the carbonyl compound and a primary amine.

**PROBLEM 19**

a. Write the mechanism for the following reactions:
   1. the acid-catalyzed hydrolysis of an imine to a carbonyl compound and a primary amine
   2. the acid-catalyzed hydrolysis of an enamine to a carbonyl compound and a secondary amine
b. How do these mechanisms differ?

**PROBLEM 20**

Give the products of the following reactions. (A catalytic amount of acid is present in each reaction.)

a. cyclopentanone + ethylamine  
   c. acetophenone + hexylamine
b. cyclopentanone + diethylamine  
   d. acetophenone + cyclohexylamine

**Formation of Imine Derivatives**

Compounds such as hydroxylamine (NH₂OH), hydrazine (NH₂NH₂), and semicarbazide (NH₂NHCONH₂) are similar to primary amines in that they all have an NH₂ group. Thus, like primary amines, they react with aldehydes and ketones to form...
imines—often called *imine derivatives* because the substituent attached to the imine nitrogen is not an R group. The imine obtained from the reaction with hydroxylamine is called an *oxime*, the imine obtained from the reaction with hydrazine is called a *hydrazone*, and the imine obtained from the reaction with semicarbazide is called a *semicarbazone*.

Phenyl-substituted hydrazines react with aldehydes and ketones to form *phenylhydrazones*.

**PROBLEM 21**

Imines can exist as stereoisomers. The isomers are named by the *E, Z* system of nomenclature. (The lone pair has the lowest priority.)

Draw the structure of each of the following compounds:

a. *(E)*-benzaldehyde semicarbazone  
   b. *(Z)*-propiophenone oxime  
   c. cyclohexanone 2,4-dinitrophenylhydrazone

**PROBLEM 22**

Semicarbazide has two NH₂ groups. Explain why only one of them forms an imine.
Before spectrophotometric techniques were available, unknown aldehydes and ketones were identified by preparing imine derivatives. For example, suppose you have an unknown ketone whose boiling point you have determined to be 140 °C. This allows you to narrow the possibilities to the five ketones (A to E) listed in the following table, based on their boiling points (ketones boiling at 139 °C and 141 °C cannot be excluded, unless your thermometer is calibrated perfectly and your laboratory technique is sensational).

<table>
<thead>
<tr>
<th>Ketone</th>
<th>2,4-Dinitrophenylhydrazone</th>
<th>Oxime</th>
<th>Semicarbazone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>bp (°C)</td>
<td>mp (°C)</td>
<td>mp (°C)</td>
</tr>
<tr>
<td>A</td>
<td>140</td>
<td>94</td>
<td>57</td>
</tr>
<tr>
<td>B</td>
<td>140</td>
<td>102</td>
<td>68</td>
</tr>
<tr>
<td>C</td>
<td>139</td>
<td>121</td>
<td>79</td>
</tr>
<tr>
<td>D</td>
<td>140</td>
<td>101</td>
<td>69</td>
</tr>
<tr>
<td>E</td>
<td>141</td>
<td>90</td>
<td>61</td>
</tr>
</tbody>
</table>

Adding 2,4-dinitrophenylhydrazine to a sample of the unknown ketone produces crystals of a 2,4-dinitrophenylhydrazone that melt at 102 °C. You can now narrow the choice to two ketones: B and D. Preparing the oxime of the unknown ketone will not distinguish between B and D because the oximes of B and D have similar melting points, but preparing the semicarbazone will allow you to identify the ketone. Finding that the semicarbazone of the unknown ketone has a melting point of 112 °C establishes that the unknown ketone is D.

The Wolff–Kishner Reduction

In Section 15.15, we saw that when a ketone or an aldehyde is heated in a basic solution of hydrazine, the carbonyl group is converted into a methylene group. This process is called deoxygenation because an oxygen is removed from the reactant. The reaction is known as the Wolff–Kishner reduction.

\[
\text{HO}^- + \text{C=O} + \text{NH}_2\text{NH}_2 \rightarrow \text{HO}^- + \text{CH}_2\text{CH}_3
\]

Hydroxide ion and heat differentiate the Wolff–Kishner reduction from ordinary hydrazone formation. Initially, the ketone reacts with hydrazine to form a hydrazone. After the hydrazone is formed, hydroxide ion removes a proton from the NH2 group. Heat is required because this proton is not easily removed. The negative charge can be delocalized onto carbon, which abstracts a proton from water. The last two steps are repeated to form the deoxygenated product and nitrogen gas.
18.7 Reactions of Aldehydes and Ketones with Oxygen Nucleophiles

Addition of Water
Water adds to an aldehyde or a ketone to form a hydrate. A hydrate is a molecule with two OH groups on the same carbon. Hydrates are also called gem-diols (gem comes from geminus, Latin for “twin”). Hydrates of aldehydes or ketones are generally too unstable to be isolated because the tetrahedral carbon is attached to two oxygen atoms.

\[
\begin{align*}
\text{an aldehyde or a ketone} & \quad + \quad \text{H}_2\text{O} & \quad \text{a hydrate} \\
\end{align*}
\]

Water is a poor nucleophile and therefore adds relatively slowly to a carbonyl group. The rate of the reaction can be increased by an acid catalyst (Figure 18.3). Keep in mind that a catalyst has no effect on the position of the equilibrium. A catalyst affects the rate at which the equilibrium is achieved. In other words, the catalyst affects the rate at which an aldehyde or a ketone is converted to a hydrate; it has no effect on the amount of aldehyde or ketone converted to hydrate (Section 24.0).

mechanism for acid-catalyzed hydrate formation

\[
\begin{align*}
\text{CH}_3\text{C}=\text{H} & \quad + \quad \text{H}_2\text{O} & \quad \text{H}_3\text{O}^+ \\
\text{CH}_3\text{C}=\text{H} & \quad + \quad \text{H}_2\text{O}^+ & \quad \text{CH}_3\text{C}=\text{H} \\
\end{align*}
\]

Most hydrates are too unstable to be isolated.

PROBLEM 23
Hydration of an aldehyde can also be catalyzed by hydroxide ion. Propose a mechanism for hydroxide-ion-catalyzed hydration.
The extent to which an aldehyde or a ketone is hydrated in an aqueous solution depends on the aldehyde or ketone. For example, only 0.2% of acetone is hydrated at equilibrium, but 99.9% of formaldehyde is hydrated. Why is there such a difference?

The equilibrium constant for a reaction depends on the relative stabilities of the reactants and products. The equilibrium constant for hydrate formation, therefore, depends on the relative stabilities of the carbonyl compound and the hydrate. We have seen that electron-donating alkyl groups make a carbonyl compound more stable (less reactive) (Section 18.2). In contrast, alkyl groups make the hydrate less stable because of steric interactions between the alkyl groups.

The electron clouds of the alkyl substituents do not interfere with each other in the carbonyl compound because the bond angles are 120°. However, the bond angles in the tetrahedral hydrate are 109.5°, so the alkyl groups are closer to one another.

Alkyl groups, therefore, shift the equilibrium to the left—toward reactants—because they stabilize the carbonyl compound and destabilize the hydrate. As a result, less acetone than formaldehyde is hydrated at equilibrium.

In conclusion, the percentage of hydrate present in solution at equilibrium depends on both electronic and steric effects. Electron donation and bulky substituents decrease the percentage of hydrate present at equilibrium, whereas electron withdrawal and small substituents increase it.
A 37% solution of formaldehyde in water is known as formalin—commonly used in the past to preserve biological specimens. Because formaldehyde is an eye and skin irritant, it has been replaced in most biology laboratories by other preservatives. One preservative frequently used is a solution of 2 to 5% phenol in ethanol with added antimicrobial agents.

If the amount of hydrate formed from the reaction of water with a ketone is too small to detect, how do we know that the reaction has even occurred? We can prove that it occurs by adding the ketone to $^{18}$O-labeled water and isolating the ketone after equilibrium has been established. Finding that the label has been incorporated into the ketone indicates that hydration has occurred.

**PROBLEM 24**

Trichloroacetaldehyde has such a large equilibrium constant for its reaction with water that the reaction is essentially irreversible. Therefore, chloral hydrate, the product of the reaction, is one of the few hydrates that can be isolated. Chloral hydrate is a sedative that can be lethal. A cocktail laced with it is commonly known—in detective novels, at least—as a “Mickey Finn.” Explain the favorable equilibrium constant.

**PROBLEM 25**

Which of the following ketones has the largest equilibrium constant for the addition of water?

**Addition of Alcohol**

The product formed when one equivalent of an alcohol adds to an aldehyde is called a hemiacetal. The product formed when a second equivalent of alcohol is added is called an acetal. Like water, an alcohol is a poor nucleophile, so an acid catalyst is required for the reaction to take place at a reasonable rate.
When the carbonyl compound is a ketone instead of an aldehyde, the addition products are called a hemiketal and a ketal, respectively.

Hemi is the Greek word for “half.” When one equivalent of alcohol has added to an aldehyde or a ketone, the compound is halfway to the final acetal or ketal, which contains groups from two equivalents of alcohol.

In the first step of acetal (or ketal) formation, the acid protonates the carbonyl oxygen, making the carbonyl carbon more susceptible to nucleophilic attack (Figure 18.3). Loss of a proton from the protonated tetrahedral intermediate gives the hemiacetal (or hemiketal). Because the reaction is carried out in an acidic solution, the hemiacetal (or hemiketal) is in equilibrium with its protonated form. The two oxygen atoms of the hemiacetal (or hemiketal) are equally basic, so either one can be protonated. Loss of water from the tetrahedral intermediate with a protonated OH group forms a compound that is very reactive because of its electron-deficient carbon. Nucleophilic attack on this compound by a second molecule of alcohol, followed by loss of a proton, forms the acetal (or ketal).

Although the tetrahedral carbon of an acetal or ketal is bonded to two oxygen atoms, causing us to predict that the acetal or ketal is not stable, the acetal or ketal can be isolated if the water eliminated from the hemiacetal (or hemiketal) is removed from the reaction mixture. This is because, if water is not available, the only compound the acetal or ketal can form is an O-methylated carbonyl compound, which is less stable than the acetal or ketal.

The acetal or ketal can be transformed back to the aldehyde or ketone in an acidic aqueous solution.
Notice that the mechanisms for imine, enamine, hydrate, and acetal (or ketal) formation are similar. After the nucleophile (a primary amine in the case of imine formation, a secondary amine in the case of enamine formation, water in the case of hydrate formation, and an alcohol in the case of acetal or ketal formation) has added to the carbonyl group, water is eliminated from the protonated tetrahedral intermediate, forming a positively charged intermediate. In imine and hydrate formation, a neutral product is achieved by losing a proton from a nitrogen and an oxygen, respectively. In enamine formation, a neutral product is achieved by losing a proton from an α-carbon. In acetal formation, a neutral compound is achieved by adding a second equivalent of alcohol. Also notice that, because the nucleophile in hydrate formation is water, elimination of water gives back the original aldehyde or ketone.

**Problem-Solving Strategy**

Explain why acetals and ketals are hydrolyzed back to the aldehyde or ketone in acidic aqueous solutions, but are stable in basic aqueous solutions.

The easiest way to approach this kind of question is to write out the structures and the mechanism that describe what the question is asking. When the mechanism is written, the answer should become apparent. In an acidic solution, the acid protonates an oxygen of the acetal. This creates a weak base that can be expelled by the other group. When the group is expelled, water can attack the reactive intermediate, and you are then on your way back to the ketone (or aldehyde).

In a basic solution, the CH₃O group cannot be protonated. Therefore, the group that would have to be eliminated to reform the ketone (or aldehyde) would be the very basic CH₃O⁻ group. A CH₃O⁻ group is too basic to be eliminated by the other CH₃O group, which has little driving force because of the positive charge that would be placed on its oxygen atom if elimination were to occur.

Now continue on to Problem 28.
Chapter 18

**Problem 28**

a. Would you expect hemiacetals to be stable in basic solutions? Explain your answer.

b. Acetal formation must be catalyzed by an acid. Explain why it cannot be catalyzed by \( CH_3O^- \).

c. Can the rate of hydrate formation be increased by hydroxide ion as well as by acid? Explain.

---

### 18.8 Protecting Groups

Ketones (or aldehydes) react with 1,2-diols to form five-membered ring ketals (or acetals) and with 1,3-diols to form six-membered ring ketals (or acetals). Recall that five- and six-membered rings are formed relatively easily (Section 11.11). The mechanism is the same as that shown in Section 18.7 for acetal formation, except that instead of reacting with two separate molecules of alcohol, the carbonyl compound reacts with the two alcohol groups of a single molecule of the diol.

If a compound has two functional groups that will react with a given reagent and you want only one of them to react, it is necessary to protect the other functional group from the reagent. A group that protects a functional group from a synthetic operation that it would not otherwise survive is called a **protecting group**.

If you have ever painted a room with a spray gun, you may have taped over the things you do not want to paint, such as baseboards and window frames. In a similar way, 1,2-diols and 1,3-diols are used to protect the carbonyl group of aldehydes and ketones. The diol is like the tape. For example, in the synthesis of the following hydroxyketone from the keto ester, LiAlH₄ can reduce both functional groups of a keto ester, and the one that you don’t want to react—the keto group—is the more reactive of the two.

If the keto group is converted to a ketal, only the ester group will react with LiAlH₄. The protecting group can be removed by acid-catalyzed hydrolysis after the ester has been reduced. It is critical that the conditions used to remove a protecting group do not affect other groups in the molecule. Acetals and ketals are good protecting groups because, being ethers, they do not react with bases, reducing agents, or oxidizing agents.
Section 18.8 Protecting Groups

PROBLEM 29

a. What would have been the product of the preceding reaction with LiAlH₄ if the keto group had not been protected?
b. What reagent could you use to reduce only the keto group?

PROBLEM 30

Why don’t acetals react with nucleophiles?

In the following reaction, the aldehyde reacts with the diol because aldehydes are more reactive than ketones. The Grignard reagent will now react only with the keto group. The protecting group can be removed by acid-catalyzed hydrolysis.

One of the best ways to protect an OH group of an alcohol is to convert it to a trimethylsilyl (TMS) ether by treating the alcohol with chlorotrimethylsilane and a tertiary amine. The ether is formed by an S_N2 reaction. Although a tertiary alkyl halide does not undergo an S_N2 reaction, the tertiary silyl compound does because Si — C bonds are longer than C — C bonds, reducing steric hindrance at the site of nucleophilic attack. The amine prevents the solution from becoming acidic by reacting with the HCl generated in the reaction. The TMS ether, which is stable in neutral and basic solutions, can be removed with aqueous acid under mild conditions.

The OH group of a carboxylic acid group can be protected by converting the carboxylic acid into an ester.
An amino group can be protected by being converted into an amide (Section 17.8). The acetyl group can subsequently be removed by acid-catalyzed hydrolysis.

Protecting groups should be used only when absolutely necessary, because each time a protecting group is used, it must be attached and then taken off. This adds two steps to the synthesis, which decreases the overall yield of the target compound (the desired product).

**PROBLEM 31**
What products would be formed from the preceding reaction if aniline’s amino group were not protected?

**PROBLEM 32**

a. In a six-step synthesis, what will be the yield of the target compound if each of the reactions employed gives an 80% yield? (An 80% yield is a relatively high laboratory yield.)

b. What would be the yield if two more steps were added to the synthesis?

**PROBLEM 33**
Show how each of the following compounds can be prepared from the given starting material. In each case, you will need to use a protecting group.

a. \( \text{HOCH}_2\text{CH}_2\text{CH}_2\text{Br} \rightarrow \text{HOCH}_2\text{CH}_2\text{CH}_2\text{CHCH}_3 \)

b. \( \text{Br} \rightarrow \text{COOH} \)
Addition of Sulfur Nucleophiles

Aldehydes and ketones react with thiols to form thioacetals and thioketals. The mechanism for addition of a thiol is the same as that for addition of an alcohol. Recall that thiols are sulfur analogs of alcohols (Section 12.10).

Thioacetal (or thioketal) formation is a synthetically useful reaction because a thioacetal (or thioketal) is desulfurized when it reacts with H₂ and Raney nickel. Desulfurization replaces the C—S bonds with C—H bonds.

Thioacetal formation followed by desulfurization provides us with a third method that can be used to convert the carbonyl group of a ketone into a methylene group. We have already seen the other two methods—the Clemmensen reduction and the Wolff–Kishner reduction (Sections 15.15 and 18.6).

The Wittig Reaction

An aldehyde or a ketone reacts with a phosphonium ylide (pronounced “ILL-id”) to form an alkene. An ylide is a compound that has opposite charges on adjacent covalently bonded atoms with complete octets. The ylide can also be written in the double-bonded form because phosphorus can have more than eight valence electrons.

The reaction of an aldehyde or a ketone with a phosphonium ylide to form an alkene is called a Wittig reaction. The overall reaction amounts to interchanging the double-bonded oxygen of the carbonyl compound and the double-bonded carbon group of the phosphonium ylide.

Georg Friedrich Karl Wittig (1897–1987) was born in Germany. He received a Ph.D. from the University of Marburg in 1926. He was a professor of chemistry at the Universities of Braunschweig, Freiberg, Tübingen, and Heidelberg, where he studied phosphorus-containing organic compounds. He received the Nobel Prize in chemistry in 1979, sharing it with H.C. Brown (Section 4.9).
Evidence has accumulated that the Wittig reaction is a concerted \([2 + 2]\) cycloaddition reaction, with the nucleophilic carbon of the ylide attacking the electrophilic carbon of the carbonyl compound. It is called a \([2 + 2]\) cycloaddition reaction because, of the four \(\pi\) electrons involved in the cyclic transition state, two come from the carbonyl group and two come from the ylide (Section 29.4). Elimination of triphenylphosphine oxide forms the alkene product.

The phosphonium ylide needed for a particular synthesis is obtained by an reaction between triphenylphosphine and an alkyl halide with the appropriate number of carbon atoms. A proton on the carbon adjacent to the positively charged phosphorus atom is sufficiently acidic \(pK_a = 35\) to be removed by a strong base such as butyllithium (Section 12.11).

If two sets of reagents are available for the synthesis of an alkene, it is better to use the one that requires the less sterically hindered alkyl halide for synthesis of the ylide. Recall that the more sterically hindered the alkyl halide, the less reactive it is in an \(S_N2\) reaction (Section 10.2). For example, it is better to use a three-carbon alkyl halide and a five-carbon carbonyl compound than a five-carbon alkyl halide and a three-carbon carbonyl compound for the synthesis of 3-ethyl-3-hexene because it would be easier to form an ylide from 1-bromopropane than from 3-bromopentane.
The Wittig reaction is a very powerful way to make an alkene because the reaction is completely regioselective—the double bond will be in only one place.

\[
\text{O} + (\text{C}_6\text{H}_5)_3\text{P} = \text{CH}_2 \rightarrow \text{CH}=\text{CH}_2 + (\text{C}_6\text{H}_5)_3\text{P} = \text{O}
\]

*The Wittig reaction also is the best way to make a terminal alkene such as methylencyclohexane because other methods would form a terminal alkene only as a minor product if at all.*

The stereoselectivity of the Wittig reaction depends on the structure of the ylide. Ylides can be divided into two types: Stabilized ylides have a group, such as a carbonyl group, that can share the carbanion’s negative charge; unstabilized ylides do not have such a group.

\[
\begin{align*}
\text{(C}_6\text{H}_5)_3\text{P}^- + \text{CH}_2\text{Br} & \rightarrow \text{CH}_2\text{CH}_3 + (\text{C}_6\text{H}_5)_3\text{P}^+ \\
\text{(C}_6\text{H}_5)_3\text{P}^- + \text{CH}_2\text{CH}_2\text{Br} & \rightarrow \text{CH}_2\text{OH} + (\text{C}_6\text{H}_5)_3\text{P}^+ \\
\text{(C}_6\text{H}_5)_3\text{P}^- + \text{CH}_2\text{OH} & \rightarrow \text{CH}_3 + (\text{C}_6\text{H}_5)_3\text{P}^+
\end{align*}
\]

The stereoselectivity of the Wittig reaction depends on the structure of the ylide. Ylides can be divided into two types: Stabilized ylides have a group, such as a carbonyl group, that can share the carbanion’s negative charge; unstabilized ylides do not have such a group.

\[
\begin{align*}
\text{(C}_6\text{H}_5)_3\text{P}^- + \text{CH} - \text{CCH}_3 & \leftrightarrow \text{(C}_6\text{H}_5)_3\text{P}^- + \text{CH} = \text{CCH}_3 \\
\text{(C}_6\text{H}_5)_3\text{P}^- + \text{CH} - \text{CCH}_3 & \leftrightarrow \text{(C}_6\text{H}_5)_3\text{P}^- + \text{CH} = \text{CCH}_3
\end{align*}
\]

Stabilized ylides form primarily \( E \) isomers, and unstabilized ylides form primarily \( Z \) isomers.
a. What carbonyl compound and what phosphonium ylide are required for the synthesis of the following alkenes?

