Organic Chemistry

Chapter 8

Nucleophilic Substitution on the Carbonyl Group

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Chapter 8

Nucleophilic Substitution on the Carbonyl Group

Chapter Outline

8.1 The Acyl Transfer Mechanism
The mechanism that transfers an acyl group from a leaving group to the nucleophile

8.2 Water and Alcohol Nucleophiles
The reaction of oxygen nucleophiles with carboxylic acid derivatives

8.3 Halide and Carboxylic Acid Nucleophiles
The reaction of halogen and carboxylic acid nucleophiles with carboxylic acid derivatives

8.4 Reaction with Nitrogen Nucleophiles
The reaction of nitrogen nucleophiles with carboxylic acid derivatives

8.5 Reaction with the Hydride Nucleophile
The reaction of hydride nucleophiles with carboxylic acid derivatives

8.6 Carbon Nucleophiles
The reaction of carbon nucleophiles with carboxylic acid derivatives

8.7 Nitriles
The reactions of oxygen, hydride, and carbon nucleophiles with the nitrile functional group

8.8 The Baeyer-Villiger Oxidation
The conversion of a ketone or aldehyde to a carboxylic acid derivative

8.9 Solving Mechanistic Problems
The use of experimental data to formulate a mechanistic interpretation for a chemical reaction
Objectives

✔ Write the acyl transfer mechanism
✔ Understand how oxygen, nitrogen, hydride, and carbon nucleophiles react with carboxylic acid derivatives
✔ Recognize the similarity of nitriles with carboxylic acid derivatives
✔ Know the reaction of nitriles with oxygen, hydride, and carbon nucleophiles
✔ Become familiar with how experimental data is interpreted mechanistically
✔ Be familiar with Baeyer-Villiger Oxidation

Science is the knowledge of consequences, and dependence of one fact upon another.

—Thomas Hobbes

The beginning of a new chapter implies the beginning of a new set of concepts. However, the concepts covered in this chapter are a continuation of those included in Chapter 7. Chapter 7 presented nucleophilic addition to a carbonyl group; this chapter looks at the nucleophilic substitution of a carbonyl group. The reaction mechanisms of both are fundamentally the same. The big difference between the two is that instead of the nucleophile adding to the double bond between the carbonyl carbon and the oxygen, as it does in a nucleophilic addition, the nucleophile substitutes itself for one of the groups bonded to the carbonyl carbon in a nucleophilic substitution.

Although the mechanism of a nucleophilic substitution is essentially the same as a nucleophilic addition, aldehydes and ketones do not undergo nucleophilic substitution reactions because they do not have the required electronegative leaving group. Carboxylic acids and their derivatives have such a leaving group. The carbonyl carbon in the carboxylic acid family bonds to at least one other electronegative group besides the carbonyl oxygen. These electronegative groups usually are oxygen, nitrogen, or a halogen. Five functional groups make up the carboxylic acid family. They are carboxylic acids, esters, amides, acyl halides, and carboxylic anhydrides.
8.1 The Acyl Transfer Mechanism

As you learned in Chapter 7, nucleophilic addition reactions are reversible reactions with the position of equilibrium dependent on the strength of the nucleophile. The stronger the nucleophile, the more the equilibrium favors the product.

The mechanistic picture of the reverse reaction involves the loss of the nucleophile to re-form the original carbonyl compound.

A nucleophilic substitution at the carbonyl group of a carboxylic acid, or a carboxylic acid derivative, combines these two steps. But in a nucleophilic substitution, the group that leaves is the electronegative group that was bonded to the carbonyl carbon. Thus, the result of a nucleophilic substitution reaction is a carbonyl compound that is different from the starting carbonyl compound. A nucleophilic substitution reaction involving a carbonyl group is often called an acyl transfer reaction, and it follows this mechanism.

An acyl transfer is a reaction in which a nucleophile displaces a less electronegative group on the carbonyl group.
The ease with which a **leaving group** leaves a compound is inversely proportional to its basicity. Thus, the more basic the leaving group, the less readily it leaves. A stronger base is more willing to donate its electron pair to an electrophile that, in this case, is the carbonyl carbon. In the carboxylic acid family, the leaving group (the electronegative group bonded to the carbonyl carbon) is a base, but is generally a weaker base than the nucleophile. For example, the acyl transfer reaction works well with an acyl halide because the halide ion is a weak base. Thus, an acyl halide has a very good leaving group. Conversely, acyl transfer reactions do not occur with aldehydes and ketones because the leaving group, either a hydride or a carbanion, is generally too strong a base to be a good leaving group.