1. $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_3$

2. $\bigcirc=\text{CHCH}_2\text{CH}_3$

3. $(\text{C}_6\text{H}_5)_3\text{C}=\text{CHCH}_3$

4. $\bigcirc=\text{CH}==\text{CH}_2$

b. What alkyl halide is required to prepare each of the phosphonium ylides?

**SOLUTION TO 34a (1)** The atoms on either side of the double bond can come from the carbonyl compound, so there are two pairs of compounds that can be used.

$$\text{CH}_3\text{CH}_2\text{CH}_3 + (\text{C}_6\text{H}_5)_3\text{P}=\text{CHCH}_2\text{CH}_2\text{CH}_3 \quad \text{or} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH} + (\text{C}_6\text{H}_5)_3\text{P}=\text{CCH}_3$$

**SOLUTION TO 34b (1)** The alkyl halide required depends on which phosphonium ylide is used; it would be either 1-bromobutane or 2-bromopropane.

$$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \quad \text{or} \quad \text{CH}_3\text{CHCH}_3$$

The primary alkyl halide would be more reactive in the $S_\text{N}2$ reaction required to make the ylide, so the best method would be to use acetone and the ylide obtained from 1-bromobutane.
A carbonyl carbon bonded to two different substituents is a **prochiral carbonyl carbon** because it will become a chirality center (asymmetric carbon) if it adds a group unlike either of the groups already bonded to it. The addition product will be a pair of enantiomers.

The carbonyl carbon and the three atoms attached to it define a plane. The nucleophile can approach either side of the plane. One side of the carbonyl compound is called the **Re** (pronounced “ree”) face, and the other side is called the **Si** (pronounced “sigh”) face; **Re** is for *rectus* and **Si** is for *sinister*—similar to **R** and **S**. To distinguish between the **Re** and **Si** faces, the three groups attached to the carbonyl carbon are assigned priorities using the Cahn–Ingold–Prelog system of priorities used in *E*, *Z* and **R**, **S** nomenclature (Sections 3.5 and 5.6 respectively). The **Re** face is the face closest to the observer when decreasing priorities are in a clockwise direction, and the **Si** face is the opposite face—the one closest to the observer when decreasing priorities are in a counterclockwise direction.

Attack by a nucleophile on the **Re** face forms one enantiomer, whereas attack on the **Si** face forms the other enantiomer. For example, attack by hydride ion on the **Re** face of butanone forms (S)-2-butanol, and attack on the **Si** face forms (R)-2-butanol.

Whether attack on the **Re** face forms the **R** or **S** enantiomer depends on the priority of the attacking nucleophile relative to the priorities of the groups attached to the carbonyl carbon. For example, we just saw that attack by hydride ion on the **Re** face of butanone forms (S)-2-butanol, but attack by a methyl Grignard reagent on the **Re** face of propanal forms (R)-2-butanol.
PROBLEM 35

Which enantiomer is formed when a methyl Grignard reagent attacks the Re face of each of the following carbonyl compounds?

a. propiophenone  
b. benzaldehyde  
c. 2-pentanone  
d. 3-hexanone

18.12 Designing a Synthesis V: Disconnections, Synthons, and Synthetic Equivalents

The synthesis of a complicated molecule from simple starting materials is not always obvious. We have seen that it is often easier to work backward from the desired product to available starting materials—a process called \textit{retrosynthetic analysis} (Section 6.11). In a retrosynthetic analysis, the chemist dissects a molecule into smaller and smaller pieces until readily available starting materials are obtained.

\textbf{retrosynthetic analysis}

\begin{align*}
\text{target molecule} & \quad \Longrightarrow \quad Y \quad \Longrightarrow \quad X \quad \Longrightarrow \quad W \quad \Longrightarrow \quad \text{starting materials}
\end{align*}

A useful step in a retrosynthetic analysis is a \textit{disconnection}—breaking a bond to produce two fragments. Typically, one fragment is positively charged and one is negatively charged. The fragments of a disconnection are called \textit{synthons}. Synthons are often not real compounds—they can be imaginary species. For example, if we consider the retrosynthetic analysis of cyclohexanol, we see that a disconnection gives two synthons—an $\alpha$-hydroxycarbocation and a hydride ion.

\textbf{retrosynthetic analysis}

\begin{align*}
\text{HO} & \quad \longrightarrow \quad \text{H} \quad \longrightarrow \quad \text{OH} \\
\text{a disconnection} & \quad \Longrightarrow \quad \text{synthons}
\end{align*}

A \textit{synthetic equivalent} is the reagent that is actually used as the source of the synthon. Cyclohexanone is the synthetic equivalent for the $\alpha$-hydroxycarbocation, and sodium borohydride is the synthetic equivalent for hydride ion. Thus, cyclohexanol, the target molecule, can be prepared by treating cyclohexanone with sodium borohydride.
When carrying out a disconnection, you must decide, after breaking the bond, which fragment gets the positive charge and which gets the negative charge. In the retrosynthetic analysis of cyclohexanol, we could have given the positive charge to the hydrogen, and many acids (HCl, HBr, etc.) could have been used for the synthetic equivalent for H⁺. However, we would have been at a loss to find a synthetic equivalent for an α-hydroxycarbanion. Therefore, when we carry out the disconnection, we assign the positive charge to the carbon and the negative charge to the hydrogen.

Cyclohexanol can also be disconnected by breaking the C—O bond instead of the C—H bond, forming a carbocation and hydroxide ion.

The problem now becomes choosing a synthetic equivalent for the carbocation. A synthetic equivalent for a positively charged synthon needs an electron-withdrawing group at just the right place. Cyclohexyl bromide, with an electron-withdrawing bromine, is a synthetic equivalent for the cyclohexyl carbocation. Cyclohexanol, therefore, can be prepared by treating cyclohexyl bromide with hydroxide ion. This method, however, is not as good as the first synthesis we proposed—reduction of cyclohexanone—because some of the alkyl halide is converted into an alkene, so the overall yield of the target compound is lower.

Retrosynthetic analysis shows that 1-methylcyclohexanol can be formed from the reaction of cyclohexanone, the synthetic equivalent for the α-hydroxycarbocation, and methylmagnesium bromide, the synthetic equivalent for the methyl anion (Section 18.4).

Other disconnections of 1-methylcyclohexanol are possible because any bond to carbon can serve as a disconnection site. For example, one of the ring C—C bonds could be broken. However, these are not useful disconnections, because the synthetic
equivalents of the synthons they produce are not easily prepared. A retrosynthetic step must lead to readily obtainable starting materials.

**PROBLEM 36**

Using bromocyclohexane as a starting material, how could you synthesize the following compounds?

- a. 
  - CH₃
  - CH₂OH
- b. 
  - CH₃
  - CH₂OH
- c. 
  - COOH
- d. 
  - CH₃
  - CH₂CH₂OH
- e. 
  - CH₃
  - CH₃
- f. 
  - Cl
  - CH₂CH₃

**SYNTHESIZING ORGANIC COMPOUNDS**

Organic chemists synthesize compounds for many reasons: to study their properties or to answer a variety of chemical questions, or because they have unusual shapes or other unusual structural features or useful properties. One reason chemists synthesize natural products is to provide us with greater supplies of these compounds than nature can produce. For example, Taxol®—a compound that has been successful in treating ovarian and breast cancer—is extracted from the bark of Taxus, the yew tree found in the Pacific Northwest. The supply of natural Taxol® is limited because yew trees are uncommon and grow very slowly and stripping the bark kills the tree. The bark of one tree provides only one dose of the drug. In addition, Taxus forests serve as habitats for the spotted owl, an endangered species, so harvesting the trees would accelerate the owl’s demise. Once chemists were successful in determining the structure of Taxol®, efforts could be undertaken to synthesize it in order to make it more widely available as an anticancer drug. Several syntheses have been successful.

**SEMISYNTHETIC DRUGS**

Taxol® is a difficult molecule to synthesize because of its complicated structure. Chemists have made the synthesis a lot easier by allowing the yew tree to carry out the first part of the synthesis. Chemists extract the drug precursor from the needles of the tree, and the precursor is converted to Taxol® in the laboratory. Thus, the precursor is isolated from a renewable resource, while the drug itself could be obtained only by killing the tree. In this manner, chemists have learned to synthesize compounds jointly with nature.
**18.13 Nucleophlic Addition to $\alpha,\beta$-Unsaturated Aldehydes and Ketones**

The resonance contributors for an $\alpha,\beta$-unsaturated carbonyl compound show that the molecule has two electrophilic sites: the carbonyl carbon and the $\beta$-carbon.

\[
\begin{align*}
\text{RCH} = & \text{CH} \quad \text{CR} \\
\text{an } \alpha,\beta\text{-unsaturated carbonyl compound} \\
\text{electrophilic site} \\
\end{align*}
\]

This means that if an aldehyde or a ketone has a double bond in the $\alpha,\beta$-position, a nucleophile can add either to the carbonyl carbon or to the $\beta$-carbon.

Nucleophilic addition to the carbonyl carbon is called **direct addition** or 1,2-addition.

**direct addition**

\[
\begin{align*}
\text{Y}^\ominus + \text{RCH} = & \text{CH} \quad \text{CR} \\
\rightarrow \quad \text{RCH} = & \text{CH} \quad \text{CR} \\
\text{OH} \\
\end{align*}
\]

Nucleophilic addition to the $\beta$-carbon is called **conjugate addition** or 1,4-addition, because addition occurs at the 1- and 4-positions (i.e., across the conjugated system). After 1,4-addition has occurred, the product—an enol—tautomizes to a ketone (or to an aldehyde, Section 6.6), so the overall reaction amounts to addition to the carbon–carbon double bond, with the nucleophile adding to the $\beta$-carbon and a proton from the reaction mixture adding to the $\alpha$-carbon. Compare these reactions with the 1,2- and 1,4-addition reactions you studied in Section 8.7.

**conjugate addition**

\[
\begin{align*}
\text{Y}^\ominus + \text{RCH} = & \text{CH} \quad \text{CR} \\
\rightarrow \quad \text{RCH} = & \text{CH} \quad \text{CR} \\
\text{H}_2\text{O}^+ \\
\end{align*}
\]

Whether the product obtained from nucleophilic addition to an $\alpha,\beta$-unsaturated aldehyde or ketone is the direct addition product or the conjugate addition product depends on the nature of the nucleophile, the structure of the carbonyl compound, and the conditions under which the reaction is carried out.

Nucleophiles that form **unstable addition products**—that is, nucleophiles that are weak bases, allowing direct addition to be reversible—form conjugate addition products because conjugate addition is *not* reversible, and the conjugate addition product is more stable. Nucleophiles in this group include halide ions, cyanide ion, thiols, alcohols, and amines.
Nucleophiles that form stable addition products—that is, nucleophiles that are strong bases, thereby making direct addition irreversible—can form either direct addition products or conjugate addition products. Nucleophiles in this group include hydride ion and carbanions. The reaction that prevails is the one that is faster, so the product that is formed will depend on the reactivity of the carbonyl group. Compounds with reactive carbonyl groups form primarily direct addition products because for those compounds, direct addition is faster, whereas compounds with less reactive carbonyl groups form primarily conjugate addition products because for those compounds, conjugate addition is faster. For example, aldehydes have more reactive carbonyl groups than do ketones, so sodium borohydride forms primarily direct addition products with aldehydes. Compared with aldehydes, ketones form less of the direct addition product and more of the conjugate addition product.

Notice that a saturated alcohol is the final product of conjugate addition in the preceding reaction because the carbonyl group of the ketone will react with a second equivalent of hydride ion.

If direct addition is the desired outcome of hydride addition, it can be achieved by carrying out the reaction in the presence of cerium chloride, a Lewis acid that activates the carbonyl group toward nucleophilic attack by complexing with the carbonyl oxygen.
Like hydride ions, Grignard reagents add irreversibly to carbonyl groups. Therefore, Grignard reagents react with $\alpha,\beta$-unsaturated aldehydes and unhindered $\alpha,\beta$-unsaturated ketones to form direct addition products. If, however, the rate of direct addition is slowed down by steric hindrance, a Grignard reagent will form a conjugate addition product because conjugate addition then becomes the faster reaction.

Only conjugate addition occurs when Gilman reagents (lithium dialkylcuprates, Section 12.12) react with $\alpha,\beta$-unsaturated aldehydes and ketones. Therefore, Grignard reagents should be used when you want to add an alkyl group to the carbonyl carbon, whereas Gilman reagents should be used when you want to add an alkyl group to the $\beta$-carbon.

Electrophiles and nucleophiles can be classified as either hard or soft. Hard electrophiles and nucleophiles are more polarized than soft ones. Hard nucleophiles prefer to react with hard electrophiles, and soft nucleophiles prefer to react with soft electrophiles. Therefore, a Grignard reagent with a highly polarized $C\equiv Mg$ bond prefers to react with the harder $C\equiv O$ bond, whereas a Gilman reagent with a much less polarized $C\equiv Cu$ bond prefers to react with the softer $C\equiv C$ bond.

**PROBLEM 37**

Give the major product of each of the following reactions:

a. 

b. 

PROBLEM 38

Which would give a higher yield of an unsaturated alcohol when treated with sodium borohydride, a sterically hindered ketone or a nonsterically hindered ketone?
**CANCER CHEMOTHERAPY**

Two compounds—vernolepin and helinalin—owe their effectiveness as anticancer drugs to conjugate addition reactions.

Cancer cells are cells that have lost their ability to control their growth; therefore, they proliferate rapidly. DNA polymerase is an enzyme that a cell needs to make a copy of its DNA for a new cell. DNA polymerase has an SH group and each of these drugs has two \( \alpha,\beta \)-unsaturated carbonyl groups. Irreversible conjugate addition of the enzyme to an \( \alpha,\beta \)-unsaturated carbonyl group inactivates the enzyme.

![Diagram of conjugate addition](image)

**18.14 Nucleophilic Addition to \( \alpha,\beta \)-Unsaturated Carboxylic Acid Derivatives**

\( \alpha,\beta \)-Unsaturated carboxylic acid derivatives, like \( \alpha,\beta \)-unsaturated aldehydes and ketones, have two electrophilic sites for nucleophilic attack: They can undergo conjugate addition or nucleophilic acyl substitution. Notice that they undergo nucleophilic acyl substitution rather than direct addition because the \( \alpha,\beta \)-unsaturated carbonyl compound had a group that can be replaced by a nucleophile. In other words, as with non-conjugated carbonyl compounds, nucleophilic acyl addition becomes nucleophilic acyl substitution if the carbonyl group is attached to a group that can be replaced by another group (Section 18.3).

Nucleophiles react with \( \alpha,\beta \)-unsaturated carboxylic acid derivatives with reactive carbonyl groups, such as acyl chlorides, to form nucleophilic acyl substitution products. Conjugate addition products are formed from the reaction of nucleophiles with less reactive carbonyl groups, such as ester and amides.
Section 18.15 Enzyme-Catalyzed Additions to $\alpha,\beta$-Unsaturated Carbonyl Compounds

Several reactions in biological systems involve addition to $\alpha,\beta$-unsaturated carbonyl compounds. The following are examples of conjugate addition reactions that occur in biological systems. Notice that the carbonyl groups are either unreactive (COO$^-$) or have low reactivity (the CoA ester) toward the nucleophile, so conjugate addition occurs in each case. The last reaction is an important step in the biosynthesis of fatty acids (Section 19.21).

**PROBLEM 39**

Give the major product of each of the following reactions:

a. $\text{CH}_3\text{CH} = \text{CH} - \text{OCH}_3 \xrightarrow{1. \text{LiAlH}_4} \xrightarrow{2. \text{H}_3\text{O}^+} \text{CH}_3\text{CH} = \text{CH} - \text{OCH}_3$

b. $\text{CH}_3\text{CH} = \text{CH} - \text{Cl} \xrightarrow{1. \text{LiAlH}_4} \xrightarrow{2. \text{H}_3\text{O}^+} \text{CH}_3\text{CH} = \text{CH} - \text{Cl}$

c. $\text{CH}_3\text{CH} = \text{CH} - \text{OCH}_3 \xrightarrow{\text{NH}_3}$

d. $\text{CH}_3\text{CH} = \text{CH} - \text{Cl} \xrightarrow{\text{excess NH}_3}\xrightarrow{\text{H}_2\text{O}}$

**18.15 Enzyme-Catalyzed Additions to $\alpha,\beta$-Unsaturated Carbonyl Compounds**

a. $\text{CH}_3\text{CH} = \text{CH} - \text{OCH}_3 + \text{CH}_3\text{CH}_2\text{NH}_2 \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$

b. $\text{CH}_3\text{CH} = \text{CH} - \text{Cl} + \text{LiAlH}_4 \rightarrow \text{CH}_3\text{CH} = \text{CH} - \text{Cl}$

c. $\text{CH}_3\text{CH} = \text{CH} - \text{Cl} \xrightarrow{\text{excess NH}_3}\xrightarrow{\text{H}_2\text{O}}$
Enzymes that catalyze the interconversion of cis and trans isomers are called cis–trans isomerases. These isomerases are all known to contain thiol (SH) groups. Thiols are weak bases and therefore add to the β-carbon of an α,β-unsaturated carbonyl compound (conjugate addition). The resulting carbon–carbon single bond rotates before the enol is able to tautomerize to the ketone. When tautomerization occurs, the thiol is eliminated. Rotation results in cis–trans interconversion.

Summary

Aldehydes and ketones are Class II carbonyl compounds; they have an acyl group attached to a group (—H, —R, or —Ar) that cannot be readily replaced by another group. Aldehydes and ketones undergo nucleophilic addition reactions with C and H nucleophiles and nucleophilic addition–elimination reactions with O and N nucleophiles. With the exception of amides, carboxylic acid derivatives (Class I carbonyl compounds) undergo nucleophilic acyl substitution reactions with C and H nucleophiles to form a Class II carbonyl compound, which then undergoes a nucleophilic addition reaction with a second equivalent of the C or H nucleophile. Notice that the tetrahedral intermediate formed by attack of a nucleophile on a carbonyl compound is stable if the newly formed tetrahedral carbon is not bonded to a second electronegative atom or group and is generally unstable if it is.

Electronic and steric factors cause an aldehyde to be more reactive than a ketone toward nucleophilic attack. Aldehydes and ketones are less reactive than acyl halides and acid anhydrides and are more reactive than esters, carboxylic acids, and amides.

Grignard reagents react with aldehydes to form secondary alcohols, with ketones and acyl halides to form tertiary alcohols, and with carbon dioxide to form carboxylic acids. Aldehydes are reduced to primary alcohols, ketones to secondary alcohols, and amides to amines.

Aldehydes and ketones undergo acid-catalyzed addition of water to form hydrates. Electron donation and bulky substituents decrease the percentage of hydrate present at equilibrium. Most hydrates are too unstable to be isolated. Acid-catalyzed addition of alcohol to aldehydes forms hemiacetals and acetals, and to ketones forms hemiketals and ketals. Acetal and ketal formation are reversible. Cyclic acetics and ketals serve as protecting groups for aldehyde and ketone functional groups. Aldehydes and ketones react with thiols to form thioacetals and thioketals; desulfurization replaces the C—S bonds with C—H bonds.

Aldehydes and ketones react with primary amines to form imines and with secondary amines to form enamines. The mechanisms are the same, except for the site from which a proton is lost in the last step of the reaction. Imine and enamine formation are reversible; imines and enamines are hydrolyzed under acidic conditions back to the carbonyl compound and amine. A pH-rate profile is a plot of the observed rate constant as a function of the pH of the reaction mixture. Hydroxide ion and heat differentiate the Wolff–Kishner reduction from ordinary hydrazone formation.