Not only is the leaving group a base, but the attacking nucleophile is also a base. With a nucleophilic substitution, a major consideration is the relative base strength of the nucleophile in comparison to the leaving group. Because the leaving groups in the carboxylic acid family are weak bases, they are stable anions. For example, the —OH group easily replaces the —Cl group. However, a —Cl group does not readily replace an —OH group. Thus, in a reaction between a strong basic nucleophile and a weaker basic leaving group in the acyl halide, the equilibrium favors the product.

The concept of a leaving group is fundamental to many areas of organic chemistry. Numerous reactions have a leaving group. In reactions with a leaving group, the behavior of the leaving group significantly affects the course of the reaction.

The reactivity of the various members of the carboxylic acid family relates to the stability of the leaving group. Acyl halides and anhydrides have the most stable leaving group, so they are the most reactive towards a substitution reaction. Esters and carboxylic acids have intermediate stability; thus, they have only intermediate reactivity. Amide leaving groups are the least stable; thus, amides are the least reactive carboxylic acid derivative. In general, the rule for reactivity is: **the more stable the leaving group, the more reactive the carboxylic acid derivative.**

**Exercise 8.1**

In a nucleophilic substitution reaction, what are the leaving groups for each of the carboxylic acid derivatives: acyl chlorides, anhydrides,
esters, amides, and carboxylic acids? Relate the stability of these leaving groups to the reactivity of the carboxylic acid derivative.

8.2 Water and Alcohol Nucleophiles

**Esterification** is the nucleophilic substitution reaction that converts a carboxylic acid, or a carboxylic acid derivative, to an ester. The reaction involves the substitution of a hydroxy group in the carboxylic acid with an alkoxy group from an alcohol. The reverse reaction, called a **hydrolysis**, is the substitution of an alkoxy group with a hydroxy group.

\[
\text{RCO}_2\text{H} + \text{ROH} \xrightarrow{\text{Esterification}} \text{RCOR'} + \text{H}_2\text{O}
\]

Carboxylic Acid          Ester

Hydrolysis

Some of the earliest investigators into the nature of chemical equilibrium studied the interconversion of esters and acids. Marcellin Berthelot and Leon Saint-Gilles, in 1860, first published some rate studies on the formation and hydrolysis of ethyl acetate. In 1879, Cato Guldberg and Peter Waage formulated the equilibrium expression for the reaction.

Equilibrium constants for esterification reactions are relatively small. The reaction of acetic acid with ethanol has an equilibrium constant of 4.

\[
\text{CH}_3\text{CO}_2\text{H} + \text{CH}_3\text{CH}_2\text{OH} \xleftrightarrow{\text{Esterification}} \text{CH}_3\text{COCH}_2\text{CH}_3 + \text{H}_2\text{O}
\]

Looking at the pKₐ values for the nucleophile and leaving group helps you to understand this equilibrium constant. Ethanol has a pKₐ of 16.3 and water 15.7. Because they are so similar, there is little thermodynamic preference between the substrate and product.

The mechanism for this reaction follows the generalized reaction mechanism shown in Section 8.1.
In the first step, the nucleophilic oxygen of the alcohol attacks the carbonyl carbon. In the second step, the proton bonded to the oxygen from the alcohol transfers to the oxygen that was the carbonyl oxygen. This proton transfer requires a base, like water, to remove the proton from one oxygen and move it to another. In the third step, the intermediate compound loses a hydroxide ion; thus, forming an ester with the carbonyl protonated. In the final step, the hydroxide ion removes the proton from the carbonyl group.

**Exercise 8.2**

For an esterification reaction consisting of a mixture of 0.5 moles each of ethanol and acetic acid in 1 liter of solution, give the amount of ethyl acetate present at equilibrium. Now increase the amount of ethanol to 5 moles. What is the amount of ethyl acetate present at equilibrium for this new mixture?

By altering the reaction conditions of a reaction, you change the equilibrium position of that reaction. By changing the equilibrium position of a reaction, you control which product forms in the greater amount. In an esterification reaction, chemists want to maximize the amount of ester obtained by the reaction. To do this, they change the reaction conditions by using one of the following two approaches. They remove one, or both, of the products as they form, particularly the water, or they add an excess of one reactant.
To remove the water from an esterification reaction, chemists usually use distillation. In the commercial distillation process, the result of the distillation is an azeotropic mixture. The azeotrope for the reaction of acetic acid and ethanol boils at 70°C and consists of 83% ethyl acetate, 8% ethanol, and 9% water. Because the ethyl acetate is largely insoluble in the mixture, chemists simply separate it from the mixture and purify it. Then they purify the ethanol from the water and recycle the alcohol. The laboratory process is very similar to the commercial process. Chemists reflux the mixture using a trap to remove the denser water. The apparatus returns the water-insoluble layer of ethyl acetate to the reaction flask for collection at the end of the reaction. See Figure 8.1.

Figure 8.1. Use of a trap in an azeotropic distillation. As the distillate fills the trap, the lower layer stays in the trap and the upper layer overflows back into the reaction flask.

Because the hydroxide ion is a poor leaving group, chemists increase the rate of esterification by adding catalytic quantities of acid to the reaction mixture. The acid protonates the leaving group, allowing a water molecule to leave. This method, known as Fischer esterification, forms a wide variety of esters.

The presence of an acid catalyst in a Fischer esterification greatly increases the reactivity of the carbonyl group. The addition of an acid protonates the carbonyl oxygen, thus enhancing the carbon’s reactivity to a nucleophile.
The protonated carboxylic acid is resonance-stabilized.

Because resonance allows several atoms to bear the partial charge, the ion has more stability and less reactivity than protonated aldehydes and ketones. The first two resonance contributors are equal in energy, but the third is only a minor contributor to the resonance. The protonated carboxylic acid then adds the alcohol to form the hydrate of an ester.

After a proton transfers from the alkoxy group to a hydroxy group, the intermediate loses water to form the ester. In the process the hydrated ester also loses a proton from the hydroxy group.

Chemists commonly use concentrated acids like sulfuric, $p$-toluenesulfonic, or phosphoric acid as the catalyst. Dilute aqueous solutions of acids are used only occasionally. Because esterification is a reversible reaction, adding water with the acid would drive the reaction the wrong way and decrease the yield of product.
Toluenesulfonic acid is the most popular choice because it is a very strong acid and because it is soluble in organic solvents.

\[
\begin{align*}
\text{SO}_3\text{H} & \\
\text{CH}_3 & \\
\text{p-Toluenesulfonic acid}
\end{align*}
\]

\(\text{p-Toluenesulfonic acid}\) is a strong acid because its conjugate base is resonance-stabilized with the negative charge distributed over all three of the oxygens bonded to the sulfur.

The Fischer method of esterification works well for most primary alcohols as they are not very sterically hindered. However, secondary and tertiary alcohols are more sterically hindered and usually have lower equilibrium constants and lower concentrations of the ester at equilibrium. To deal with these difficulties, chemists first convert the carboxylic acid to the acid chloride—the chloride is a good leaving group. The acid chloride then rapidly forms the ester in a reaction with an alcohol.

The synthesis of acid chlorides is discussed in Section 8.3, page 000.

**Synthesis of Isoamyl Acetate (Banana Oil)**

To a reaction flask, add 265 mg (3 mmol) of 3-methyl-1-butanol, 960 mg (16 mmol) of acetic acid, and 100 mg of Amberlyst® 15 ion exchange resin. This resin provides a convenient source of acid catalyst. Add a boiling stone or magnetic stir bar. Reflux the reaction mixture for at least 1 hour. Cool to room temperature. Filter the cool mixture to remove the ion exchange resin. Prepare a chromatography column from a slurry of 8 mL of methylene chloride and 2 g of silica gel. Add 2 g of potassium carbonate to the top of the silica gel. Drain the methylene chloride from the column until the solvent level just reaches the top of the potassium carbonate layer. Transfer the reaction mixture to the column using 1 mL of methylene chloride. Drain the column again until the solvent just reaches the potassium carbonate. Wash the resin and reaction flask with 1 mL of methylene chloride and add to the column. Drain the column again. Finally, complete the product elution or washing, with 2 mL of additional methylene chloride and drain the column. Combine all the methylene chloride solvent portions and evaporate under a stream of air or nitrogen in the hood. The expected yield of ester is 280 mg (72%); the boiling point is 141-143°C.

**Discussion Questions**
1. In this reaction the molar ratio of alcohol:acid is 0.003:0.016. Why is such a large excess of acid used in this reaction?
2. What is the function of the potassium carbonate in the chromatography column?
3. Using the above procedure as a model, outline the synthesis expected to produce 500 mg of cyclohexyl acetate.

**Exercise 8.3**

Show the use of the Fischer esterification reaction in the synthesis of the following esters.

a) Ethyl benzoate  

b) CH₃COOC₆H₅

c) Methyl methanoate  

d) Methyl cyclopentanecarboxylate

**Sample solution**

c) This is preparation of methyl methanoate (sometimes called methyl formate) from methanoic acid (HCOOH) and methanol (CH₃OH) with a catalytic quantity of acid.

\[
\text{HCOH} + \text{CH₃OH} \rightleftharpoons \text{HCOCH₃} + \text{H₂O}
\]

As chemists worked with ester hydrolysis reactions, they came up with two possible mechanisms for the reaction. First, they proposed the formation of the tetrahedral intermediate that occurs in an esterification reaction. In this proposed intermediate, the nucleophile and the leaving group bond to the same carbon. However, no one had ever actually isolated and identified this intermediate.