An aldehyde or a ketone reacts with a phosphonium ylide in a Wittig reaction to form an alkene. A Wittig reaction is a concerted [2 + 2] cycloaddition reaction; it is completely regioselective. Stabilized ylides form primarily E isomers; unstabilized ylides form primarily Z isomers.

A prochiral carbonyl carbon is a carbonyl carbon that is bonded to two different substituents. The Re face is the one closest to the observer when decreasing priorities are in a clockwise direction; the Si face is the opposite face. Attack by a nucleophile on either the Re face or the Si face forms a pair of enantiomers.

A useful step in a retrosynthetic analysis is a disconnection—breaking a bond to produce two fragments. Synthons are fragments of a disconnection. A synthetic equivalent is the reagent used as the source of the synthon.
Nucleophilic addition to the carbonyl carbon of an $\alpha,\beta$-unsaturated Class II carbonyl compound is called **direct addition**; addition to the $\beta$-carbon is called **conjugate addition**. Whether direct or conjugate addition occurs depends on the nature of the nucleophile, the structure of the carbonyl compound, and the reaction conditions. Nucleophiles that form unstable direct addition products—halide ions, cyanide ion, thiols, alcohols, and amines—form conjugate addition products. Nucleophiles that form stable addition products—hydride ion and carbanions—form direct addition products with reactive carbonyl groups and conjugate addition products with less reactive carbonyl groups. A Grignard reagent with a highly polarized C—Mg bond reacts with the harder C=O bond; a Gilman reagent with a less polarized C—Cu bond reacts with the softer C=C bond.

Nucleophiles form nucleophilic acyl substitution products with $\alpha,\beta$-unsaturated Class I carbonyl compounds that have reactive carbonyl groups and conjugate addition products with compounds with less reactive carbonyl groups.

### Summary of Reactions

1. Reaction of *carbonyl compounds* with carbon nucleophiles (Section 18.4).

   a. Reaction of *formaldehyde* with a Grignard reagent forms a primary alcohol:

   \[
   \text{CH}_3\text{MgBr} + \text{HCHO} \rightarrow \text{CH}_3\text{CH}_2\text{OH}
   \]

   b. Reaction of an *aldehyde* (other than formaldehyde) with a Grignard reagent forms a secondary alcohol:

   \[
   \text{R'CH}=\text{CHR} \text{CH}_3\text{MgBr} \rightarrow \text{R'=CH}_2\text{OH}
   \]

   c. Reaction of a *ketone* with a Grignard reagent forms a tertiary alcohol:

   \[
   \text{R'=CHR'}\text{CH}_3\text{MgBr} \rightarrow \text{R'=CH}_2\text{OH}
   \]

   d. Reaction of an *ester* with a Grignard reagent forms a tertiary alcohol with two identical substituents:

   \[
   \text{R'=OCR'=CH}_3\text{MgBr} \rightarrow \text{R'=CH}_2\text{OH}
   \]

   e. Reaction of an *acyl chloride* with a Grignard reagent forms a tertiary alcohol with two identical substituents:

   \[
   \text{R'CH}=\text{C}=\text{O}\text{CH}_3\text{MgBr} \rightarrow \text{R'=CH}_2\text{OH}
   \]

   f. Reaction of CO$_2$ with a Grignard reagent forms a carboxylic acid:

   \[
   \text{O}=\text{C}=\text{O} + \text{CH}_3\text{MgBr} \rightarrow \text{CH}_3\text{COOH}
   \]
g. Reaction with acetylide ions:

\[
\text{RC} \equiv \text{C} \xrightarrow{1.} \text{RC} \equiv \text{CR}
\]

h. Reaction with cyanide ion:

\[
\text{RC} \equiv \text{C} \xrightarrow{\text{HCl}} \text{RC} \equiv \text{CN}
\]

2. Reactions of carbonyl compounds with hydride ion donors (Section 18.5).

a. Reaction of an aldehyde with sodium borohydride forms a primary alcohol:

\[
\text{RC} = \text{H} \xrightarrow{1.} \text{RCH}_2\text{OH}
\]

b. Reaction of a ketone with sodium borohydride forms a secondary alcohol:

\[
\text{RC} \text{R'} \xrightarrow{1.} \text{RCH} - \text{R'
}\]

c. Reaction of an ester with lithium aluminum hydride forms two alcohols:

\[
\text{RC} \text{OR'} \xrightarrow{1.} \text{RCH}_2\text{OH} + \text{R'OH}
\]

d. Reaction of an ester with diisobutylaluminum hydride forms an aldehyde:

\[
\text{RC} \text{OR'} \xrightarrow{1.} \text{RCH} = \text{H}
\]

e. Reaction of a carboxylic acid with lithium aluminum hydride forms a primary alcohol:

\[
\text{RC} \xrightarrow{1.} \text{RCH}_2\text{OH}
\]

f. Reaction of an acyl chloride with lithium aluminum hydride forms a primary alcohol:

\[
\text{RC} = \text{Cl} \xrightarrow{1.} \text{RCH}_2\text{OH}
\]
Reactions of an amide with lithium aluminum hydride forms an amine:

\[
\begin{align*}
\text{amide} + \text{LiAlH}_4 & \rightarrow \text{ammine} \\
\text{amide} + \text{LiAlH}_4 & \rightarrow \text{amine}
\end{align*}
\]

Reactions of aldehydes and ketones with amines (Section 18.6).

\(\text{a. Reaction with a primary amine forms an imine:}\)

\[
\begin{align*}
\text{R} + \text{H}_2\text{NZ} & \xrightleftharpoons{\text{catalytic } \text{H}^+} \text{R} + \text{H}_2\text{O} \\
\text{R} + \text{H}_2\text{NZ} & \xrightleftharpoons{\text{catalytic } \text{H}^+} \text{R} + \text{H}_2\text{O}
\end{align*}
\]

When \(Z = R\), the product is a Schiff base; \(Z\) can also be OH, NH\(_2\), NH\(_2\)H\(_2\), NH\(_2\)H\(_3\)(NO\(_2\))\(_2\), or NHCONH\(_2\).

\(\text{b. Reaction with a secondary amine forms an enamine:}\)

\[
\begin{align*}
\text{C} = \text{O} + \text{RNHR} & \xrightleftharpoons{\text{catalytic } \text{H}^+} \text{C} = \text{NH} + \text{H}_2\text{O} \\
\text{C} = \text{O} + \text{RNHR} & \xrightleftharpoons{\text{catalytic } \text{H}^+} \text{C} = \text{NH} + \text{H}_2\text{O}
\end{align*}
\]

\(\text{c. The Wolff–Kishner reduction converts a carbonyl group to a methylene group:}\)

\[
\begin{align*}
\text{R} = \text{C} = \text{O} + \text{NH}_2\text{NH}_2\text{HO}^- & \xrightarrow{\Delta} \text{R} = \text{CH}_2\text{R}' \\
\text{R} = \text{C} = \text{O} + \text{NH}_2\text{NH}_2\text{HO}^- & \xrightarrow{\Delta} \text{R} = \text{CH}_2\text{R}'
\end{align*}
\]

Reactions of an aldehyde or a ketone with oxygen nucleophiles.

\(\text{a. Reaction of an aldehyde or a ketone with water forms a hydrate (Section 18.7):}\)

\[
\begin{align*}
\text{R} = \text{C} = \text{O} + \text{H}_2\text{O} & \xrightarrow{\text{HCl}} \text{R} = \text{C} = \text{OH} \\
\text{R} = \text{C} = \text{O} + \text{H}_2\text{O} & \xrightarrow{\text{HCl}} \text{R} = \text{C} = \text{OH}
\end{align*}
\]

\(\text{b. Reaction of an aldehyde or a ketone with excess alcohol forms an acetal or a ketal (Section 18.8):}\)

\[
\begin{align*}
\text{R} = \text{C} = \text{O} + 2\text{R}''\text{OH} & \xrightarrow{\text{HCl}} \text{R} = \text{C} = \text{OH} + \text{R}''\text{OR}'' \\
\text{R} = \text{C} = \text{O} + 2\text{R}''\text{OH} & \xrightarrow{\text{HCl}} \text{R} = \text{C} = \text{OH} + \text{R}''\text{OR}''
\end{align*}
\]
5. Protecting groups (Section 18.8).

a. Aldehydes and ketones can be protected by being converted to acetals:

\[
\text{RCHO} + \text{HOCH}_2\text{CH}_2\text{OH} \xrightarrow{HCl} \text{RCON} + \text{H}_2\text{O}
\]

b. The OH group of an alcohol can be protected by being converted to a TMS ether:

\[
\text{R} \text{OH} + \text{(CH}_3\text{)}_3\text{SiCl} \xrightarrow{(\text{CH}_3\text{CH}_2\text{)}_3\text{N}} \text{ROSi(CH}_3\text{)_3}
\]

c. The OH group of a carboxylic acid can be protected by being converted to an ester:

\[
\text{RCOOH} + \text{CH}_3\text{OH} \xrightarrow{\text{excess } HCl} \text{RCOCH}_3 + \text{H}_2\text{O}
\]

d. An amino group can be protected by being converted to an amide:

\[
\text{RNH}_2 + \text{R} \text{CON} \xrightarrow{\text{HCl}} \text{RNH} + \text{HCl}
\]

6. Reaction of an aldehyde or a ketone with a thiol forms a thioacetal or a thioketal (Section 18.9):

\[
\text{RCHO} + 2 \text{R''SH} \xrightarrow{HCl} \text{RSC} + \text{H}_2\text{O}
\]

7. Desulfurization of thiaoacetals and thioketals forms alkanes (Section 18.9):

\[
\text{RSC} \xrightarrow{\text{Raney Ni}} \text{RCH}_2\text{R'}
\]

8. Reaction of an aldehyde or a ketone with a phosphonium ylide (a Wittig reaction) forms an alkene (Section 18.10):

\[
\text{RCHO} + (\text{C}_6\text{H}_5)\text{P} \xrightarrow{\text{HCl}} \text{RCHC} + (\text{C}_6\text{H}_5)\text{P} = \text{O}
\]

9. Reactions of \(\alpha,\beta\)-unsaturated aldehydes and ketones with nucleophiles (Section 18.13):

Nucleophiles that are weak bases (\(^{-}\text{CN}, \text{RSH}, \text{RNH}_2, \text{Br}^-\)) and \(\text{R}_2\text{CuLi}\) form conjugate addition products. Nucleophiles that are strong bases (\(\text{RLi}, \text{RMgBr}, \text{and } \text{H}^-\)) form direct addition products with reactive carbonyl groups and conjugate addition products with less reactive carbonyl groups.
10. Reactions of α,β-unsaturated carboxylic acid derivatives with nucleophiles (Section 18.14):

\[
\text{RCH} = \text{CHCCl} + \text{NuH} \rightarrow \text{RCH} = \text{CHCNu} + \text{HCl}
\]

\text{Nucleophilic acyl substitution}

\[
\text{RCH} = \text{CHCNR} + \text{NuH} \rightarrow \text{RCHCNR}
\]

\text{Conjugate addition}

Nucleophiles form nucleophilic acyl substitution products with reactive carbonyl groups and conjugate addition products with less reactive carbonyl groups.

**Key Terms**

- acetal (p. 755)
- aldehyde (p. 731)
- conjugate addition (p. 769)
- cyanohydrin (p. 741)
- deoxygenation (p. 752)
- disconnection (p. 766)
- direct addition (p. 769)
- enamine (p. 747)
- gem-diol (p. 753)
- hemiacetal (p. 755)
- hemiketal (p. 756)
- hydrate (p. 753)
- hydrazone (p. 751)
- imine (p. 747)
- ketone (p. 736)
- ketone (p. 731)
- nucleophilic acyl substitution (p. 737)
- nucleophilic acyl substitution (p. 731)
- nucleophilic addition (p. 737)
- nucleophilic addition–elimination reaction (p. 738)
- oxime (p. 751)
- phenylhydrazone (p. 751)
- pH–rate profile (p. 749)
- prochiral carbon (p. 765)
- protecting group (p. 758)
- Re and Si faces (p. 765)
- reduction reaction (p. 743)
- Schiff base (p. 747)
- semicarbazone (p. 751)
- synthetic equivalent (p. 766)
- synthet (p. 766)
- Wittig reaction (p. 761)
- ylide (p. 761)

**Problems**

40. Draw the structure for each of the following compounds:
   a. isobutyaldehyde
   b. 4-hexenal
   c. diisopentyl ketone
   d. 3-methylcyclohexanone
   e. 2,4-pentanedione
   f. 4-bromo-3-heptanone
   g. γ-bromocaproic acid
   h. 2-ethylcyclopentane carboxaldehyde
   i. 4-methyl-5-oxohexanal
   j. benzene-1,3-dicarboxaldehyde

41. Give the products of each of the following reactions:
   a. \(\text{CH}_3\text{CH}_2\text{CH}_2\text{OH} + \text{CH}_3\text{CH}_2\text{CH} = \text{O}\) \(\text{HCl}\) excess
   b. \(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 + \text{NH}_2\text{NH}_2\) \(\text{H}^+\) catalytic
   c. \(\text{CH}_3\text{CH}_2\text{CH} = \text{O} + \text{NH}_2\text{NH}_2\) \(\text{H}^+\) \(\Delta\)
   d. \(\text{CH}_3\text{CH}_2\text{CCl}_3\) \(1. \text{NaBH}_4\) \(2. \text{H}_2\text{O}^+\)
   e. \(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 + \text{NaC} = \text{N}\) \(\text{HCl}\) excess
   f. \(\text{CH}_3\text{CH}_2\text{CH}_2\text{COCH}_2\text{CH}_3\) \(1. \text{LiAlH}_4\) \(2. \text{H}_2\text{O}^+\)
   g. \(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 + \text{HOCH}_2\text{CH}_2\text{OH}\) \(\text{HCl}\)
   h. \(\text{CH}_3\text{C} = \text{CH}_2\) \(\text{NaC} = \text{N}\) excess \(\text{HCl}\)
42. List the following compounds in order of decreasing reactivity toward nucleophilic attack:

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{C}\text{H}_{2}\text{CH}_3 & \quad \text{CH}_3\text{CH}_2\text{CH} & \quad \text{CH}_3\text{CH}_2\text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3\text{CH}_2\text{CH} & \quad \text{CH}_3\text{CH}_2\text{CH}_3
\end{align*}
\]

43. a. Show the reagents required to form the primary alcohol.

\[
\begin{align*}
\text{R} & \quad \text{R}'\text{CH} & \quad \text{RCH}_2\text{Br} \\
\text{R} & \quad \text{RCH}_2\text{OH} & \quad \Delta \text{RCH}_2\text{OCH}_3 \\
\text{R} & \quad \text{R} & \quad \text{H}_2\text{C} & \quad \text{O}
\end{align*}
\]

b. Which of the reactions cannot be used for the synthesis of isobutyl alcohol?

c. Which of the reactions changes the carbon skeleton of the starting material?

44. Using cyclohexanone as the starting material, describe how each of the following compounds could be synthesized:

a. \[\text{HOCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}\]

b. \[\text{CH}_2\text{NH}_2\]

c. \[\text{CH}_2\text{Br}\]

d. \[\text{CH}_2\text{NH}_2\]

e. \[\text{N(CH}_3)_2\]

f. \[\text{CH}_2\text{CH}_3\]

(Show two methods)

45. Propose a mechanism for the following reaction:

\[
\text{HOCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H} \quad \text{HCl} \quad \text{CH}_3\text{OH} \quad \text{OCH}_3
\]

46. List the following compounds in order of decreasing \(K_{eq}\) for hydrate formation:

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{CH}_3 \\
\text{C} & \quad \text{C} & \quad \text{O} & \quad \text{CH}_3 \\
\text{Cl} & \quad \text{Cl} & \quad \text{O}_2\text{N} & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]
47. Fill in the boxes:
   a. CH₃OH $\rightarrow$ CH₃Br $\rightarrow$ 1. $\rightarrow$ CH₃CH₂OH
   b. CH₄ $\rightarrow$ CH₃Br $\rightarrow$ 1. $\rightarrow$ CH₃CH₂CH₂OH

48. Give the products of each of the following reactions:
   a. $\text{C}=\text{NCH₂CH₃} + \text{H₂O} \xrightarrow{\text{HCl}}$
   b. CH₃CH₂CCH₃ $\xrightarrow[1. \text{CH₃CH₂MgBr}]{2. \text{H₂O}^+}$
   c. $\text{O} + (\text{C₆H₅})₃\text{P} \xrightarrow{\text{CH₂}}$
   d. CH₃CH₂COCH₃ $\xrightarrow[1. \text{CH₃CH₂MgBr excess}]{2. \text{H₂O}^+}$
   e. $\text{O} + \text{CH₃OH} \xrightarrow{\text{HCl}}$

49. Thiols can be prepared from the reaction of thiourea with an alkyl halide, followed by hydroxide-ion-promoted hydrolysis.
   a. Propose a mechanism for the reaction.
   b. What thiol would be formed if the alkyl halide employed were pentyl bromide?

50. The only organic compound obtained when compound Z undergoes the following sequence of reactions gives the $^1\text{H NMR}$ spectrum shown. Identify compound Z.

   Compound Z $\xrightarrow[1. \text{phenylmagnesium bromide}]{2. \text{H₂O}^+}$ MnO₂ $\Delta$

   Offset: 0.2 ppm.
51. Propose a mechanism for each of the following reactions:

   a.  

   b.  

   c.  

52. How many signals would the product of the following reaction show in these spectra

   a. its $^1$HNMR spectrum
   b. its $^{13}$C NMR spectrum

   O
   CH₂CH₂CH₂COCH₃

   1. excess CH₃MgBr
   2. H₃O⁺

53. Give the products of the following reactions. Show all stereoisomers that are formed.

   a.  

   b.  

   c.  

   d.  

54. List three different sets of reagents (a carbonyl compound and a Grignard reagent) that could be used to prepare each of the following tertiary alcohols:

   a. CH₃CH₂CCH₂CH₂CH₂CH₃
   b. CH₃CH₂CCH₂CH₂CH₂CH₂CH₃

55. Give the product of the reaction of 3-methyl-2-cyclohexenone with each of the following reagents:

   a. CH₃MgBr followed by H₃O⁺
   b. excess NaCN, HCl
   c. H₂, Pd
   d. HBr
   e. (CH₃CH₂)₂CuLi followed by H₃O⁺
   f. CH₃CH₂SH

56. Norlutin® and Enovid® are ketones that suppress ovulation. Consequently, they have been used clinically as contraceptives. For which of these compounds would you expect the infrared carbonyl absorption (C=O stretch) to be at a higher frequency? Explain.
57. A compound gives the following IR spectrum. Upon reaction with sodium borohydride followed by acidification, the product with the following $^1$HNMR spectrum is formed. Identify the compounds.

58. Unlike a phosphonium ylide, which reacts with an aldehyde or ketone to form an alkene, a sulfonium ylide reacts with an aldehyde or ketone to form an epoxide. Explain why one ylide forms an alkene, whereas the other forms an epoxide.

\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{COH} \]

59. Indicate how the following compounds could be prepared from the given starting materials:

a. \[ \text{O} \quad \text{COCH}_3 \quad \rightarrow \quad \text{OH} \quad \text{CHCH}_3 \]

b. \[ \text{O} \quad \text{COCH}_3 \quad \rightarrow \quad \text{O} \quad \text{CH} \]

c. \[ \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{COH} \]
60. Propose a reasonable mechanism for each of the following reactions:

a. \[
\begin{align*}
\text{CH}_3\text{CCH}_2\text{CH}_2\text{COCH}_2\text{CH}_3 & \xrightarrow{1. \text{CH}_3\text{MgBr}} \xrightarrow{2. \text{H}_2\text{O}} \text{CH}_3\text{CCH}_2\text{CH}_2\text{COCH}_2\text{CH}_3 + \text{CH}_3\text{CH}_2\text{OH} \\
\end{align*}
\]

b. \[
\begin{align*}
\text{CH} & \xrightarrow{\text{HCl}} \text{O} \\
\text{HCl} & \xrightarrow{\text{CH}_3\text{OH}} \text{O}
\end{align*}
\]

61. a. In aqueous solution, \(\alpha\)-glucose exists in equilibrium with two six-membered ring compounds. Draw the structures of these compounds.

\[
\text{O} \quad \text{H} \quad \text{OH} \\
\text{CH}_2\text{OH} \quad \text{CH}_2\text{OH} \\
\alpha\text{-glucose}
\]

b. Which of the six-membered ring compounds will be present in greater amount?