A suggested alternate reaction mechanism involved the following transition state. This mechanism seemed much simpler than the mechanism with the tetrahedral intermediate.
To decide which of these two possibilities actually happens, chemists carefully designed an experiment. As they planned, they compared the two mechanisms. In the intermediate of the first mechanism, the carbonyl oxygen becomes singly bonded to the carbonyl carbon, and in the transition state of the second mechanism, it remains doubly bonded to the carbonyl carbon. Thus, they wanted their experiment to follow what happens to the carbonyl oxygen. To provide evidence for the first mechanism, they needed a way to show that the carbonyl oxygen did not stay doubly bonded to the carbonyl carbon all the way through the reaction. Conversely, to provide evidence for the second mechanism, they needed a way to show that the carbonyl oxygen did stay doubly bonded to the carbonyl carbon throughout the reaction.

Isotopic labeling is synthesizing a molecule so that one or more of its atoms has a higher concentration of a specific isotope than occurs naturally. The isotopes that chemists commonly use for isotopic labeling are $^2\text{H}$, $^{13}\text{C}$, $^{14}\text{C}$, $^{15}\text{N}$, and $^{18}\text{O}$. Each of these isotopes occurs in less than 1% concentration in natural sources.

To follow the carbonyl carbon, they first prepared an ester with a marked carbonyl oxygen using a technique called isotopic labeling. They then followed the marked oxygen through a hydrolysis reaction. (Remember? The reaction goes through the same steps for either an esterification or a hydrolysis—just in reverse order. This is called the principle of microscopic reversibility.)

The principle of microscopic reversibility states that the forward and reverse reactions occur through the same set of intermediates and the same reaction conditions.

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The ester they prepared was ethyl benzoate. As they ran the ester synthesis, they labeled the carbonyl oxygen with $^{18}\text{O}$. Then they reacted the ethyl benzoate with unlabeled $\text{H}_2\text{O}$. As the hydrolysis proceeded, they removed samples and isolated the ester. A portion of the ester had no labeled oxygen, indicating that some of the marked carbonyl oxygen had undergone an exchange of oxygen with the unlabeled water. The only way for this exchange to occur was for the reaction to proceed through an intermediate in which the carbonyl oxygen was no longer doubly bonded. The only reasonable way for an exchange of labels to occur is through the tetrahedral intermediate of the first proposed mechanism.
Chemists concluded that ester hydrolysis is the reverse reaction of the formation of an ester. In an ester hydrolysis, the ester reacts with an excess of water and an acid catalyst. The thermodynamics of the reaction requires that the reverse reaction proceed through the same set of intermediates (in reverse order) as the forward reaction. Of course, that also assumes identical reaction conditions. These reaction requirements illustrate the principle of microscopic reversibility.

**Exercise 8.4**

A proposed experiment to distinguish between the two mechanisms for the hydrolysis of an ester might be to label the *other* oxygen in the ester. Write a mechanism for the hydrolysis of ethyl benzoate with the ethoxy oxygen labeled with $^{18}$O using both mechanisms above. Would this help to confirm one mechanism or the other? Why or why not?

Base assisted ester hydrolysis follows much the same pathway as acid catalyzed hydrolysis. With base, the first step is the reaction of an ester in a nucleophilic reaction of the base at the carbonyl carbon. This is followed by loss of the alkoxide ion. Finally, a proton exchange leaves the alcohol and the carboxylate anion product. Little reverse reaction takes place because the alcohol is too weak of a nucleophile to react with the carboxylate anion. Because of the lack of a reverse reaction chemists prefer using the base assisted ester hydrolysis to the acid-catalyzed hydrolysis.
A lactone is a cyclic ester in which the atoms of the ester functional group are part of the ring.

**Lactones** are cyclic esters. The formation of five- or six-membered lactone rings occurs from compounds containing a hydroxy group and a carboxylic acid group.

In these reactions the equilibrium is more favorable than other reactions of alcohols and carboxylic acids. There is a preference for five- and six-membered rings because those ring sizes are low in ring strain and thus quite easy to form. This is a theme you will see repeatedly throughout organic chemistry.

### Solved Exercise 8.1

Write a mechanism showing the formation of 5-hydroxypentanoic acid lactone.