62. The \(^1\text{H NMR}\) spectrum of the alkyl bromide used to make the ylide to form a compound with molecular formula \(\text{C}_{11}\text{H}_{14}\) is shown below. What product is obtained from the Wittig reaction?

63. In the presence of an acid catalyst, acetaldehyde forms a trimer known as paraldehyde. Because it induces sleep when it is administered to animals in large doses, paraldehyde is used as a sedative or hypnotic. Propose a mechanism for the formation of paraldehyde.

64. The addition of hydrogen cyanide to benzaldehyde forms a compound called mandelonitrile. \((R)\)-Mandelonitrile is formed from the hydrolysis of amygdalin, a compound found in the pits of peaches and apricots. Amygdalin is the principal constituent of laetrile, a compound that was once highly touted as a treatment for cancer. The drug was subsequently found to be ineffective. Is \((R)\)-mandelonitrile formed by attack of cyanide ion on the \(Re\) face or the \(Si\) face of benzaldehyde?
65. What carbonyl compound and what phosphonium ylide are needed to synthesize the following compounds?

a. \[\text{\begin{tabular}{c}
\text{CH=CHCH=CHCH}_{2}\text{CH}_{3}
\end{tabular}}\]

b. \[\text{CHCH}_{2}\text{CH}_{3}\]

c. \[\text{\begin{tabular}{c}
\text{CH=CH=CH} \text{CH=CH}_{2}
\end{tabular}}\]

d. \[\text{\begin{tabular}{c}
\text{CH} \text{=CH}_{2}
\end{tabular}}\]

66. Identify compounds A and B:

\[\text{A} \xrightarrow{1. (\text{CH}_2=\text{CH})_2\text{CuLi}} \xrightarrow{2. \text{H}_2\text{O}} \text{B} \xrightarrow{1. \text{CH}_3\text{Li}} \xrightarrow{2. \text{H}_2\text{O}} \text{CH}_3 \text{OH} \]
\[\text{CH=CHCH=CHCH}_{2}\text{CHCH}_{3}\]

67. Propose a reasonable mechanism for each of the following reactions:

a. \[\text{CH}_3\text{O} \xrightarrow{\text{HCl}} \Delta \text{CH}_3\text{O} \]

b. \[\text{\begin{tabular}{c}
\text{CH}=\text{CH}\text{OH} + \text{HCHO} \\
\text{C} \text{H}_3 \text{OH}
\end{tabular}} \rightarrow \text{\begin{tabular}{c}
\text{CH}=\text{CH}\text{N} \text{H} \text{C} \text{H}_3 \text{OH}
\end{tabular}}\]

68. A compound reacts with methylmagnesium bromide followed by acidification to form the product with the following \(^1\text{H} \text{NMR}\) spectrum. Identify the compound.

![1H NMR Spectrum]

69. Show how each of the following compounds can be prepared from the given starting material. In each case, you will need to use a protecting group.

a. \[\text{CH}_3\text{CHCH}_{2}\text{COCH}_3 \rightarrow \text{CH}_3\text{CHCH}_{2}\text{CCH}_{3}\]

b. \[\text{\begin{tabular}{c}
\text{Cl} \text{OH} \\
\text{OH}
\end{tabular}} \rightarrow \text{\begin{tabular}{c}
\text{COOH} \text{OH}
\end{tabular}}\]

c. \[\text{\begin{tabular}{c}
\text{Br} \text{C} \text{CH}_3 \\
\text{OH}
\end{tabular}} \rightarrow \text{\begin{tabular}{c}
\text{CH}_2\text{CH}_{2}\text{OH} \text{C} \text{CH}_3
\end{tabular}}\]
CHAPTER 18 Carbonyl Compounds II

70. When a cyclic ketone reacts with diazomethane, the next larger cyclic ketone is formed. This is called a ring expansion reaction. Provide a mechanism for this reaction.

\[
\text{cyclohexanone} + \text{diazomethane} \rightarrow \text{cycloheptanone} + \text{N}_2
\]

71. The \( pK_a \) values of oxaloacetic acid are 2.22 and 3.98.

a. Which carboxyl group is more acidic?

b. The amount of hydrate present in an aqueous solution of oxaloacetic acid depends on the pH of the solution: 95% at pH = 0, 81% at pH = 1.3, 35% at pH = 3.1, 13% at pH = 4.7, 6% at pH = 6.7, and 6% at pH = 12.7. Explain this pH dependence.

72. The Horner–Emmons modification is a variation of a Wittig reaction in which a phosphonate-stabilized carbanion is used instead of a phosphonium ylide.

The phosphonate-stabilized carbanion is prepared from an appropriate alkyl halide. This is called the Arbuzov reaction.

Because the Arbuzov reaction can be carried out with an \( \alpha \)-bromo ketone or an \( \alpha \)-bromo ester (in which case it is called a Perkow reaction), it provides a way to synthesize \( \alpha,\beta \)-unsaturated ketones and esters.

a. Propose a mechanism for the Arbuzov reaction.

b. Propose a mechanism for the Horner–Emmons modification.

c. Show how the following compounds can be prepared from the given starting material:

1. \( \text{CH}_3\text{CH}_2\text{CH} = \text{CHC}_3 \)

2. \( \text{O} \)

\[
\text{O} \quad \rightarrow \quad \text{O} \quad \rightarrow \quad \text{O} \quad \rightarrow
\]

\[
\text{CH}_3\text{CH}_2\text{Br} \]

\[
\text{CH}_3\text{CH}_2\text{Br} \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{Br}
\]
73. In order to solve this problem, you must read the description of the Hammett $\sigma$, $\rho$ treatment given in Chapter 17, Problem 76. When the rate constants for the hydrolysis of several morpholine enamines of para-substituted propiophenones are determined at $\text{pH} = 4.7$, the $\rho$ value is positive; however, when the rates of hydrolysis are determined at $\text{pH} = 10.4$, the $\rho$ value is negative.

a. What is the rate-determining step of the hydrolysis reaction when it is carried out in a basic solution?

b. What is the rate-determining step of the reaction when it is carried out in an acidic solution?

![a morpholine enamine of a para-substituted propiophenone]

\[
\begin{align*}
\log k_{\text{obsd}} (s^{-1}) \\
\sigma
\end{align*}
\]

74. Propose a mechanism for each of the following reactions:

a. \[
\begin{align*}
\text{Br} &\quad \text{HCl, H}_2\text{O} \\
\text{C} &\quad \text{OCH}_3 \\
\text{CH}_3 &\quad \text{C} \quad \text{C-CH}_3
\end{align*}
\]

b. \[
\begin{align*}
\text{HCl} &\quad \text{H}_2\text{O} \\
\text{O} &\quad \text{O} \\
\text{O} &\quad \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{(HOCH}_2\text{CH}_2\text{CH}_2\text{)}_2\text{C-CH_3}
\end{align*}
\]

c. \[
\begin{align*}
\text{OH} &\quad \text{SCH}_2\text{CH}_3 \\
\text{OH} &\quad \text{OH} \\
\text{O} &\quad \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{SH} \\
\text{HOCH}_2\text{CH}_2\text{CH}_2\text{C-CH_3}
\end{align*}
\]

d. \[
\begin{align*}
\text{CH}_3\text{CH=CHCCH}_3 &\quad \text{N} \\
\text{O} &\quad \text{O} \\
\text{CH}_3 &\quad \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CCH}_3 &\quad \text{N} \\
\text{H} &\quad \text{H}
\end{align*}
\]
When you studied the reactions of carbonyl compounds in Chapters 17 and 18, you saw that their site of reactivity is the partially positively charged carbonyl carbon, which is attacked by nucleophiles.

When you studied the reactions of carbonyl compounds in Chapters 17 and 18, you saw that their site of reactivity is the partially positively charged carbonyl carbon, which is attacked by nucleophiles.

**Acetyl-CoA**

\[
\text{RCH}_2\text{C} - \text{R} \quad \text{RCH}_2\text{C} - \text{R}
\]

Aldehydes, ketones, esters, and \(N,N\)-disubstituted amides have a second site of reactivity. A hydrogen bonded to a carbon adjacent to a carbonyl carbon is sufficiently acidic to be removed by a strong base. The carbon adjacent to a carbonyl carbon is called an \(\alpha\)-carbon. A hydrogen bonded to an \(\alpha\)-carbon is called an \(\alpha\)-hydrogen.

\[
\text{RCH}_2\text{C} - \text{R} \quad \text{RCH}_2\text{C} - \text{R}
\]

In Section 19.1, you will find out why a hydrogen bonded to a carbon adjacent to a carbonyl carbon is more acidic than other hydrogens attached to \(sp^3\) hybridized carbons, and you will look at some reactions that result from this acidity. At the end of this chapter, you will see that a proton is not the only substituent that can be removed from an \(\alpha\)-carbon: A carboxyl group bonded to an \(\alpha\)-carbon can be removed as CO\(_2\). Finally, you will be introduced to some synthetic schemes that rely on being able to remove protons and carboxyl groups from \(\alpha\)-carbons.
Hydrogen and carbon have similar electronegativities, which means that the electrons binding them together are shared almost equally by the two atoms. Consequently, a hydrogen bonded to a carbon is usually not acidic. This is particularly true for hydrogens bonded to \(sp^3\) hybridized carbons, because these carbons are the most similar to hydrogen in electronegativity (Section 6.9). The high \(pK_a\) of ethane is evidence of the low acidity of hydrogens bonded to \(sp^3\) hybridized carbons.

\[
\text{CH}_3\text{CH}_3 \quad pK_a = 50
\]

A hydrogen bonded to an \(sp^3\) hybridized carbon adjacent to a carbonyl carbon is much more acidic than hydrogens bonded to other \(sp^3\) hybridized carbons. For example, the \(pK_a\) for dissociation of an \(\alpha\)-hydrogen from an aldehyde or a ketone ranges from 16 to 20, and the \(pK_a\) for dissociation of an \(\alpha\)-hydrogen from an ester is about 25 (Table 19.1). Notice that, although an \(\alpha\)-hydrogen is more acidic than most other carbon-bound hydrogens, it is less acidic than a hydrogen of water (\(pK_a = 15.7\)). A compound that contains a relatively acidic hydrogen bonded to an \(sp^3\) hybridized carbon is called a **carbon acid**.

![Diagram of \(\alpha\)-hydrogens with \(pK_a\) values](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>(pK_a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH(_2)CN(CH(_3))(_2)</td>
<td>30</td>
</tr>
<tr>
<td>CH(_2)COCH(_2)CH(_3)</td>
<td>25</td>
</tr>
<tr>
<td>CH(_3)C(\equiv)N</td>
<td>25</td>
</tr>
<tr>
<td>CH(_2)CH(_3)</td>
<td>20</td>
</tr>
<tr>
<td>CH(_2)CH</td>
<td>17</td>
</tr>
<tr>
<td>CH(_3)CHNO(_2)</td>
<td>8.6</td>
</tr>
<tr>
<td>N(\equiv)CCHC(\equiv)N</td>
<td>11.8</td>
</tr>
<tr>
<td>CH(_3)CCHCC(_3)</td>
<td>8.9</td>
</tr>
<tr>
<td>CH(_3)CHCH</td>
<td>5.9</td>
</tr>
<tr>
<td>CH(_3)CHNO(_2)</td>
<td>3.6</td>
</tr>
</tbody>
</table>
Why is a hydrogen bonded to an \( sp^3 \) hybridized carbon that is adjacent to a carbonyl carbon so much more acidic than hydrogens bonded to other \( sp^3 \) hybridized carbons? An \( \alpha \)-hydrogen is more acidic because the base formed when the proton is removed from the \( \alpha \)-carbon is more stable than the base formed when a proton is removed from other \( sp^3 \) hybridized carbons, and acid strength is determined by the stability of the conjugate base that is formed when the acid gives up a proton (Section 1.17).

Why is the base more stable? When a proton is removed from ethane, the electrons left behind reside solely on a carbon atom. Because carbon is not very electronegative, a carbanion is relatively unstable and therefore difficult to form. As a result, the \( pK_a \) of its conjugate acid is very high.

\[
\text{CH}_3\text{CH}_3 \quad \overset{\text{localized electrons}}{\longleftarrow} \quad \text{CH}_3\text{CH}_2^+ + \text{H}^+
\]

When a proton is removed from a carbon adjacent to a carbonyl carbon, two factors combine to increase the stability of the base that is formed. First, the electrons left behind when the proton is removed are delocalized, and electron delocalization increases the stability of a compound (Section 7.6). More important, the electrons are delocalized onto an oxygen, an atom that is better able to accommodate the electrons because it is more electronegative than carbon.

PROBLEM 1
The \( pK_a \) of propene is 42, which is greater than the \( pK_a \) of the carbon acids listed in Table 19.1, but less than the \( pK_a \) of an alkane. Explain.

Now we can understand why aldehydes and ketones (\( pK_a = 16–20 \)) are more acidic than esters (\( pK_a = 25 \)). The electrons left behind when an \( \alpha \)-hydrogen is removed from an ester are not as readily delocalized onto the carbonyl oxygen as are the electrons left behind when an \( \alpha \)-hydrogen is removed from an aldehyde or a ketone. Because a lone pair on the oxygen of the OR group of the ester can also be delocalized onto the carbonyl oxygen, the two pairs of electrons compete for delocalization onto oxygen.

Nitroalkanes, nitriles, and \( N,N \)-disubstituted amides also have relatively acidic \( \alpha \)-hydrogens (Table 19.1) because in each case the electrons left behind when the proton is removed can be delocalized onto an atom that is more electronegative than carbon.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{NO}_2 & \quad \text{nitroethane} \quad \text{\( pK_a = 8.6 \)} \\
\text{CH}_3\text{CH}_2\text{C}=\text{N} & \quad \text{propanenitrile} \quad \text{\( pK_a = 26 \)} \\
\text{CH}_3\text{CN(CH}_3\text{)}_2 & \quad \text{\( N,N \)-dimethylacetamide} \quad \text{\( pK_a = 30 \)}
\end{align*}
\]
If the $\alpha$-carbon is between two carbonyl groups, the acidity of an $\alpha$-hydrogen is even greater (Table 19.1). For example, an $\alpha$-hydrogen of ethyl 3-oxobutyrate, a compound with an $\alpha$-carbon between a ketone carbonyl group and an ester carbonyl group, has a $pK_a$ of 10.7. An $\alpha$-hydrogen of 2,4-pentanedione, a compound with an $\alpha$-carbon between two ketone carbonyl groups, has a $pK_a$ of 8.9. Ethyl 3-oxobutyrate is classified as a $\beta$-keto ester because the ester has a carbonyl group at the $\beta$-position. 2,4-Pentanedione is a $\beta$-diketone.

The acidity of $\alpha$-hydrogens bonded to carbons flanked by two carbonyl groups increases because the electrons left behind when the proton is removed can be delocalized onto two oxygen atoms. $\beta$-Diketones have lower $pK_a$ values than $\beta$-keto esters because electrons are more readily delocalized onto ketone carbonyl groups than they are onto ester carbonyl groups.

![Resonance contributors for the 2,4-pentanedione anion](image)

**Problem 2**

Give an example of

a. a $\beta$-keto nitrile  
   b. a $\beta$-diester

**Problem 3**

List the compounds in each of the following groups in order of decreasing acidity:

a. $\text{CH}_2\text{==CH}_2$  
   $\text{CH}_3\text{CH}_3$  
   $\text{CH}_3\text{CH}$  
   $\text{HC}==\text{CH}$

b. $\text{CH}_3\text{CH}==\text{CH}_2\text{CCH}_3$  
   $\text{CH}_3\text{OCCH}_2\text{COCH}_3$  
   $\text{CH}_3\text{CCH}_2\text{COCH}_3$  
   $\text{CH}_3\text{CCH}_3$

c. $\text{NCH}_3$  
   $\text{O}$  
   $\text{O}$

**Section 19.2 Keto–Enol Tautomerism**

A ketone exists in equilibrium with its enol tautomer. You were introduced to tautomers in Section 6.6. Recall that *tautomers* are isomers that are in rapid equilibrium. Keto–enol tautomers differ in the location of a double bond and a hydrogen.
For most ketones, the enol tautomer is much less stable than the keto tautomer. For example, an aqueous solution of acetone exists as an equilibrium mixture of more than 99.9% keto tautomer and less than 0.1% enol tautomer.

\[
\begin{align*}
\text{CH}_3\text{C} & \text{CH}_3 \\
\text{CH}_2\text{C} & \text{OH} \\
\text{keto tautomer} & \text{enol tautomer}
\end{align*}
\]

The fraction of the enol tautomer in an aqueous solution is considerably greater for a \(\beta\)-diketone because the enol tautomer is stabilized by intramolecular hydrogen bonding and by conjugation of the carbon–carbon double bond with the second carbonyl group.

\[
\begin{align*}
\text{H}_3\text{C} & \text{CH}_2\text{C} \text{CH}_3 \\
\text{85\% keto tautomer} & \text{15\% enol tautomer}
\end{align*}
\]

Phenol is unusual in that its enol tautomer is more stable than its keto tautomer because the enol tautomer is aromatic, but the keto tautomer is not.

\[
\begin{align*}
\text{enol tautomer} & \quad \text{keto tautomer}
\end{align*}
\]

**PROBLEM 4**

Only 15% of 2,4-pentanediione exists as the enol tautomer in water, but 92% exists as the enol tautomer in hexane. Explain why this is so.

Now that we know that a hydrogen on a carbon adjacent to a carbonyl carbon is somewhat acidic, we can understand why keto and enol tautomers interconvert as we first saw in Chapter 6. **Keto–enol interconversion** is also called **keto–enol tautomerization** or **enolization**. The interconversion of the tautomers can be catalyzed by either acids or bases.

In a basic solution, hydroxide ion removes a proton from the \(\alpha\)-carbon of the keto tautomer. The anion that is formed has two resonance contributors: a carbanion and an enolate ion. The enolate ion contributes more to the resonance hybrid because the negative charge is better accommodated by oxygen than by carbon. Protonation on oxygen forms the enol tautomer, whereas protonation on the \(\alpha\)-carbon reforms the keto tautomer.

**base-catalyzed keto–enol interconversion**
In an acidic solution, the carbonyl oxygen of the keto tautomer is protonated and water removes a proton from the $\alpha$-carbon, forming the enol.

**acid-catalyzed keto–enol interconversion**

Notice that the steps are reversed in the base- and acid-catalyzed reactions. In the base-catalyzed reaction, the base removes the $\alpha$-proton in the first step and the oxygen is protonated in the second step. In the acid-catalyzed reaction, the acid protonates the oxygen in the first step and the $\alpha$-proton is removed in the second step. Notice also how the catalyst is regenerated in both the acid- and base-catalyzed mechanisms.

**PROBLEM 5**

Draw the enol tautomers for each of the following compounds. For those compounds that have more than one enol tautomer, indicate which is more stable.

a. CH$_3$CH$_2$CCH$_2$CH$_3$

b. CCH$_3$

c. 

d. 

e. CH$_3$CH$_2$CCH$_2$CCH$_2$CH$_3$

f. CH$_3$CH$_2$CCH$_2$CH$_3$

---

**19.3 How Enols and Enolate Ions React**

The carbon–carbon double bond of an enol suggests that it is a nucleophile—like an alkene. An enol is more electron rich than an alkene because the oxygen atom donates electrons by resonance. An enol, therefore, is a better nucleophile than an alkene.

Carbonyl compounds that form enols undergo substitution reactions at the $\alpha$-carbon. When an $\alpha$-substitution reaction takes place under acidic conditions, water removes a proton from the $\alpha$-carbon of the protonated carbonyl compound. The nucleophilic enol then reacts with an electrophile. The overall reaction is an $\alpha$-substitution reaction—one electrophile ($E^-$) is substituted for another ($H^+$).
When an reaction takes place under basic conditions, a base removes a proton from the and the nucleophilic enolate ion then reacts with an electrophile. Enolate ions are much better nucleophiles than enols because they are negatively charged.

The resonance contributors of the enolate ion show that it has two electron-rich sites: the and the oxygen. The enolate ion is an example of an ambident nucleophile (ambi is Latin for “both”; dent is Latin for “teeth”). An ambident nucleophile is a nucleophile with two nucleophilic sites (“two teeth”).

Which nucleophilic site (C or O) reacts with the electrophile depends on the electrophile and on the reaction conditions. Protonation occurs preferentially on oxygen because of the greater concentration of negative charge on the more electronegative oxygen atom. However, when the electrophile is something other than a proton, carbon is more likely to be the nucleophile because carbon is a better nucleophile than oxygen.

Notice the similarity between keto–enol interconversion and α-substitution. Actually, keto–enol interconversion is an α-substitution reaction in which hydrogen serves as both the electrophile that is removed from the α-carbon and the electrophile that is added to the α-carbon (when the enol or enolate reverts back to the keto tautomer).

As various α-substitution reactions are discussed in this chapter, notice that they all follow basically the same mechanism: A base removes a proton from an α-carbon and the resulting enol or enolate reacts with an electrophile. The reactions differ only in the nature of the base and the electrophile—and in whether the reactions are carried out under acidic or basic conditions.
**Problem 6**

Explain why the aldehydic hydrogen (the one attached to the carbonyl carbon) is not exchanged with deuterium.

![Reaction diagram](image)

**19.4 Halogenation of the α-Carbon of Aldehydes and Ketones**

**Acid-Catalyzed Halogenation**

When Br₂, Cl₂, or I₂ is added to an acidic solution of an aldehyde or a ketone, a halogen replaces one of the α-hydrogens of the carbonyl compound.

\[
\text{RCH₂CHO + Cl}_2 \xrightarrow{\text{H}_3\text{O}^+} \text{RCHClCH}_2\text{CHO} + \text{HCl}
\]

In the first step of this acid-catalyzed reaction, the carbonyl oxygen is protonated. Water is the base that removes a proton from the α-carbon, forming an enol that reacts with an electrophilic halogen.

**Base-Promoted Halogenation**

When excess Br₂, Cl₂, or I₂ is added to a basic solution of an aldehyde or a ketone, the halogen replaces all the α-hydrogens.

\[
\text{RCH₂CHO + Br}_2 \xrightarrow{\text{excess HO}^-} \text{RCHBrCHBrCHO} + 2 \text{Br}^-
\]

Under basic conditions, all the α-hydrogens are substituted for halogens.
In the first step of this base-promoted reaction, hydroxide ion removes a proton from the \( \alpha \)-carbon. The enolate ion then reacts with the electrophilic bromine. These two steps are repeated until all the \( \alpha \)-hydrogens are replaced by bromine.

Each successive halogenation is more rapid than the previous one because the electron-withdrawing bromine increases the acidity of the remaining \( \alpha \)-hydrogens. This is why all the \( \alpha \)-hydrogens are replaced by bromines. Under acidic conditions, on the other hand, each successive halogenation is slower than the previous one because the electron-withdrawing bromine decreases the basicity of the carbonyl oxygen, thereby making protonation of the carbonyl oxygen less favorable.

### The Haloform Reaction

In the presence of excess base and excess halogen, a methyl ketone is first converted into a trihalo-substituted ketone. Then hydroxide ion attacks the carbonyl carbon of the trihalo-substituted ketone. Because the trihalomethyl ion is a weaker base than hydroxide ion (the \( pK_a \) of CHI\(_3\) is 14; the \( pK_a \) of H\(_2\)O is 15.7), the trihalomethyl ion is the group more easily expelled from the tetrahedral intermediate, so the final product is a carboxylic acid. The conversion of a methyl ketone to a carboxylic acid is called a **haloform reaction** because one of the products is haloform—CHCl\(_3\) (chloroform), CHBr\(_3\) (bromoform), or CHI\(_3\) (iodoform). Before spectroscopy became a routine analytical tool, the haloform reaction served as a test for methyl ketones. The presence of a methyl ketone was indicated by the formation of iodoform, a bright yellow compound.

### Problem 7

Why do only methyl ketones undergo the haloform reaction?

### Problem 8

A ketone undergoes acid-catalyzed bromination, acid-catalyzed chlorination, and acid-catalyzed deuterium exchange at the \( \alpha \)-carbon, all at about the same rate. What does this tell you about the mechanism of the reactions?

### 19.5 Halogenation of the \( \alpha \)-Carbon of Carboxylic Acids: The Hell–Volhard–Zelinski Reaction

Carboxylic acids do not undergo substitution reactions at the \( \alpha \)-carbon because a base will remove a proton from the OH group rather than from the \( \alpha \)-carbon, since the OH group is more acidic. If, however, a carboxylic acid is treated with PBr\(_3\) and Br\(_2\), then the \( \alpha \)-carbon can be brominated. (Red phosphorus can be used in place of PBr\(_3\), since P and excess Br\(_2\) react to form PBr\(_3\).) This halogenation reaction is called the Hell–Volhard–Zelinski...
**Section 19.6 α-Halogenated Carbonyl Compounds in Synthesis**

You have seen that when a base removes a proton from an α-carbon of an aldehyde or a ketone (Section 19.2), the α-carbon becomes nucleophilic—it reacts with electrophiles.

However, when the α-position is halogenated, the α-carbon becomes electrophilic—it reacts with nucleophiles. Therefore, both electrophiles and nucleophiles can be placed on α-carbons.

---

**reaction** or, more simply, the HVZ reaction. You will see when you examine the mechanism of the HVZ reaction that α-substitution occurs because an acyl bromide, rather than a carboxylic acid, is the compound that undergoes α-substitution.

The HVZ reaction

\[
\begin{align*}
\text{RCH(OH)COH} & \xrightarrow{1. \text{PBr}_3 \text{ (or P)}_2, \text{Br}_2} \text{RCHBrCOH} \\
\text{RCHBrCOH} & \xrightarrow{2. \text{H}_2\text{O}} \text{RCOCH} \tag{1.1}
\end{align*}
\]

In the first step of the HVZ reaction, PBr₃ converts the carboxylic acid into an acyl bromide by a mechanism similar to the one by which PBr₃ converts an alcohol into an alkyl bromide (Section 12.3). (Notice that in both reactions PBr₃ replaces an OH with a Br.) The acyl bromide is in equilibrium with its enol. Bromination of the enol forms the α-brominated acyl bromide, which is hydrolyzed to the α-brominated carboxylic acid.

**mechanism for the Hell–Volhard–Zelinski reaction**

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{C} \equiv \text{O} & \xrightarrow{\text{PBr}_3} \text{CH}_3\text{CH}_2\text{C} \equiv \text{Br} \\
\text{CH}_3\text{CH}_2\text{C} \equiv \text{Br} & \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{CH} \equiv \text{Br} + \text{HBr}
\end{align*}
\]

**Carl Magnus von Hell** (1849–1926) was born in Germany. He studied with Hermann von Fehling at the University of Stuttgart and with Richard Erlenmeyer (1825–1909) at the University of Munich. Von Hell reported the HVZ reaction in 1881, and the reaction was independently confirmed by both Volhard and Zelinski in 1887.

**Jacob Volhard** (1834–1910) was also born in Germany. Brilliant, but lacking direction, he was sent by his parents to England to be with August von Hofmann (Section 21.5), a family friend. After working with Hofmann, Volhard became a professor of chemistry, first at the University of Munich, then at the University of Erlangen, and later at the University of Halle. He was the first to synthesize sarcosine and creatine.

**Nikolai Dimitrievich Zelinski** (1861–1953) was born in Moldavia. He was a professor of chemistry at the University of Moscow. In 1911, he left the university to protest the firing of the entire administration by the Ministry of Education. He went to St. Petersburg, where he directed the laboratory of the Ministry of Finances. In 1917, after the Russian Revolution, he returned to the University of Moscow.
α-Brominated carbonyl compounds are also useful to synthetic chemists because once a bromine has been introduced into the α-position of a carbonyl compound, an α,β-unsaturated carbonyl compound can be prepared by means of an E2 elimination reaction, using a strong and bulky base to encourage elimination over substitution (Section 11.8).

\[
\begin{align*}
\text{O} & \quad \text{Br} \\
\text{O} & \quad \text{ tert-BuO}^- \quad \text{ tert-BuOH} \\
\text{an α,β-unsaturated} & \quad \text{carbonyl compound}
\end{align*}
\]

**PROBLEM 9**

How would you prepare the following compounds from the given starting materials?

a. \( \text{CH}_3\text{CH}_2\text{CH} \xrightarrow{} \text{CH}_3\text{CHCHN(CH}_3)_2 \)

b. \( \text{CH}_3\text{CH}_2\text{CH} \xrightarrow{} \text{CH}_3\text{CHCHOH} \)

c. \( \text{cyclohexane} \xrightarrow{} \text{cyclohexanone} \)

d. \( \text{cyclopentane} \xrightarrow{} \text{cyclopentane} \)

**PROBLEM 10**

How could the following compounds be prepared from a carbonyl compound with no carbon–carbon double bonds?

a. \( \text{CH}_3\text{CH=CHCCH}_{2}\text{CH}_3 \)

b. \( \text{cyclohexene} \)

**PROBLEM 11**

How could the following compounds be prepared from cyclohexanone?

a. \( \text{cyclohexanone} \xrightarrow{} \text{cyclohexanone} \)

b. \( \text{cyclohexanone} \xrightarrow{} \text{cyclohexanone} \)

**19.7 Using LDA to Form an Enolate**

The amount of carbonyl compound converted to enolate depends on the \( pK_a \) of the carbonyl compound and the particular base used to remove the α-hydrogen. For example, when hydroxide ion (the \( pK_a \) of its conjugate acid is 15.7) is used to remove an α-hydrogen from cyclohexanone (\( pK_a = 17 \)), only a small amount of the carbonyl...
compound is converted into the enolate because hydroxide ion is a weaker base than the base being formed. (Recall that the equilibrium of an acid–base reaction favors reaction of the strong acid and formation of the weak acid, Section 1.17.)

\[
\text{LDA} + \text{THF} \rightarrow \text{LDA} \quad (pK_a \approx 50)
\]

In contrast, when lithium diisopropylamide (LDA) is used to remove the \(\alpha\)-proton (the \(pK_a\) of LDA’s conjugate acid is about 35), essentially all the carbonyl compound is converted to enolate because LDA is a much stronger base than the base being formed (Section 1.17). Therefore, LDA is the base of choice for those reactions that require the carbonyl compound to be completely converted to enolate before it reacts with an electrophile.

Using a nitrogen base to form an enolate can be a problem because a nitrogen base can also react as a nucleophile and attack the carbonyl carbon (Section 18.6). However, the two bulky alkyl substituents bonded to the nitrogen of LDA make it difficult for the nitrogen to get close enough to the carbonyl carbon to react with it. Consequently, LDA is a strong base but a poor nucleophile, so it removes an \(\alpha\)-hydrogen much faster than it attacks a carbonyl carbon. LDA is easily prepared by adding butyllithium to diisopropylamine (DIA) in THF at \(-78^\circ\text{C}\).

**19.8 Alkylation of the \(\alpha\)-Carbon of Carbonyl Compounds**

Alkylation of the \(\alpha\)-carbon of a carbonyl compound is an important reaction because it gives us another way to form a carbon–carbon bond. Alkylation is carried out by first removing a proton from the \(\alpha\)-carbon with a strong base such as LDA and then adding the appropriate alkyl halide. Because the alkylation is an \(S_N2\) reaction, it works best with methyl halides and primary alkyl halides (Section 10.2).

Ketones, esters, and nitriles can be alkylated at the \(\alpha\)-carbon in this way. Aldehydes, however, give poor yields of \(\alpha\)-alkylated products (Section 19.11).
Two different products can be formed when the ketone is not symmetrical, because either α-carbon can be alkylated. For example, methylation of 2-methylcyclohexanone with one equivalent of methyl iodide forms both 2,6-dimethylcyclohexanone and 2,2-dimethylcyclohexanone. The relative amounts of the two products depend on the reaction conditions.

The enolate leading to 2,6-dimethylcyclohexanone is the \( \textit{kinetic} \) enolate because the \( \alpha \)-hydrogen that is removed to make this enolate is more accessible (particularly if a hindered base like LDA is used) and slightly more acidic. So 2,6-dimethylcyclohexanone is formed faster and is the major product if the reaction is carried out at \(-78^\circ C\).

The enolate leading to 2,2-dimethylcyclohexanone is the \( \textit{thermodynamic} \) enolate because it has the more substituted double bond, making it the more stable enolate. (Alkyl substitution increases enolate stability for the same reason that alkyl substitution increases alkene stability, Section 4.11.) Therefore, 2,2-dimethylcyclohexanone is the major product if the reaction is carried out under conditions that cause enolate formation to be reversible and if a less hindered base (KH) is used.

The less substituted α-carbon can be alkylated—without having to control the conditions to make certain that the reaction does not become reversible—by first making the \( N,N \)-dimethylhydrazone of the ketone.
The \(N,N\)-dimethylhydrazone will form so that the dimethylamino group is pointing away from the more substituted \(\alpha\)-carbon. The nitrogen of the dimethylamino group directs the base to the less substituted carbon by coordinating with the lithium ion of butyllithium (Bu\(^{-}\)), the base generally employed in this reaction. Hydrolysis of the hydrazone reforms the ketone (Section 18.6).

#### THE SYNTHESIS OF ASPIRIN

The first step in the industrial synthesis of aspirin is known as the Kolbe–Schmitt carboxylation reaction. The phenolate ion reacts with carbon dioxide under pressure to form \(\alpha\)-hydroxybenzoic acid, also known as salicylic acid. Acetylation of salicylic acid with acetic acid forms acetylsalicylic acid (aspirin).

During World War I, the American subsidiary of the Bayer Company bought as much phenol as it could from the international market, knowing that eventually all the phenol could be converted into aspirin. This left little phenol available for other countries to purchase for the synthesis of 2,4,6-trinitrophenol (TNT), a common explosive.

Hermann Kolbe (1818–1884) and Rudolph Schmitt (1830–1898) were born in Germany. Kolbe was a professor at the Universities of Marburg and Leipzig. Schmitt received a Ph.D. from the University of Marburg and was a professor at the University of Dresden. Kolbe discovered how to prepare aspirin in 1859. Schmitt modified the synthesis in 1885, making aspirin available in large quantities at a low price.

PROBLEM 12◆

What compound is formed when cyclohexanone is shaken with NaOD in \(D_2O\) for several hours?

PROBLEM 13

Explain why alkylation of an \(\alpha\)-carbon works best if the alkyl halide used in the reaction is a primary alkyl halide and why it does not work at all if it is a tertiary alkyl halide.

PROBLEM-SOLVING STRATEGY

How could you prepare 4-methyl-3-hexanone from a ketone containing no more than six carbon atoms?

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CCHCH}_2\text{CH}_3 & \quad \text{CH}_3 \\
\text{4-methyl-3-hexanone} \\
\text{CH}_3\text{CH}_2\text{CCHCH}_2\text{CH}_3 + \text{CH}_3\text{Br} & \quad \text{CH}_3\text{CH}_2\text{CCHCH}_2\text{CH}_3 + \text{CH}_3\text{CH}_2\text{Br} \\
\text{3-hexanone} & \quad \text{3-pentanone}
\end{align*}
\]

Two sets of ketone and alkyl halide could be used for the synthesis: 3-hexanone and a methyl halide or 3-pentanone and an ethyl halide.

3-Pentanone and an ethyl halide are the preferred starting materials. Because 3-pentanone is symmetrical, only one \(\alpha\)-substituted ketone will be formed. In contrast, 3-hexanone can form two different enolates, so two \(\alpha\)-substituted ketones can be formed.
PROBLEM 14

How could each of the following compounds be prepared from a ketone and an alkyl halide?

a. CH₃CCH₂CH₂CH==CH₂  

b. CH₃CH₂CCHCH₂CH₃

19.9 Alkylation and Acylation of the \( \alpha \)-Carbon via an Enamine Intermediate

We have seen that an enamine is formed when an aldehyde or a ketone reacts with a secondary amine (Section 18.6).

Enamines react with electrophiles in the same way that enolates do.
This means that electrophiles can be added to the α-carbon of an aldehyde or a ketone by first converting the carbonyl compound to an enamine (by treating the carbonyl compound with a secondary amine), adding the electrophile, and then hydrolyzing the imine back to the ketone.

Because the alkylation step is an \( S_N2 \) reaction, only primary alkyl halides or methyl halides should be used (Section 10.2).

One advantage to using an enamine intermediate to alkylate an aldehyde or a ketone is that only the monoalkylated product is formed.

In contrast, when a carbonyl compound is alkylated directly, dialkylated and O-alkylated products can also be formed.

In addition to being able to be alkylated, aldehydes and ketones can also be acylated via an enamine intermediate.

Notice that the α-carbon of an aldehyde or a ketone can be made to react with an electrophile either by first treating the carbonyl compound with LDA or by converting the carbonyl compound to an enamine.
Alternatively, the α-carbon of an aldehyde or a ketone can be made to react with a nucleophile by first brominating the α-position of the carbonyl compound.

![Chemical structure](image)

**PROBLEM 15**

Describe how the following compounds could be prepared using an enamine intermediate:

a. ![Chemical structure](image)  
b. ![Chemical structure](image)

---

### 19.10 Alkylation of the β-Carbon: The Michael Reaction

In Section 18.13, you saw that nucleophiles react with α,β-unsaturated aldehydes and ketones, forming either direct addition products or conjugate addition products; in Section 18.14, you saw that nucleophiles react with α,β-unsaturated carboxylic acid derivatives, forming either nucleophilic acyl substitution products or conjugate addition products.

![Chemical structure](image)

When the nucleophile is an enolate, the addition reaction has a special name—it is called a Michael reaction. The enolates that work best in Michael reactions are those that are flanked by two electron-withdrawing groups: enolates of β-diketones, β-diesters, β-keto esters, and β-keto nitriles. Because these enolates are relatively weak bases, addition occurs at the β-carbon of α,β-unsaturated aldehydes and ketones. The enolates also add to the β-carbon of α,β-unsaturated esters and amides because of the low reactivity of the carbonyl group. Notice that Michael reactions form 1,5-dicarbonyl compounds—if one carbonyl carbon is given the 1-position, the other carbonyl carbon is at the 5-position.

---

Arthur Michael (1853–1942) was born in Buffalo, New York. He studied at the University of Heidelberg, the University of Berlin, and L’École de Médecine in Paris. He was a professor of chemistry at Tufts and Harvard Universities, retiring from Harvard when he was 83.
All these reactions take place by the same mechanism: A base removes a proton from the α-carbon of the carbon acid, the enolate adds to the β-carbon of an α,β-unsaturated carbonyl compound, and the α-carbon obtains a proton from the solvent.

Notice that if either of the reactants in a Michael reaction has an ester group, the base used to remove the α-proton is the same as the leaving group of the ester. This is done because the base, in addition to being able to remove an α-proton, can react as a nucleophile and attack the carbonyl group of the ester. If the nucleophile is identical to the OR group of the ester, nucleophilic attack on the carbonyl group will not change the reactant.

Enamines can be used in place of enolates in Michael reactions. When an amine is used as a nucleophile in a Michael reaction, the reaction is called a Stork enamine reaction.

Gilbert Stork was born in Belgium in 1921. He graduated from the University of Florida and received a Ph.D. from the University of Wisconsin. He was a professor of chemistry at Harvard University and has been a professor at Columbia University since 1953. He is responsible for the development of many new synthetic procedures in addition to the one bearing his name.
PROBLEM 16

What reagents would you use to prepare the following compounds?

a. 

b. CH₃CCH₂CH₂CH(COCH₂CH₃)₂

19.11 The Aldol Addition

In Chapter 18, we saw that aldehydes and ketones are electrophiles and therefore react with nucleophiles. In the preceding sections of this chapter, we have seen that when a proton is removed from the α-carbon of an aldehyde or a ketone, the resulting anion is a nucleophile and therefore reacts with electrophiles. An aldol addition is a reaction in which both of these activities are observed: One molecule of a carbonyl compound—after a proton is removed from an α-carbon—reacts as a nucleophile and attacks the electrophilic carbonyl carbon of a second molecule of the carbonyl compound.