**Solution**
The first step in the mechanism is a 1,3-electron pair displacement reaction initiated by the —OH group on C5 on the carbonyl carbon.
The next step in the mechanism is a proton transfer, moving a proton from one oxygen to another.

\[
\begin{array}{c}
\text{H} & \text{OH}_2 \quad \text{H} & \text{OH} \\
\text{H} & \text{OH}_2 \quad \text{H} & \text{OH}
\end{array}
\]

The loss of the $-\text{OH}_2$ group from the cyclic intermediate formed above produces the final product.

\[
\begin{array}{c}
\text{H} & \text{OH} \\
\text{H} & \text{OH}
\end{array}
\]

The reactions of both water and an alcohol with other members of the carboxylic acid family are mechanistically identical to the reaction described in Solved Exercise 8.1. Water and alcohols react very rapidly with acyl halides and almost as fast with anhydrides. In both cases the leaving group is a very stable anion. It is either a halide or carboxylate (RCOO$^-$) anion.

Amides are much less reactive than any of the other carboxylic acid derivatives. Hydrolysis of an amide with either an acid or a base requires heat and a longer reaction time than does an ester when producing a carboxylic acid.

Some examples of the reaction of carboxylic acid derivatives with water and alcohols are following.

\[
\text{CH}_3\text{CH}_2\text{OCH}_2\text{H} + \text{H}_2\text{SO}_4 \rightarrow \text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3
\]

Ethyl propanoate

\[
\text{NH}_2 \quad \text{O}
\]

2-Phenyl propanoic acid

(87%)
Exercise 8.5

Write a mechanism for the hydrolysis of acetamide (CH₃CONH₂) in aqueous acid.

8.3 Halide and Carboxylic Acid Nucleophiles

Acyl halides and anhydrides are the most reactive members of the carboxylic acid family of derivatives because they have the most stable leaving groups. The leaving group for an acyl halide is a halide anion (e.g., Cl⁻), and the leaving group for an anhydride is a carboxylate anion (RCOO⁻).

The leaving group of an acyl halide is the conjugate base of a very strong acid (pKₐ < 1). In comparison, the leaving group of an anhydride is the conjugate base of a much weaker acid (pKₐ ~ 5). Thus, the position of equilibrium for nucleophilic substitution is more favorable for an acyl halide than for an anhydride. Because of their reactivity, chemists usually synthesize either acyl halides or anhydrides as reactive intermediates rather than end products.

The only acyl halides that chemists generally use are the acyl chlorides. Acyl bromides and acyl iodides are more expensive to make, more unstable as compounds, and more difficult to handle than are the acyl chlorides, so they give little advantage over acyl chlorides. Chemists use acyl fluorides even less than acyl bromides and acyl iodides.

To synthesize acyl chlorides from carboxylic acids, chemists use either thionyl chloride, SOCl₂, or one of the phosphorus chlorides, PCl₃ or PCl₅. All of these reagents are the acid halides of an inorganic acid.
The following reaction of a carboxylic acid with thionyl chloride shows the mechanism for the preparation of an acyl halide. The reaction first produces a mixed anhydride consisting of the organic acid and the inorganic acid chloride. Note that this mechanism is an equivalent of a nucleophilic substitution reaction on the sulfur oxygen double bond.

The reaction then follows a typical nucleophilic substitution on the carbonyl.

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As the reaction progresses, the sulfur leaves as SO₂, and the second chloride leaves as HCl. Because both of these products are gasses, they readily bubble out of the reaction solution. Once the evolution of the gasses stops, the chemist distills the excess thionyl chloride (b.p. 76°C) from the reaction mixture leaving relatively pure acyl chloride. Because of the ease of reaction, chemists prefer thionyl chloride as the reagent for the preparation of acid chlorides. This reaction substitutes the —OH group of the original carboxylic acid with a Cl, an extremely good leaving group. The compound is now ready to act as an intermediate in another reaction.

Exercise 8.6

Write a detailed mechanism for the reaction of butanoic acid with phosphorus trichloride.

Oxalyl chloride (ClCOCOCl) is fast becoming the reagent of choice for the synthesis of acyl chlorides. It is easier to handle and use than thionyl chloride or the phosphorus chlorides. Like thionyl chloride, the by-products are CO₂, CO, and HCl.

Chemists make only a limited number of anhydrides because acyl halides are more readily available and more reactive than the anhydrides. Also, most subsequent reactions involving anhydrides use only one of the two acyl groups. That means half of a potentially
expensive, or scarce, starting material must be discarded. However, preparing anhydrides is simple. The preparation involves the reaction of an acyl halide with a carboxylic acid in the presence of a non-nucleophilic base such as pyridine.

\[
\text{Cyclopentanecarboxylic anhydride (95%)}
\]

The mechanism for the formation of an anhydride is another example of the acyl transfer mechanism. A weak base, like pyridine, reacts with the acidic proton of the carboxylic acid forming a carboxylate anion. The negatively charged oxygen reacts with the carbonyl carbon of the acyl halide. The resulting tetrahedral intermediate loses a chloride ion forming the anhydride.