An aldol addition is a reaction between two molecules of an aldehyde or two molecules of a ketone. When the reactant is an aldehyde, the addition product is a β-hydroxyaldehyde, which is why the reaction is called an aldol addition (“ald” for aldehyde, “ol” for alcohol). When the reactant is a ketone, the addition product is a β-hydroxyketone. Because the addition reaction is reversible, good yields of the addition product are obtained only if it is removed from the solution as it is formed.

aldol additions

The new C—C bond formed in an aldol addition is between the α-carbon of one molecule and the carbon that formerly was the carbonyl carbon of the other molecule.

In the first step of an aldol addition, a base removes an α-proton from the carbonyl compound, creating an enolate. The enolate adds to the carbonyl carbon of a second molecule of the carbonyl compound, and the resulting negatively charged oxygen is protonated by the solvent.
Ketones are less susceptible than aldehydes to attack by nucleophiles (Section 18.2), so aldol additions occur more slowly with ketones. The relatively high reactivity of aldehydes in competing aldol addition reactions is what causes them to give low yields of \( \alpha \)-alkylation products (Section 19.8).

Because an aldol addition reaction occurs between two molecules of the same carbonyl compound, the product has twice as many carbons as the reacting aldehyde or ketone.

**PROBLEM 17**

Show the aldol addition product that would be formed from each of the following compounds:

a. \( \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH} \)

b. \( \text{CH}_3\text{CHCH}_2\text{CH}_2\text{CH} \)

c. \( \text{CH}_3\text{CH}_2\text{CCH}_2\text{CH}_3 \)

d. [Diagram]

**PROBLEM 18**

For each of the following compounds, indicate the aldehyde or ketone from which it would be formed by an aldol addition:

a. 2-ethyl-3-hydroxyhexanal

b. 4-hydroxy-4-methyl-2-pentanone

c. 2,4-dicyclohexyl-3-hydroxybutanal

d. 5-ethyl-5-hydroxy-4-methyl-3-heptanone

**PROBLEM 19**

An aldol addition can be catalyzed by acids as well as by bases. Propose a mechanism for the acid-catalyzed aldol addition of propanal.

**19.12 Dehydration of Aldol Addition Products: Formation of \( \alpha,\beta \)-Unsaturated Aldehydes and Ketones**

You have seen that alcohols are dehydrated when they are heated with acid (Section 12.5). The \( \beta \)-hydroxaldehyde and \( \beta \)-hydroxyketone products of aldol addition reactions are easier to dehydrate than many other alcohols because the double bond formed as the result of dehydration is conjugated with a carbonyl group. Conjugation increases the stability of the product (Section 8.3) and, therefore, makes it easier to form. If the product of an aldol addition is dehydrated, the overall reaction is called an **aldol condensation**. A **condensation reaction** is a reaction that combines two molecules while removing a small molecule (usually water or an alcohol).

An aldol addition product loses water to form an aldol condensation product.
β-Hydroxyaldehydes and β-hydroxyketones can also be dehydrated under basic conditions, so heating the aldol addition product in either acid or base leads to dehydration. The product of dehydration is called an enone—“ene” for the double bond and “one” for the carbonyl group.

Dehydration sometimes occurs under the conditions in which the aldol addition is carried out, without additional heating. In such cases, the β-hydroxy carbonyl compound is an intermediate and the enone is the final product of the reaction. For example, the β-hydroxy ketone formed from the aldol addition of acetophenone loses water as soon as it is formed, because the double bond formed by loss of water is conjugated not only with the carbonyl group, but also with the benzene ring. Conjugation stabilizes the dehydrated product and therefore makes it relatively easy to form.

**PROBLEM 20 SOLVED**

How could you prepare the following compounds using a starting material containing no more than three carbon atoms?

- a. CH₃CH₂CH₂COH
- b. CH₃CH₂CHCH═O
- c. CH₃CH₂CH₂CCH₃

**SOLUTION TO 20a** A compound with the correct four-carbon skeleton can be obtained if a two-carbon aldehyde undergoes an aldol addition. Dehydration of the addition product forms an α,β-unsaturated aldehyde. Catalytic hydrogenation forms an aldehyde. Some of the α,β-unsaturated aldehyde might be reduced to an alcohol, but that’s all right because both the aldehyde and the alcohol can be oxidized by an acidic solution of CrO₃ to the target compound (Section 20.2).

**19.13 The Mixed Aldol Addition**

If two different carbonyl compounds are used in an aldol addition, four products can be formed because each enolate can react both with another molecule of the carbonyl compound from which the enolate was formed and with the other carbonyl compound. In the following example, both carbonyl compound A and carbonyl compound B can...
lose a proton from an \( \alpha \)-carbon to form enolates A\(^-\) and B\(^-\); A\(^-\) can react with either A or B, and B\(^-\) can react with either A or B:

The preceding reaction is called a **mixed aldol addition** or a **crossed aldol addition**. The four products have similar physical properties, making them difficult to separate. Consequently, a mixed aldol addition that forms four products is not a synthetically useful reaction.

Under certain conditions, a mixed aldol addition can lead primarily to one product. If one of the carbonyl compounds does not have any \( \alpha \)-hydrogens, it cannot form an enolate. This reduces the number of possible products from four to two. A greater amount of one of the two products will be formed if the compound without \( \alpha \)-hydrogens is always present in excess, because the enolate will be more likely to react with it, rather than with another molecule of the carbonyl compound from which the enolate was formed, if there is more of the compound without \( \alpha \)-hydrogens in solution. Therefore, the compound with \( \alpha \)-hydrogens should be added slowly to a basic solution of the compound without \( \alpha \)-hydrogens.

If both carbonyl compounds have \( \alpha \)-hydrogens, primarily one aldol product can be obtained if LDA is used to remove the \( \alpha \)-hydrogen that creates the enolate. Because LDA is a strong base (Section 19.7), all the carbonyl compound will be converted into an enolate, so there will be no carbonyl compound left with which the enolate could react in an aldol addition. An aldol addition will not be able to occur until the second carbonyl compound is added to the reaction mixture. If the second carbonyl compound is added slowly, the chance that it will form an enolate and then react with another molecule of its parent carbonyl compound will be minimized.
PROBLEM 21

Give the products obtained from mixed aldol additions of the following compounds:

a. \( \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O} + \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O} \)

b. \( \text{CH}_3\text{CCH}_3 + \text{CH}_3\text{CH}_2\text{CCH}_2\text{CH}_3 \)

c. \( \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O} + \text{CH}_3\text{CH}_2\text{O} \)

d. \( \text{HCH} + \text{CH}_3\text{CH}_2\text{O} \)

PROBLEM 22

Describe how the following compounds could be prepared using an aldol addition in the first step of the synthesis:

a. \( \text{CH}_3\text{CH}_2\text{CCHCH}_2\text{OH} \)

b. \( \text{CH}_3\text{CH}_2\text{CH}==\text{CCHCH2CH3} \)

c. \( \text{CH}_3\text{CH}_2\text{CH}==\text{CCHCH2CH3} \)

PROBLEM 23

Propose a mechanism for the following reaction:

\[
\text{HO}^- + \text{CH}_3\text{CH}_2\text{CCHCH}_2\text{OH} \rightarrow \text{CH}_3\text{CH}_2\text{CCHCH}_2\text{OH} + \text{HO}^-
\]

Ludwig Claisen (1851–1930) was born in Germany and received a Ph.D. from the University of Bonn, studying under Kekulé. He was a professor of chemistry at the University of Bonn, Owens College (Manchester, England), the University of Munich, the University of Aachen, the University of Kiel, and the University of Berlin.

19.14 The Claisen Condensation

When two molecules of an ester undergo a condensation reaction, the reaction is called a Claisen condensation. The product of a Claisen condensation is a \( \beta \)-keto ester.

\[
2 \text{CH}_3\text{CH}_2\text{COCH}_2\text{CH}_3 \xrightarrow{1. \text{CH}_3\text{CH}_2\text{O}^-} \xrightarrow{2. \text{HCl}} \text{CH}_3\text{CH}_2\text{C}==\text{CHCOCH}_2\text{CH}_3 + \text{CH}_3\text{CH}_2\text{OH}
\]

As in an aldol addition, in a Claisen condensation one molecule of carbonyl compound is converted into an enolate when an \( \alpha \)-hydrogen is removed by a strong base. The enolate attacks the carbonyl carbon of a second molecule of ester. The base employed corresponds to the leaving group of the ester so that the reactant is not changed if the base acts as a nucleophile and attacks the carbonyl group (Section 19.10).
After nucleophilic attack, the Claisen condensation and the aldol addition differ. In the Claisen condensation, the negatively charged oxygen reforms the carbon–oxygen bond and expels the group. In the aldol addition, the negatively charged oxygen obtains a proton from the solvent.

The difference between the last step of the Claisen condensation and the last step of the aldol addition arises from the difference between esters and aldehydes or ketones. With esters, the carbon to which the negatively charged oxygen is bonded is also bonded to a group that can be expelled. With aldehydes or ketones, the carbon to which the negatively charged oxygen is bonded is not bonded to a group that can be expelled. Thus, the Claisen condensation is a substitution reaction, whereas the aldol addition is an addition reaction.

Expulsion of the alkoxide ion is reversible because the alkoxide ion can readily reform the tetrahedral intermediate by reacting with the β-keto ester. The condensation reaction can be driven to completion, however, if a proton is removed from the β-keto ester. Removing a proton prevents the reverse reaction from occurring, because the negatively charged alkoxide ion will not react with the negatively charged β-keto ester anion. It is easy to remove a proton from the β-keto ester because its central α-carbon is flanked by two carbonyl groups, making its α-hydrogen much more acidic than the α-hydrogens of the ester starting material.
Consequently, a successful Claisen condensation requires an ester with two \( \alpha \)-hydrogens and an equivalent amount of base rather than a catalytic amount of base. When the reaction is over, addition of acid to the reaction mixture reprotonates the \( \beta \)-keto ester anion. Any remaining alkoxide ion that could cause the reaction to reverse would also be protonated.

\[
\begin{align*}
\text{RCH}_2\text{C} & \quad \text{COO} \quad + \quad \text{CH}_3\text{CH}_2\text{O}^- \quad \text{HCl} \quad \rightarrow \\
\text{RCH}_2\text{C} & \quad \text{CH} \quad \text{COO} \quad + \quad \text{CH}_3\text{CH}_2\text{OH}
\end{align*}
\]

**PROBLEM 24**

Give the products of the following reactions:

a. \( \text{CH}_3\text{CH}_2\text{CH}_2\text{COCH}_3 \quad 1. \text{CH}_3\text{CH}_2\text{O}^- \quad 2. \text{HCl} \)

b. \( \text{CH}_3\text{CHCH}_2\text{COCH}_2\text{CH}_3 \quad 1. \text{CH}_3\text{CH}_2\text{O}^- \quad 2. \text{HCl} \)

**PROBLEM 25**

Explain why a Claisen condensation product is not obtained from esters such as ethyl benzoate and ethyl 2-methylbutanoate.

### 19.15 The Mixed Claisen Condensation

A *mixed Claisen condensation* is a condensation reaction between two different esters. Like a mixed aldol addition, a mixed Claisen condensation is a useful reaction only if it is carried out under conditions that foster the formation of primarily one product. Otherwise, a mixture of products that are difficult to separate will be formed. Primarily one product will be formed if one of the esters has no \( \alpha \)-hydrogens (and therefore cannot form an enolate) and the other ester is added slowly so that the ester without \( \alpha \)-hydrogens is always in excess.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{COCH}_2\text{CH}_3 & \quad + \quad \text{excess} \quad \text{add slowly} \\
\rightarrow & \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{COCH}_3 \quad \text{CH}_3\text{CH}_2\text{OH} \quad \text{CH}_3\text{CH}_2\text{O}^- \quad 1. \text{HCl} \quad 2. \text{HCl}
\end{align*}
\]

A reaction similar to a mixed Claisen condensation is the condensation of a ketone and an ester. Because the \( \alpha \)-hydrogens of a ketone are more acidic than those of an ester, primarily one product is formed if the ketone and the base are each added slowly to the ester. The product is a \( \beta \)-diketone. Because of the difference in acidities of the \( \alpha \)-hydrogens, primarily one condensation product is obtained even if both reagents have \( \alpha \)-hydrogens.

\[
\begin{align*}
\text{add slowly} & \quad \text{ethyl acetate} \\
\rightarrow & \quad \text{a } \beta \text{-diketone} \quad \text{add slowly}
\end{align*}
\]
A β-keto aldehyde is formed when a ketone condenses with a formate ester.

\[
\text{ketone} + \text{ethyl formate} \xrightarrow{\text{add slowly}} \underbrace{\text{excess}}_{\text{excess}} \xrightarrow{1. \text{CH}_3\text{CH}_2\text{O}^-} \xrightarrow{2. \text{HCl}} \text{a β-keto aldehyde} + \text{CH}_3\text{CH}_2\text{OH}
\]

A β-keto ester is formed when a ketone condenses with diethyl carbonate.

\[
\text{ketone} + \text{diethyl carbonate} \xrightarrow{\text{add slowly}} \underbrace{\text{excess}}_{\text{excess}} \xrightarrow{1. \text{CH}_3\text{CH}_2\text{O}^-} \xrightarrow{2. \text{HCl}} \text{a β-keto ester} + \text{CH}_3\text{CH}_2\text{OH}
\]

**PROBLEM 26**

Give the product of each of the following reactions:

a. \(\text{CH}_3\text{CH}_2\text{COCH}_3 + \text{CH}_3\text{COCH}_3 \xrightarrow{1. \text{CH}_3\text{CH}_2\text{O}^-} \xrightarrow{2. \text{HCl}}\)

b. \(\text{CCH}_3 + \text{COCH}_2\text{CH}_3 \xrightarrow{1. \text{CH}_3\text{CH}_2\text{O}^-} \xrightarrow{2. \text{HCl}}\)

c. \(\text{HCOCH}_3 + \text{CH}_3\text{CH}_2\text{CH}_2\text{COCH}_3 \xrightarrow{1. \text{CH}_3\text{CH}_2\text{O}^-} \xrightarrow{2. \text{HCl}}\)

d. \(\text{CH}_3\text{CH}_2\text{OCOCH}_2\text{CH}_3 + \text{CH}_3\text{CH}_2\text{COCH}_2\text{CH}_3 \xrightarrow{1. \text{CH}_3\text{CH}_2\text{O}^-} \xrightarrow{2. \text{HCl}}\)

**PROBLEM 27 SOLVED**

Show how the following compounds could be prepared, starting with 3-cyanocyclohexanone:

a. \(\text{O} \quad \text{O} \quad \text{CCH}_2\text{CH}_3 \quad \text{C=N}\)

b. \(\text{O} \quad \text{CH}_2\text{CH}_2\text{CCH}_3 \quad \text{C=N}\)

**SOLUTION TO 27a** Because the desired compound is a 1,3-dicarbonyl compound, it can be prepared by treating an enolate with an ester.
SOLUTION TO 27b  Because the desired compound is a 1,5-dicarbonyl compound, it can be prepared by a Michael reaction—treating an enolate with an \( \alpha,\beta \)-unsaturated carbonyl compound.

19.16 Intramolecular Condensation and Addition Reactions

We have seen that if a compound has two functional groups that can react with each other, an intramolecular reaction readily occurs if the reaction leads to the formation of five- or six-membered rings (Section 11.11). Consequently, if base is added to a compound that contains two carbonyl groups, an intramolecular reaction occurs if a product with a five- or six-membered ring can be formed. Thus, a compound with two ester groups undergoes an intramolecular Claisen condensation, and a compound with two aldehyde or ketone groups undergoes an intramolecular aldol addition.

Intramolecular Claisen Condensations

The addition of base to a 1,6-diester causes the diester to undergo an intramolecular Claisen condensation, thereby forming a five-membered ring \( \beta \)-keto ester. An intramolecular Claisen condensation is called a Dieckmann condensation.

![Diagram of Dieckmann condensation]

A six-membered ring \( \beta \)-keto ester is formed from a Dieckmann condensation of a 1,7-diester.

![Diagram of Dieckmann condensation]

The mechanism of the Dieckmann condensation is the same as the mechanism of the Claisen condensation. The only difference between the two reactions is that the attacking enolate and the carbonyl group undergoing nucleophilic attack are in different molecules in the Claisen condensation, but are in the same molecule in the Dieckmann condensation. The Dieckmann condensation, like the Claisen condensation, is driven...
to completion by carrying out the reaction with enough base to remove a proton from the α-carbon of the β-keto ester product. When the reaction is over, acid is added to reprotonate the condensation product.

**Problem 28**

Write the mechanism for the base-catalyzed formation of a cyclic β-keto ester from a 1,7-diester.

### Intramolecular Aldol Additions

Because a 1,4-diketone has two different sets of α-hydrogens, two different intramolecular addition products can potentially form—one with a five-membered ring, the other with a three-membered ring. The greater stability of five- and six-membered rings causes them to be formed preferentially (Section 2.11). In fact, the five-membered ring product is the only product formed from the intramolecular aldol addition of a 1,4-diketone.

The intramolecular aldol addition of a 1,6-diketone potentially can lead to either a seven- or a five-membered ring product. Again, the more stable product—the one with the five-membered ring—is the only product of the reaction.

1,5-Diketones and 1,7-diketones undergo intramolecular aldol additions to form six-membered ring products.
PROBLEM 29
If the preference for formation of a six-membered ring were not so great, what other cyclic product would be formed from the intramolecular aldol addition of
a. 2,6-heptanedione?  
b. 2,8-nonanedione?

PROBLEM 30
Can 2,4-pentanedione undergo an intramolecular aldol addition? If so, why? If not, why not?

PROBLEM 31 SOLVED
What products can be obtained if the following keto aldehyde is treated with a base? Which would you expect to be the major product?

SOLUTION  Three products are possible because there are three different sets of α-hydrogens. More B and C are formed than A because a five-membered ring is formed in preference to a seven-membered ring. The major product depends on the reaction conditions. B is the thermodynamic product because it is formed from the more stable enolate. C is the kinetic product because the α-hydrogen of the aldehyde is more acidic than the α-hydrogen of the ketone (Table 19.1).
PROBLEM 32

Give the product of the reaction of each of the following compounds with a base:

a. \[
\begin{array}{c}
\text{O} \\
\text{CH}_2\text{CH}_2\text{CCH}_3
\end{array}
\]

b. \[
\begin{array}{c}
\text{O} \\
\text{CH}_2\text{CH}_2\text{CCH}_3
\end{array}
\]

c. \[
\begin{array}{c}
\text{O} \\
\text{HCCCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}
\end{array}
\]

d. \[
\begin{array}{c}
\text{O} \\
\text{CH}_2\text{CH}_2\text{CCH}_3
\end{array}
\]

The Robinson Annulation

Reactions that form carbon–carbon bonds are important to synthetic chemists. Without such reactions, large organic molecules could not be prepared from smaller ones. We have seen that Michael reactions and aldol additions form carbon–carbon bonds. The Robinson annulation is a reaction that puts these two carbon–carbon bond-forming reactions together, providing a route to the synthesis of many complicated organic molecules. “Annulation” comes from annulus, Latin for “ring.” Thus, an annulation reaction is a ring-forming reaction.

The first stage of a Robinson annulation is a Michael reaction that forms a 1,5-diketone. You just saw that a 1,5-diketone undergoes an intramolecular aldol addition when treated with base—this is the second stage of the Robinson annulation. Notice that a Robinson annulation results in a product that has a 2-cyclohexenone ring.

Sir Robert Robinson (1886–1975) was born in England, the son of a manufacturer. After receiving a Ph.D. from the University of Manchester, he joined the faculty at the University of Sydney in Australia. He returned to England three years later, becoming a professor of chemistry at Oxford in 1929. Robinson was an accomplished mountain climber. Knighted in 1939, he received the 1947 Nobel Prize in chemistry for his work on alkaloids.