Heating two molecules of a carboxylic acid together to form an anhydride with loss of a molecule of water seems like a plausible reaction pathway. However, simply heating the carboxylic acids does not produce an anhydride, except when the reaction can form a five- or six-membered ring.
Beyond the heating, two important factors in the formation of five- and six-membered cyclic anhydrides are the stability of those sized rings and the proximity effect. For example, an important conformation of succinic acid and glutaric acid (pentanedioic acid) brings the two carboxylic acid groups close together—much closer than is normal for two separate molecules. Thus, the apparent concentration of the carboxylic acid group is very high, pushing the equilibrium towards completion of the reaction. As shown below, the —OH groups of succinic acid are close to the electron deficient carbonyl carbons.

Many anhydrides form via an anhydride exchange. An anhydride exchange involves heating the relatively inexpensive acetic anhydride with a carboxylic acid. Because acetic acid boils at a lower temperature than nearly all other carboxylic acids, it distills from the reaction mixture to make the equilibrium more favorable.

Exercise 8.7
Propose a mechanism for the thermal dehydration of phthalic acid (benzene-1,2-dicarboxylic acid) to its anhydride.

Exhibit 8.8

Predict the major products of each of the following reactions.

a)

b)

c)

d)

e)
Aspirin and acetaminophen are two examples of compounds known as analgesics. An analgesic is a painkiller. There are two classes of analgesics: (1) those that act at the site of the pain and (2) those that act on the central nervous system to modify the brain’s processing of the pain signals.

Analgesics that act on the brain generally alter the mood and become addictive. Examples of addictive analgesics are morphine, codeine, and heroin. Analgesics that act on the site of the pain do not alter the mood directly nor are they addictive. Examples of non-addictive analgesics are aspirin and acetaminophen.

Many of the milder non-addictive analgesics on the market are derivatives of salicylic acid.
Salicylic acid

At first, chemists derived salicylic acid from the glycoside salicin. A glycoside consists of a non-sugar organic molecule attached to some sugar. Salicin is a naturally occurring substance found in the bark of the sweet, or white, willow tree (*Salix alba*).

![Salicin](image)

From the time of the ancient Greeks, people have used willow bark preparations as pain relievers. Because these willow bark preparations were very bitter, they were typically used externally. In addition, taking salicylic acid internally also caused a number of side effects. However, converting salicylic acid to acetylsalicylic acid takes care of most of the side effects. Acetylsalicylic acid was marketed as aspirin in 1899.

![Acetylsalicylic acid](image)

The synthesis of aspirin starts with phenol. Phenol is reacted with CO₂ to form salicylic acid. Then salicylic acid is reacted with acetic anhydride to form acetylsalicylic acid.

![Synthesis of aspirin](image)
Acetaminophen is not a naturally occurring substance. It was only by accident that chemists discovered its analgesic properties. This accident occurred when a pharmacist added acetanilide to a patient’s prescription by mistake.

Acetanilide is toxic. In a person’s body, part of the acetanilide converts to acetaminophen, accounting for its analgesic properties, but another portion converts to aniline, which is toxic. With the discovery of acetaminophen’s analgesic properties, chemists began looking for some less toxic way of providing acetaminophen to the body.

The molecular shapes of aspirin and acetaminophen are quite similar. Because of this similarity, the enzyme prostaglandin cyclooxygenase recognizes both, allowing both to inhibit its function. Prostaglandin cyclooxygenase aids the body in the production of prostaglandins, and prostaglandins possess a remarkable variety of actions. One of the body processes involving prostaglandins is the modification of the signals, particularly pain signals, transmitted across the synapses. Another possible process may be the dilation of blood vessels that cause the pain associated with headaches, if the vessels are within the skull, or with the pain associated with migraines, if the vessels are external to the skull. Analgesics such as aspirin and acetaminophen inhibit the synthesis of these prostaglandins; thus, inhibiting the transmission of pain or the dilation of the blood vessels.

8.4 Reaction with Nitrogen Nucleophiles

The nitrogen nucleophiles studied most in carbonyl chemistry are ammonia (NH₃), primary amines (RNH₂), and secondary amines
(R₂NH). All react with carboxylic acid and its derivatives to produce amides.

$$\text{RCO} + \text{NH}_2 \rightarrow \text{RCO-NH}_2$$

The most common method used to prepare amides is the reaction of a carboxylic acid or an acyl halide with ammonia or an amine. This procedure gives excellent yields of product with the addition of an extra mole of the amine, or a mole of some other base that is less nucleophilic than the amine. This extra base neutralizes the hydrogen halide that the reaction produces.

$$\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl} + 2\text{NH}_3 \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{CNH}_2 + \text{NH}_4\text{Cl}$$

**Ethylcyclohexanecarbamide** (99%)

$$\text{CH}_3\text{CH}_2\text{NH}_2 + \text{CH}_3\text{CH}_2\text{NH}_2 \rightarrow \text{NHCH}_2\text{CH}_3$$

**N-Ethylcyclohexanecarbamide** (97%)

$$+ \text{CH}_3\text{CH}_2\text{NH}_3 \text{Cl}$$

Acid, or acyl, anhydrides react in similar ways to acyl halides, but are less reactive.

$$\text{CH}_3\text{COOCCH}_3 + (\text{CH}_3)_2\text{NE} \rightarrow \text{CH}_3\text{CN(CH}_3)_2 + \text{CH}_2\text{COH}$$

**NN-Dimethylethanesamide** (85%)
The mechanism for the formation of an amide by the reaction of an amine with an acid anhydride is similar to the mechanisms presented earlier. The amine nitrogen reacts with a carbonyl carbon to form a tetrahedral intermediate. The tetrahedral intermediate loses a carboxylate ion to form the amide.

Amides can also be synthesized from the direct reaction of an amine with a carboxylic acid. In this reaction, the amine forms a salt with the carboxylic acid because the amine is a good base.
The water is then removed from the ammonium salt to produce the corresponding amide. Dehydration requires a high temperature. This type of thermal dehydration is useful in industrial synthesis, but chemists seldom use it in the laboratory. It is easier and cheaper to control a high temperature synthesis on an industrial scale than on a laboratory scale.

![Equation showing the reaction of acetic anhydride with ammonia to form benzamide.]

**Lactams** are cyclic amides. These five- and six-membered rings form easily from compounds that contain an amino group and a carboxylic acid group. The equilibrium reaction of a lactam is more favorable than the other reactions of amines and carboxylic acids.

![Equation showing the equilibrium reaction of 5-aminopentanoic acid lactam (2-Piperidone).]

**Exercise 8.9**

Propose a mechanism for the reaction of ammonia with acetic anhydride.

**8.5 Reaction with the Hydride Nucleophile**

Chapter 7 discusses the reactivity of lithium aluminum hydride and sodium borohydride, two complex metal hydrides, with aldehydes and ketones. These two compounds also react with the carbonyl group of the carboxylic acid family. Lithium aluminum hydride is much more reactive than sodium borohydride but, because of its decreased reactivity, sodium borohydride is much more selective than lithium aluminum hydride. The usual course of reaction of these complex...
metal hydrides with a carboxylic acid is a reduction reaction. This reduction reaction is a two step process. The hydride first initiates a nucleophilic substitution followed by the loss of the leaving group to form an aldehyde or ketone. A second hydride reacts with this ketone or aldehyde to form an alcohol. The lithium aluminum hydride reduction reaction of all carboxylic acid derivatives, except the amides, forms primary alcohols.

\[
\begin{align*}
\text{RC} - \text{L} & \rightarrow 1) \text{LiAlH}_4 \rightarrow \text{RCH}_2\text{OH} \\
\text{RC} - \text{L} & \rightarrow 2) \text{H}_3\text{O}^+ \\
\text{RC} - \text{L} & \rightarrow \text{RCH}_2\text{OH}
\end{align*}
\]

Amides react with LiAlH\(_4\) to form amines.

\[
\begin{align*}
\text{RC} - \text{NH}_2 & \rightarrow 1) \text{LiAlH}_4 \rightarrow \text{RCH}_2\text{NH}_2 \\
\text{RC} - \text{NH}_2 & \rightarrow 2) \text{H}_3\text{O}^+ \\
\text{RC} - \text{NH}_2 & \rightarrow \text{RCH}_2\text{NH}_2
\end{align*}
\]

A reduction reaction proceeds in two steps. The first step is the now familiar reaction of the nucleophile with the electrophilic carbonyl carbon. In this case, the nucleophile is a hydride ion.

\[
\begin{align*}
\text{RC} - \text{L} & \rightarrow \text{H}_2\text{O} \\
\text{RC} - \text{L} & \rightarrow \text{H}_2\text{O} \\
\text{RC} - \text{L} & \rightarrow \text{H}_2\text{O}
\end{align*}
\]

The tetrahedral intermediate is unstable, so the leaving group departs. The tetrahedral intermediate then forms an aldehyde, because the leaving group is a weaker base than the hydride ion.

\[
\begin{align*}
\text{RC} - \text{L} & \rightarrow \text{RCH}_2\text{OH} \\
\text{RC} - \text{L} & \rightarrow \text{RCH}_2\text{OH} \\
\text{RC} - \text{L} & \rightarrow \text{RCH}_2\text{OH}
\end{align*}
\]

In the second step, the aldehyde immediately reacts to form an alcohol because the aldehyde is \textit{more} reactive than the starting carboxylic acid derivative. The aldehyde intermediate reacts so rapidly with LiAlH\(_4\) to form the alcohol that it is impossible to isolate the aldehyde.
In practice, chemists start the reaction in anhydrous ethyl ether. After the reaction proceeds for a period of time, they add aqueous acid to protonate the conjugate bases of the products. Here are examples of the reaction of lithium aluminum hydride with an acyl halide and an ester.