PROBLEM-SOLVING STRATEGY

Propose a synthesis for each of the following compounds, using a Robinson annulation:

a. \[
\begin{array}{c}
\text{O} \\
\text{CH}_2\text{CH} = \text{CCH}_3
\end{array}
\]

b. \[
\begin{array}{c}
\text{O} \\
\text{CH}_2\text{CH} = \text{CCH}_3
\end{array}
\]

By analyzing a Robinson annulation, we will be able to determine which part of the molecule comes from which reactant. This, then, will allow us to choose appropriate reactants for any other Robinson annulation. Analysis shows that the keto group of the cyclohexenone comes from the \(\alpha,\beta\)-unsaturated carbonyl compound and the double bond results from attack of the enolate of the \(\alpha,\beta\)-unsaturated carbonyl compound on the carbonyl group of the other reactant. Thus, we can arrive at the appropriate reactants by cutting through the double bond and cutting between the \(\beta\)- and \(\gamma\)-carbons on the other side of the carbonyl group.
Therefore, the required reactants for (a) are:

\[
\text{CH}_2=\text{CHCH}_3 + \text{CH}_3\text{CH}_2\text{CH} \xrightleftharpoons[\Delta]{\text{HO}^-} \text{CH}_3\text{C} (=\text{O})\text{C}=\text{O}
\]

By cutting through (b), we can determine the required reactants for its synthesis:

Therefore, the required reactants for (b) are:

\[
\text{CH}_2=\text{CCH}_3 + \text{CH}_3\text{CCH}_3 \xrightarrow[\Delta]{\text{HO}^-} \text{CH}_3\text{C} (=\text{O})\text{C}=\text{O}
\]

Now continue on to Problem 33.

**PROBLEM 33**

Propose a synthesis for each of the following compounds, using a Robinson annulation:

a. 

b. 

c. 

d. 

---

**19.17 Decarboxylation of 3-Oxocarboxylic Acids**

Carboxylate ions do not lose CO₂, for the same reason that alkanes such as ethane do not lose a proton—because the leaving group would be a carbanion. Carbanions are very strong bases and therefore are very poor leaving groups.
If, however, the CO₂ group is bonded to a carbon that is adjacent to a carbonyl
carbon, the CO₂ group can be removed because the electrons left behind can be delo-
calized onto the carbonyl oxygen. Consequently, 3-oxocarboxylate ions (carboxylate
ions with a keto group at the 3-position) lose CO₂ when they are heated. Loss of CO₂
from a molecule is called **decarboxylation**.

Notice the similarity between removal of CO₂ from a 3-oxocarboxylate ion and
removal of a proton from an α-carbon. In both reactions, a substituent—CO₂ in one
case, H⁺ in the other—is removed from an α-carbon and its bonding electrons are
delocalized onto an oxygen.

Decarboxylation is even easier if the reaction is carried out under acidic conditions,
because the reaction is catalyzed by an intramolecular transfer of a proton from the
carboxyl group to the carbonyl oxygen. The enol that is formed immediately tau-
tomerizes to a ketone.

We saw in Section 19.1 that it is harder to remove a proton from an α-carbon if
the electrons are delocalized onto the carbonyl group of an ester rather than onto the
carbonyl group of a ketone. For the same reason, a higher temperature is required to
decarboxylate a β-dicarboxylic acid such as malonic acid than to decarboxylate a
β-keto acid.
In summary, carboxylic acids with a carbonyl group at the 3-position (both \(\beta\)-ketocarboxylic acids and \(\beta\)-dicarboxylic acids) lose \(\text{CO}_2\) when they are heated.

\[
\begin{align*}
\text{3-oxohexanoic acid} \quad &\xrightarrow{\Delta} \quad \text{2-pentanone} + \text{CO}_2 \\
\text{2-oxocyclohexane-carboxylic acid} \quad &\xrightarrow{\Delta} \quad \text{cyclohexanone} + \text{CO}_2 \\
\text{\(\alpha\)-methylmalonic acid} \quad &\xrightarrow{\Delta} \quad \text{propionic acid} + \text{CO}_2
\end{align*}
\]

The Hunsdiecker Reaction

Heinz and Clare Hunsdiecker found that a carboxylic acid can be decarboxylated if a heavy metal salt of the carboxylic acid is heated with bromine or iodine. The product is an alkyl halide with one less carbon atom than the starting carboxylic acid. The heavy metal can be silver ion, mercuric ion, or lead(IV). The reaction is now known as the Hunsdiecker reaction.

\[
\begin{align*}
\text{pentanoic acid} + \text{Ag}_2\text{O} \quad &\xrightarrow{2. \text{Br}_2, \Delta} \quad \text{bromobutane} + \text{CO}_2 + \text{AgBr} \\
\end{align*}
\]

The reaction involves formation of a hypobromite as a result of precipitation of AgBr. A radical reaction is initiated by homolytic cleavage of the O-Br bond of the hypobromite. The carboxyl radical loses \(\text{CO}_2\), and the alkyl radical thus formed abstracts a bromine radical from the hypobromite to propagate the reaction.

\[
\begin{align*}
\text{RCO}^-\text{Ag}^+ + \text{Br}_2 \quad &\rightarrow \quad \text{RCO}^-\text{Br} + \text{AgBr} \\
\end{align*}
\]

a hypobromite

PROBLEM 34

Which of the following compounds would be expected to decarboxylate when heated?

a. \[
\begin{align*}
\text{HO} &\quad \text{OH} \\
\end{align*}
\]

b. \[
\begin{align*}
\text{O} &\quad \text{O} \\
\end{align*}
\]

c. \[
\begin{align*}
\text{HO} &\quad \text{OH} \\
\end{align*}
\]

d. \[
\begin{align*}
\text{O} &\quad \text{O} \\
\end{align*}
\]
The Malonic Ester Synthesis: Synthesis of Carboxylic Acids

A combination of two of the reactions discussed in this chapter—alkylation of an α-carbon and decarboxylation of a β-dicarboxylic acid—can be used to prepare carboxylic acids of any desired chain length. The procedure is called the malonic ester synthesis because the starting material for the synthesis is the diethyl ester of malonic acid. The first two carbons of the carboxylic acid come from malonic ester, and the rest of the carboxylic acid comes from the alkyl halide used in the second step of the reaction.

In the first part of the malonic ester synthesis, the α-carbon of the diester is alkylated (Section 19.8). A proton is easily removed from the α-carbon because it is flanked by two ester groups \( (pK_a = 13) \). The resulting α-carbanion reacts with an alkyl halide, forming an α-substituted malonic ester. Because alkylation is an \( S_N2 \) reaction, it works best with methyl halides and primary alkyl halides (Section 10.2). Heating the α-substituted malonic ester in an acidic aqueous solution hydrolyzes it to an α-substituted malonic acid, which, upon further heating, loses \( CO_2 \), forming a carboxylic acid with two more carbons than the alkyl halide.

**PROBLEM 35**

What alkyl bromide(s) should be used in the malonic ester synthesis of each of the following carboxylic acids?

a. propanoic acid  

b. 2-methylpropanoic acid  

c. 3-phenylpentanoic acid  

d. 4-methylpentanoic acid
Carboxylic acids with two substituents bonded to the α-carbon can be prepared by carrying out two successive α-carbon alkylations.

PROBLEM 36

Explain why the following carboxylic acids cannot be prepared by the malonic ester synthesis:

a. \( \text{CH}_2\text{CH}_2\text{COH} \)

b. \( \text{CH}_2=\text{CHCH}_2\text{COH} \)

c. \( \text{CH}_3\text{CCH}_2\text{COH} \)

19.19 The Acetoacetic Ester Synthesis: Synthesis of Methyl Ketones

The only difference between the acetoacetic ester synthesis and the malonic ester synthesis is the use of acetoacetic ester rather than malonic ester as the starting material. The difference in starting material causes the product of the acetoacetic ester synthesis to be a methyl ketone rather than a carboxylic acid. The carbonyl group of the methyl ketone and the carbon atoms on either side of it come from acetoacetic ester, and the rest of the ketone comes from the alkyl halide used in the second step of the reaction.
The mechanisms for the acetoacetic ester synthesis and the malonic ester synthesis are similar. The last step in the acetoacetic ester synthesis is the decarboxylation of a substituted acetoacetic acid rather than a substituted malonic acid.

PROBLEM 37 SOLVED

Starting with methyl propanoate, how could you prepare 4-methyl-3-heptanone?

Because the target molecule has several more carbon atoms than the starting material, a Claisen condensation appears to be a good way to start this synthesis. The Claisen condensation forms a β-keto ester that can be alkylated at the desired carbon because it is flanked by two carbonyl groups. Acid-catalyzed hydrolysis will form a 3-oxocarboxylic acid that will decarboxylate when heated.

PROBLEM 38

What alkyl bromide should be used in the acetoacetic ester synthesis of each of the following methyl ketones?

a. 2-pentanone
b. 2-octanone
c. 4-phenyl-2-butane
### 19.20 Designing a Synthesis VI: Making New Carbon–Carbon Bonds

When you are planning the synthesis of a compound that requires the formation of a new carbon–carbon bond, first locate the new bond that must be made. For example, in the synthesis of the following β-diketone, the new bond is the one that makes the second five-membered ring:

Next, determine which of the atoms that form the bond should be the nucleophile and which should be the electrophile. In this case, it is easy to choose between the two possibilities because you know that a carbonyl carbon is an electrophile.

Now you need to determine what compound you could use that would give you the desired electrophilic and nucleophilic sites. If the starting material is indicated, use it as a clue to arrive at the desired compound. For example, an ester carbonyl group would be a good electrophile for this synthesis because it has a group that would be eliminated. Furthermore, the α-hydrogens of the ketone are more acidic than the α-hydrogens of the ester, so it would be easy to obtain the desired nucleophile. The ester can be easily prepared from the carboxylic acid starting material.

In the next synthesis, two new carbon–carbon bonds must be formed.

After determining the electrophilic and nucleophilic sites, you can see that two successive alkylations of a diester of malonic acid, using 1,5-dibromopentane for the alkyl halide, will produce the desired compound.
In planning the following synthesis, the diester that is given as the starting material suggests that you should use a Dieckmann condensation to obtain the cyclic compound:

After the cyclopentanone ring is formed from a Dieckmann condensation of the starting material, alkylation of the $\alpha$-carbon followed by hydrolysis of the $\beta$-keto ester and decarboxylation forms the desired product.

**PROBLEM 39**

Design a synthesis for each of the following compounds:

a. \[
\begin{align*}
\text{O} & \quad \text{CCH}_3 \\
& \rightarrow \\
& \text{O} \quad \text{CCH}_2\text{CH}_3
\end{align*}
\]

b. \[
\begin{align*}
\text{CH}_3\text{OCCH}_2\text{CH}_2\text{COCH}_3 & \rightarrow \\
& \text{O} \quad \text{O} \quad \text{CH}_3\text{CH}_2
\end{align*}
\]

c. \[
\begin{align*}
\text{CH} & \rightarrow \\
& \text{CH}=\text{CHCOH}
\end{align*}
\]

d. \[
\begin{align*}
\text{CH}_3\text{OCCH}_2\text{COCH}_3 & \rightarrow \\
& \text{O} \quad \text{O} \quad \text{COH}
\end{align*}
\]
Many reactions that occur in biological systems involve reactions at the \( \alpha \)-carbon—the kinds of reactions you have studied in this chapter. We will now look at a few examples.

**A Biological Aldol Addition**

\( \text{D-Glucose} \), the most abundant sugar found in nature, is synthesized by biological systems from two molecules of pyruvate. The series of reactions that convert two molecules of pyruvate into \( \text{D-glucose} \) is called **gluconeogenesis**. The reverse process—the breakdown of \( \text{D-glucose} \) into two molecules of pyruvate—is called **glycolysis** (Section 25.1).

Because \( \text{D-glucose} \) has twice as many carbons as pyruvate, it should not be surprising that one of the steps in the biosynthesis of \( \text{D-glucose} \) is an aldol addition. An enzyme called aldolase catalyzes an aldol addition between dihydroxyacetone phosphate and \( \text{D-glyceraldehyde-3-phosphate} \). The product is \( \text{D-fructose-1,6-diphosphate} \), which is subsequently converted to \( \text{D-glucose} \). The mechanism of this reaction is discussed in Section 24.9.

**PROBLEM 40**

Propose a mechanism for the formation of \( \text{D-fructose-1,6-diphosphate} \) from dihydroxyacetone phosphate and \( \text{D-glyceraldehyde-3-phosphate} \), using \( \text{HO}^- \) as the catalyst.

**A Biological Aldol Condensation**

Collagen is the most abundant protein in mammals, amounting to about one-fourth of the total protein. It is the major fibrous component of bone, teeth, skin, cartilage, and tendons. It also is responsible for holding groups of cells together in discrete units. Individual collagen molecules—called tropocollagen—can be isolated only from tissues of young animals. As animals age, the individual molecules become cross-linked, which is why meat from older animals is tougher than meat from younger ones. Collagen cross-linking is an example of an aldol condensation.
Before collagen molecules can cross-link, the primary amino groups of the lysine residues of collagen must be converted to aldehyde groups. The enzyme that catalyzes this reaction is called lysyl oxidase. An aldol condensation between two aldehyde residues results in a cross-linked protein.

**A Biological Claisen Condensation**

Fatty acids are long-chain, unbranched carboxylic acids (Sections 17.13 and 26.1). Most naturally occurring fatty acids contain an even number of carbons because they are synthesized from acetate, which has two carbon atoms.

In Section 17.20, you saw that carboxylic acids can be activated in biological systems by being converted to thioesters of coenzyme A.

\[
\text{CH}_3\text{C}(-\text{O})^- + \text{CoASH} + \text{ATP} \rightarrow \text{CH}_3\text{C}(-\text{S})\text{CoA} + \text{AMP} + \text{pyrophosphate}
\]

One of the necessary reactants for fatty acid synthesis is malonyl-CoA, which is obtained by carboxylation of acetyl-CoA. The mechanism for this reaction is discussed in Section 25.5.

\[
\text{CH}_3\text{C}(-\text{S})\text{CoA} + \text{HCO}_3^- \rightarrow \text{H}_2\text{C}\text{C}(-\text{S})\text{CoA}
\]

Before fatty acid synthesis can occur, however, the acyl groups of acetyl-CoA and malonyl-CoA are transferred to other thiols by means of a transesterification reaction.

\[
\text{CH}_3\text{C}(-\text{S})\text{CoA} + \text{RSH} \rightarrow \text{CH}_3\text{C}(-\text{S})\text{R} + \text{CoASH}
\]

\[
\text{H}_2\text{C}\text{C}(-\text{S})\text{CoA} + \text{RSH} \rightarrow \text{H}_2\text{C}\text{C}(-\text{S})\text{R} + \text{CoASH}
\]
The first step in the biosynthesis of a fatty acid is a Claisen condensation between a molecule of acetyl thioester and a molecule of malonyl thioester. You have seen that, in the laboratory, the nucleophile needed for a Claisen condensation is obtained by using a strong base to remove an α-hydrogen. Strong bases are not available for biological reactions because they take place at neutral pH. So the required nucleophile is generated by removing — rather than a proton—from the α-carbon of malonyl thioester. (Recall that 3-oxocarboxylic acids are easily decarboxylated; Section 19.17.) Loss of CO₂ also serves to drive the condensation reaction to completion. The product of the condensation reaction undergoes a reduction, a dehydration, and a second reduction to give a four-carbon thioester.

The four-carbon thioester undergoes a Claisen condensation with another molecule of malonyl thioester. Again, the product of the condensation reaction undergoes a reduction, a dehydration, and a second reduction, this time to form a six-carbon thioester. The sequence of reactions is repeated, and each time two more carbons are added to the chain. This mechanism explains why naturally occurring fatty acids are unbranched and generally contain an even number of carbons.

Once a thioester with the appropriate number of carbon atoms is obtained, it undergoes a transesterification reaction with glycerol in order to form fats, oils, and phospholipids (Sections 26.3 and 26.4).

### PROBLEM 41

Palmitic acid (hexadecanoic acid) is a saturated 16-carbon fatty acid. How many moles of malonyl-CoA are required for the synthesis of one mole of palmitic acid?

### PROBLEM 42

a. If the biosynthesis of palmitic acid were carried out with CD₃COSR and nondeuterated malonyl thioester, how many deuteriums would be incorporated into palmitic acid?
b. If the biosynthesis of palmitic acid were carried out with OOCDCO₂COSR and nondeuterated acetyl thioester, how many deuteriums would be incorporated into palmitic acid?

### A Biological Decarboxylation

An example of a decarboxylation that occurs in biological systems is the decarboxylation of acetoacetate. Acetoacetate decarboxylase, the enzyme that catalyzes the reaction, first forms an imine with acetoacetate. The imine is protonated under physiological conditions...
and therefore readily accepts the pair of electrons left behind when the substrate loses CO₂. Decarboxylation forms an enamine. Hydrolysis of the enamine produces the decarboxylated product (acetone) and regenerates the enzyme (Section 18.6).

PROBLEM 43

When the enzymatic decarboxylation of acetoacetate is carried out in H₂¹⁸O, the acetone that is formed contains ¹⁸O. What does this tell you about the mechanism of the reaction?

Summary

A hydrogen bonded to an α-carbon of an aldehyde, ketone, ester, or N,N-disubstituted amide is sufficiently acidic to be removed by a strong base because the base that is formed when the proton is removed is stabilized by delocalization of its negative change onto an oxygen. A carbon acid is a compound with a relatively acidic hydrogen bonded to an sp³ hybridized carbon. Aldehydes and ketones (pKₐ ≈ 16–20) are more acidic than esters (pKₐ ≈ 25). β-Diketones (pKₐ ≈ 9) and β-keto esters (pKₐ ≈ 11) are even more acidic.

Keto–enol interconversion can be catalyzed by acids or by bases. Generally, the keto tautomer is more stable. When an α-substitution reaction takes place under acidic conditions, an enol reacts with an electrophile; when the reaction takes place under basic conditions, an enolate ion reacts with an electrophile. Whether C or O reacts with the electrophile depends on the electrophile and the reaction conditions.

Aldehydes and ketones react with Br₂, Cl₂, or I₂. Under acidic conditions, a halogen replaces one of the α-hydrogens of the carbonyl compound; under basic conditions, halogens replace all the α-hydrogens. The HVZ reaction brominates the α-carbon of a carboxylic acid. When the α-position is halogenated, the α-carbon reacts with nucleophiles.

LDA is used to form an enolate in reactions that require the carbonyl compound to be completely converted to enolate before it reacts with an electrophile. If the electrophile is an alkyl halide, the enolate is alkylated. The less substituted α-carbon is alkylated when the reaction is under kinetic control; the more substituted α-carbon is alkylated when the reaction is under thermodynamic control. Aldehydes and ketones can be alkylated or acylated via an enamine intermediate. Enolates of β-diketones, β-diesters, β-keto esters, and β-keto nitriles undergo Michael reactions with α,β-unsaturated carbonyl compounds. Michael reactions form 1,5-dicarbonyl compounds.

In an aldol addition, the enolate of an aldehyde or a ketone reacts with the carbonyl carbon of a second molecule of aldehyde or ketone, forming a β-hydroxylaldehyde or a β-hydroxyketone. The new C—C bond forms between the α-carbon of one molecule and the carbon that formerly was the carbonyl carbon of the other molecule. The product of an aldol addition can be dehydrated to give an aldol condensation product. In a Claisen condensation, the enolate of an ester reacts with a second molecule of ester, eliminating an −OR group to form a β-keto ester. A Dieckmann condensation is an intramolecular Claisen condensation. A Robinson annulation is a ring-forming reaction in which a Michael reaction and an intramolecular aldol addition occur sequentially.

Carboxylic acids with a carbonyl group at the 3-position decarboxylate when they are heated. Carboxylic acids can be prepared by a malonic ester synthesis; the α-carbon of the diester is alkylated and the α-substituted malonic ester undergoes acid-catalyzed hydrolysis and decarboxylation;
the resulting carboxylic acid has two more carbon atoms than the alkyl halide. Similarly, methyl ketones can be prepared by an acetoacetic ester synthesis; the carbonyl group and the carbon atoms on either side of it come from acetoacetic ester, and the rest of the methyl ketone comes from the alkyl halide.

When planning the synthesis of a compound that requires the formation of a new carbon–carbon bond, first locate the new bond that must be made, and then determine which of the atoms that form the bond should be the nucleophile and which should be the electrophile.

**Summary of Reactions**

1. Halogenation of the $\alpha$-carbon of aldehydes and ketones (Section 19.4).

\[
\text{RCH}_2\text{CH} + \text{X}_2 \xrightarrow{\text{H}_2\text{O}^+} \text{RCH}_2\text{CH} + \text{HX}
\]

\[
\text{RCH}_2\text{CR} + \text{X}_2 \xrightarrow{\text{HO}^- \text{ excess}} \text{RCH}_2\text{CR} + 2\text{X}^-
\]

\[X_2 = \text{Cl}_2, \text{Br}_2, \text{or I}_2\]

2. Halogenation of the $\alpha$-carbon of carboxylic acids: the Hell–Volhard–Zelinski reaction (Section 19.5).

\[
\text{RCH}_2\text{COH} \xrightarrow{1. \text{PBr}_3 (or \text{P}), \text{Br}_2} \xrightarrow{2. \text{H}_2\text{O}} \text{RCHCOH}
\]

3. The $\alpha$-carbon can serve as a nucleophile and react with an electrophile (Section 19.6).

\[
\text{RCHCR} \xrightarrow{\text{base}} \text{RCHCR} \xrightarrow{\text{E}^+} \text{RCHCR}
\]

4. The $\alpha$-carbon can serve as an electrophile and react with a nucleophile (Section 19.6).

\[
\text{RCHCR} \xrightarrow{\text{H}_2\text{O}^+} \text{Br}_2 \xrightarrow{\text{Br}} \text{RCHCR} \xrightarrow{\text{Nu}} \text{RCHCR}
\]

5. Compounds with halogenated $\alpha$-carbons can form $\alpha,\beta$-unsaturated carbonyl compounds (Section 19.6).

\[
\text{RCH}_2\text{CHCR} \xrightarrow{\text{base}} \text{RCH} \equiv \text{CHCR}'
\]
6. Alkylation of the α-carbon of carbonyl compounds (Section 19.8).

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{HCl}^+ \\
\text{O} & \\
\text{RCH}_2\text{CR}' & \quad \text{1. LDA/THF} \\
\text{2. RCH}_2\text{X} & \quad \text{RCHCR'} \\
\text{X} = \text{halogen} & \\
\text{O} & \\
\text{RCH}_2\text{COR}' & \quad \text{1. LDA/THF} \\
\text{2. RCH}_2\text{X} & \quad \text{RCHCOR'} \\
\text{RCH}_2\text{C}==\text{N} & \quad \text{1. LDA/THF} \\
\text{2. RCH}_2\text{X} & \quad \text{RCHC}==\text{N}
\end{align*}
\]

7. Alkylation and acylation of the α-carbon of aldehydes and ketones by means of an enamine intermediate (Sections 19.9 and 19.10).

8. Michael reaction: attack of an enolate on an α,β-unsaturated carbonyl compound (Section 19.10).

9. Aldol addition of two aldehydes, two ketones, or an aldehyde and a ketone (Sections 19.11 and 19.13).

10. Aldol condensation: dehydration of the product of an aldol addition (Section 19.12).

12. Condensation of a ketone and an ester (Section 19.15).

\[
\begin{align*}
\text{O} & \quad \text{O} \\
+ \quad & \quad \text{RCOCH}_3 \quad \text{excess} \quad 1. \text{CH}_3\text{O}^- \quad 2. \text{HCl} \quad \text{CR} \quad + \quad \text{CH}_3\text{OH} \\
\text{O} & \quad \text{O} \\
+ \quad & \quad \text{HCOCH}_2\text{CH}_3 \quad \text{excess} \quad 1. \text{CH}_3\text{CH}_2\text{O}^- \quad 2. \text{HCl} \quad \text{} \quad + \quad \text{CH}_3\text{CH}_2\text{OH} \\
\text{O} & \quad \text{O} \\
+ \quad & \quad \text{CH}_3\text{CH}_2\text{OCOCH}_2\text{CH}_3 \quad \text{excess} \quad 1. \text{CH}_3\text{CH}_2\text{O}^- \quad 2. \text{HCl} \quad \text{COCH}_2\text{CH}_3 \quad + \quad \text{CH}_3\text{CH}_2\text{OH}
\end{align*}
\]

13. Robinson annulation (Section 19.16).

\[
\begin{align*}
\text{CH}_2=\text{CHCCH}_3 & \quad + \quad \text{O} \\
\text{base} & \quad \text{a Michael reaction} \quad \text{an intramolecular aldol addition} \quad \Delta \quad \text{HO} \\
\text{O} & \quad \text{O} \\
\text{RCCH}_2\text{COH} & \quad \text{RCCH}_3 \quad \text{CO}_2 \quad + \quad \text{H}_2\text{O}
\end{align*}
\]


\[
\begin{align*}
\text{O} & \quad \text{O} \\
\Delta & \quad \text{RCCH}_2\text{COH} \quad \text{RCCH}_3 \quad \text{CO}_2
\end{align*}
\]

15. Malonic ester synthesis: preparation of carboxylic acids (Section 19.18).

\[
\begin{align*}
\text{C}_2\text{H}_5\text{OCCH}_2\text{COCH}_2\text{H}_3 & \quad 1. \text{CH}_3\text{CH}_2\text{O}^- \\
2. \text{RBr} \quad 3. \text{HCl, H}_2\text{O, } \Delta & \quad \text{RCH}_2\text{COH} \quad + \quad \text{CO}_2
\end{align*}
\]


\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{CH}_3\text{CH}_2\text{OCOCH}_2\text{H}_3 & \quad 1. \text{CH}_3\text{CH}_2\text{O}^- \\
2. \text{RBr} \quad 3. \text{HCl, H}_2\text{O, } \Delta & \quad \text{RCH}_2\text{CCH}_3 \quad + \quad \text{CO}_2
\end{align*}
\]

**Key Terms**

- acetoacetic ester synthesis (p. 822)
- α-carbon (p. 788)
- decarboxylation (p. 819)
- aldol addition (p. 806)
- carbon acid (p. 789)
- Dieckmann condensation (p. 814)
- aldol condensation (p. 807)
- Claisen condensation (p. 810)
- β-diketone (p. 791)
- ambident nucleophile (p. 794)
- condensation reaction (p. 807)
- enolization (p. 792)
- annulation reaction (p. 817)
- crossed aldol addition (p. 809)
- gluconeogenesis (p. 826)
Problems

44. Write a structure for each of the following:
   a. ethyl acetoacetate
   b. α-methylmalonic acid
   c. a β-keto ester
   d. the enol tautomer of cyclopentanone
   e. the carboxylic acid obtained from the malonic ester synthesis when the alkyl halide is propyl bromide

45. Give the products of the following reactions:
   a. diethyl heptanediode: (1) sodium ethoxide; (2) HCl
   b. pentanoic acid + PBr₃ + Br₂, followed by hydrolysis
   c. acetone + ethyl acetate: (1) sodium ethoxide; (2) HCl
   d. diethyl 2-ethylhexanediode: (1) sodium ethoxide; (2) HCl
   e. diethyl malonate: (1) sodium ethoxide; (2) isobutyl bromide; (3) HCl, H₂O + Δ
   f. acetoephone + diethyl carbonate: (1) sodium ethoxide; (2) HCl
   g. 1,3-cyclohexanediene + allyl bromide + sodium hydroxide
   h. dibenzyl ketone + methyl vinyl ketone + excess sodium hydroxide
   i. cyclopentanone: (1) pyrrolidine + catalytic H⁺; (2) ethyl bromide; (3) HCl, H₂O
   j. γ-butyrolactone + LDA in THF followed by methyl iodide
   k. 2,7-octanediene + sodium hydroxide
   l. cyclohexanone + NaOD in D₂O
   m. diethyl 1,2-benzencarboxylate + ethyl acetate: (1) excess sodium ethoxide; (2) HCl

46. The chemical shifts of nitromethane, dinitromethane, and trinitromethane are at δ 6.10, δ 4.33, and δ 7.52. Match each chemical shift with the compound. Explain how chemical shift correlates with pKₐ.

47. a. Explain why a racemic mixture of 2-methyl-1-phenyl-1-butane is formed when (R)-2-methyl-1-phenyl-1-butane is dissolved in an acidic or basic aqueous solution.
   b. Give an example of another ketone that would undergo acid- or base-catalyzed racemization.

48. Identify A–L. (Hint: A shows three singlets in its ¹H NMR spectrum with integral ratios 3 : 2 : 3 and gives a positive iodoform test; see Section 19.4)
49. Show how the following compounds could be prepared from cyclohexanone:

50. A β,γ-unsaturated carbonyl compound rearranges to a more stable conjugated α,β-unsaturated compound in the presence of either acid or base.
   a. Propose a mechanism for the base-catalyzed rearrangement.
   b. Propose a mechanism for the acid-catalyzed rearrangement.

51. There are other condensation reactions similar to the aldol and Claisen condensations:
   a. The Perkin condensation is the condensation of an aromatic aldehyde and acetic anhydride. Give the product obtained from the following Perkin condensation:

   b. What compound would result if water were added to the product of the Perkin condensation?
   c. The Knoevenagel condensation is the condensation of an aldehyde or a ketone that has no α-hydrogens and a compound such as diethyl malonate that has an α-carbon flanked by two electron-withdrawing groups. Give the product obtained from the following Knoevenagel condensation:

   d. What product would be obtained if the product of the Knoevenagel condensation were heated in an aqueous acidic solution?

52. The Reformatsky reaction is an addition reaction in which an organozinc reagent is used instead of a Grignard reagent to attack the carbonyl group of an aldehyde or a ketone. Because the organozinc reagent is less reactive than a Grignard reagent, a nucleophilic addition to the ester group does not occur. The organozinc reagent is prepared by treating an α-bromo ester with zinc.
Describe how each of the following compounds could be prepared, using a Reformatsky reaction:

a. CH₃CH₂CH₂CHCH₂COCH₃  
   \[ \text{ZnBr} \]  
   \[ \longrightarrow \]  
   CH₃CH₂CHCHCOCH₃  
   [\text{an organozinc reagent}]  
   \[ \longrightarrow \]  
   CH₃CH₂CHCHCOCH₃  
   a \beta\text{-hydroxy ester}

53. The ketone whose \(^1\)H NMR spectrum is shown here was obtained as the product of an acetoacetic ester synthesis. What alkyl halide was used in the synthesis?

54. Indicate how the following compounds could be synthesized from cyclohexanone and any other necessary reagents:

a. \( \text{CH}_3\text{CH}_2\text{CH}_2\text{CHCH}_2\text{COCH}_3 \)

b. \( \text{CH}_3\text{CH}_2\text{CHCHCOH} \)

55. Compound A with molecular formula C₆H₁₀ has two peaks in its \(^1\)H NMR spectrum, both of which are singlets (with ratio 9 : 1). Compound A reacts with an acidic aqueous solution containing mercuric sulfate to form compound B that gives a positive iodoform test (Section 19.4) and that has an \(^1\)H NMR spectrum that shows two singlets (with ratio 3 : 1). Identify A and B.
56. Indicate how each of the following compounds could be synthesized from the given starting material and any other necessary reagents:

a. \( \text{CH}_3\text{CH}_3 \rightarrow \text{CH}_3\text{CH}_2\text{CH} \)

b. \( \text{CH}_3\text{CCH}_2\text{COCH}_2\text{CH}_3 \rightarrow \text{CH}_3\text{CHCH}_2 \)

c. \( \text{CH}_2\text{CCH}_3 \rightarrow \text{CH}_2\text{CCH}_2\text{CH}_2\text{COH} \)

d. \( \text{CH}_3\text{C(CH}_2\text{)_3COCH}_3 \rightarrow \text{O} \)

e. \( \text{O} \rightarrow \text{O} \)

f. \( \text{CH}_3\text{CH}_2\text{OC(CH}_2\text{)_4COCH}_2\text{CH}_3 \rightarrow \text{O} \)

57. Bupropion hydrochloride is an antidepressant marketed under the trade name Wellbutrin®. Propose a synthesis of bupropion hydrochloride, starting with benzene.

\[
\begin{align*}
\text{Cl} & \quad \text{C} \quad \text{CH}_3 \\
\text{Cl} & \quad \text{C} \quad \text{NH}_3 \\
\text{C} & \quad \text{CH}_3 \\
\text{C} & \quad \text{C} \\
\text{H}_2 & \quad \text{C} \\
\text{H}_2 & \quad \text{C}
\end{align*}
\]

\( \text{bupropion hydrochloride} \)

58. What reagents would be required to carry out the following transformations?

\[
\begin{align*}
\text{CH} & \rightarrow \text{CHCH}_3 \\
\text{CH} & \rightarrow \text{CHCH}_3 \\
\text{CH} & \rightarrow \text{CHCO}^{-} \\
\text{CH} & \rightarrow \text{CHCOCH}_2\text{CH}_3 \\
\end{align*}
\]

59. Give the products of the following reactions:

a. \( 2 \text{CH}_3\text{CH}_2\text{OCCH}_2\text{CH}_2\text{COCH}_2\text{CH}_3 \xrightarrow{1. \text{CH}_3\text{CH}_2\text{O}^{-}} \xrightarrow{2. \text{H}_2\text{O}^{+}} \)

b. \( \begin{align*}
\text{CH} & \quad \text{O} \\
\text{CH} & \quad \text{O} \\
\end{align*} + \begin{align*}
\text{CH} & \quad \text{O} \\
\text{CH} & \quad \text{O} \\
\end{align*} \xrightarrow{\text{HO}^{-}} \)

60. a. Show how the amino acid alanine can be synthesized from propanoic acid.

b. Show how the amino acid glycine can be synthesized from phthalimide and diethyl 2-bromomalonate.
61. Cindy Synthon tried to prepare the following compounds using aldol condensations. Which of these compounds was she successful in synthesizing? Explain why the other syntheses were not successful.

a. \( \text{CH}_2=\text{CCH}_3 \)  
d. \( \text{CH}_3\text{C}=\text{CHCH}_3 \)  
g. \( \text{CH}_3\text{C}=\text{CH} \)

b. \( \text{CH}_3\text{C}=\text{CCH}_3 \)  
e. \( \text{CH}_2=\text{CHCH}_3 \)  
h. \( \text{CH}_3\text{C}=\text{CHCH}_3 \)

c. \( \text{CH}_2=\text{CHCCH}_2\text{CH}_3 \)  
f. \( \text{CH}_3\text{C}=\text{CHCH}_3 \)  
i. \( \text{CH}_3\text{C}=\text{CHCH}_3 \)

62. Explain why the following bromoketone forms different bicyclic compounds under different reaction conditions:

63. Explain why the product obtained in the following reactions depends on the number of equivalents of base used in the reaction:

64. A Mannich reaction puts an \( \text{NCH}_2^- \) group on the \( \alpha \)-carbon of a carbon acid. Propose a mechanism for the reaction.
65. What carbonyl compounds are required to prepare a compound with molecular formula C₁₀H₁₆O whose ¹H NMR spectrum is shown?

[Image of NMR spectrum]

66. Ninhydrin reacts with an amino acid to form a purple-colored compound. Propose a mechanism to account for the formation of the colored compound.

\[
\text{ninhydrin} + \text{H₂NCHCO}^- \xrightarrow{\text{catalytic } \text{H}^+} \text{purple-colored compound}
\]

67. A carboxylic acid is formed when an α-haloketone reacts with hydroxide ion. This reaction is called a Favorskii reaction. Propose a mechanism for the following Favorskii reaction. \((\text{Hint: In the first step, } \text{HO}^- \text{ removes a proton from the } \alpha\text{-carbon that is not bonded to Br; a three-membered ring is formed in the second step; and } \text{HO}^- \text{ is a nucleophile in the third step.})\)

\[
\begin{align*}
\text{CH₃CHCCH₂CH₃} & \xrightarrow{\text{HO}^-/\text{H₂O}} \text{CH₃CH₂CHCO}^- \text{ Br}
\end{align*}
\]

68. Give the products of the following reactions. \((\text{Hint: See Problem 67.})\)

a. \[
\begin{align*}
\text{Br} & \xrightarrow{\text{HO}^-/\text{H₂O}} \text{a product}
\end{align*}
\]
b. \[
\begin{align*}
\text{OCCH₃} & \xrightarrow{\text{HO}^-/\text{H₂O}} \text{a product}
\end{align*}
\]

69. An α,β-unsaturated carbonyl compound can be prepared by a reaction known as a selenenylation–oxidation reaction. A selenoxide is formed as an intermediate. Propose a mechanism for the reaction.

\[
\begin{align*}
\text{1. LDA/THF} & \quad \text{2. C₆H₅SeBr} & \quad \text{3. } \text{H₂O₂} \quad \text{a selenoxide}
\end{align*}
\]
70. a. What carboxylic acid would be formed if the malonic ester synthesis were carried out with one equivalent of malonic ester, one equivalent of 1,5-dibromopentane, and two equivalents of base?
   b. What carboxylic acid would be formed if the malonic ester synthesis were carried out with two equivalents of malonic ester, one equivalent of 1,5-dibromopentane, and two equivalents of base?

71. A Cannizaro reaction is the reaction of an aldehyde that has no α-hydrogens with concentrated aqueous sodium hydroxide. In this reaction, half the aldehyde is converted to a carboxylic acid and the other half is converted to an alcohol. Propose a reasonable mechanism for the following Cannizaro reaction:

$$\text{CH}_3\text{CHO} \xrightarrow{\text{concentrated NaOH}} \text{CH}_3\text{CO}^- + \text{CH}_3\text{CH}_2\text{OH}$$

72. Propose a reasonable mechanism for each of the following reactions:

a.  

b. 

73. The following reaction is known as the benzoin condensation. The reaction will not take place if sodium hydroxide is used instead of sodium cyanide. Propose a mechanism for the reaction.

$$\text{CH} = \text{C} - \text{H} \xrightarrow{\text{NaC}≡\text{N} \text{CH}_3\text{OH}} \text{CH} = \text{C} - \text{CH}_2\text{OH}$$

74. Orsellinic acid, a common constituent of lichens, is synthesized from the condensation of acetyl thioester and malonyl thioester. If a lichen were grown on a medium containing acetate that was radioactively labeled with $^{14}$C at the carbonyl carbon, which carbons would be labeled in orsellinic acid?

75. A compound known as Hagemann’s ester can be prepared by treating a mixture of formaldehyde and ethyl acetoacetate first with base and then with acid and heat. Write the structure for the product of each of the steps.
   a. The first step is an aldol-like condensation.
   b. The second step is a Michael addition.
   c. The third step is an intramolecular aldol condensation.
   d. The fourth step is a hydrolysis followed by a decarboxylation.

76. Amobarbital is a sedative marketed under the trade name Amytal®. Propose a synthesis of amobarbital, using diethyl malonate and urea as two of the starting materials.
77. Propose a reasonable mechanism for each of the following reactions:

\[
\text{O} \quad \text{O} \\
\begin{align*}
\text{CH}_3\text{CH}_2\text{COCH}_2\text{CH}_3 & \quad \text{1. CH}_3\text{CH}_2\text{O}^- \\
& \quad \text{2. O} \\
\end{align*}
\]

\[
\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3 \\
\]

b. \[
\begin{align*}
\text{O} & \quad \text{CH}_3\text{Br} \\
\end{align*}
\]

\[
\Delta \quad \text{OH} \\
\]

78. Tyramine is an alkaloid found in mistletoe, ripe cheese, and putrefied animal tissue. Dopamine is a neurotransmitter involved in the regulation of the central nervous system.

a. Give two ways to prepare β-phenylethylamine from β-phenylethyl chloride.
b. How can β-phenylethylamine be prepared from benzyl chloride?
c. How can β-phenylethylamine be prepared from benzaldehyde?
d. How can tyramine be prepared from β-phenylethylamine?
e. How can dopamine be prepared from tyramine?

79. Show how estrone, a steroid hormone, can be prepared from the given starting materials. (Hint: Start with a Robinson annulation.)

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{CH}_2\text{CH}_2\text{CH}_2\text{CCH} \equiv \text{CH}_2 \\
+ & \quad \text{H}_3\text{C} \quad \text{O} \\
\end{align*}
\]

\[
\text{HO} \\
\text{estrone} \\
\]

80. a. Ketoprofen, like ibuprofen, is an anti-inflammatory analgesic. How could ketoprofen be synthesized from the given starting material?

\[
\begin{align*}
\text{O} & \quad \text{CH}_3 \\
\end{align*}
\]

b. Ketoprofen and ibuprofen both have a propanoic acid substituent (see Problem 70 in Chapter 17). Explain why the identical subunits are synthesized in different ways.