When lithium aluminum hydride reacts with a carboxylic acid in an acid-base reaction, the hydride ion is a strong base. The hydride ion reacts with the acidic hydrogen in an exothermic reaction to produce hydrogen gas. In the process, the carboxylic acid consumes one hydride from the LiAlH₄.

This reaction produces a negatively charged ion. Any subsequent reduction reaction involving the carbonyl group of the product requires a nucleophile strong enough to react with the carbonyl carbon despite the negative charge of the product above. Lithium aluminum hydride is strong enough to react with the carbonyl carbon, but there is a complication. The initial product is usually insoluble in the reaction mixture, thus, the rate of reaction with the hydride ion is greatly reduced.
Next, the reaction mixture is treated with dilute aqueous acid to produce an alcohol product.

Because of the insolubility of the negatively charged ion and the subsequent slowness of reaction, chemists find it much easier to convert the carboxylic acid to a methyl or ethyl ester before reduction with a hydride. Converting to a methyl or ethyl ester also produces a better yield.

The reduction reaction of an amide with lithium aluminum hydride produces an amine.

The mechanism for this transformation is not well known, but chemists widely agree that it follows a pathway via an imine. As with the reduction of carboxylic acids, the first step is an acid-base reaction between a hydride and a proton on the nitrogen to form hydrogen and an amide salt.

The amide salt rearranges; thus, allowing for a subsequent reaction with the hydride. This reaction forms the tetrahedral intermediate.
Because oxygen is a better leaving group than nitrogen, the intermediate loses oxygen to form an imine.

Then, because the imine is more reactive than an aldehyde, it reduces to the amine as soon as it forms.

This reaction is an excellent synthesis of amines as it easily produces a variety of amines. Following are some examples.

Chemists have found a way to prepare an aldehyde from an acyl halide. They commonly use lithium tri-tert-butoxyaluminum hydride (LiAl(OC(CH₃)₃)₃H). First, they synthesize LiAl(OC(CH₃)₃)₃H by adding tert-butyl alcohol to LiAlH₄.
In this reaction the bulky tert-butoxy groups replace three of the original four hydrides. The product, lithium tri-tert-butoxyaluminum hydride, is much less reactive and more selective as a reducing agent than is lithium aluminum hydride. It is more selective because the tert-butoxy groups are very large, making the transfer of the hydride more difficult than with LiAlH₄. In addition, the oxygens of the tert-butoxy groups are electron withdrawing which deactivates the hydride. After completing the synthesis of lithium tri-tert-butoxyaluminum hydride, the chemists react it with an acyl halide to get an aldehyde. This procedure, developed by H. C. Brown of Purdue University, gives good yields of aldehydes from a variety of acyl chlorides.

The use of lithium tri-tert-butoxyaluminum hydride allows selective reduction of one carbonyl group in a complex molecule containing more than one carbonyl group. For example, pregnan-3-ol-20-one acetate, a steroid molecule, contains both a ketone and an ester. Because of the selectivity of lithium tri-tert-butoxyaluminum hydride, only the ketone is reduced.
Sodium borohydride is a much weaker hydride donor than lithium aluminum hydride. The only carboxylic acid derivatives that sodium borohydride reduces are the acyl halides.

Solved Exercise 8.2

Propose a synthesis of the N-methylbenzyl amine from benzoic acid.

Solution
The only method for synthesizing an amine from a carboxylic acid is via an amide that is reduced by LiAlH₄. N-Methylbenzamide reacts with LiAlH₄ to produce N-methylbenzyl amine.
[Image of organic chemical structures and reactions]

*N-Methylbenzamide is prepared, in turn, by a reaction of benzoyl chloride with methylamine.*

\[ \text{Benzoyl chloride} \quad \text{CH}_3\text{NH}_2 \quad \rightarrow \quad \text{N-Methylbenzamide} \]

Benzoyl chloride is synthesized from benzoic acid by reaction with thionyl chloride.

\[ \text{Benzoic acid} \quad \text{SOCl}_2 \quad \rightarrow \quad \text{Benzoyl chloride} \]

**Exercise 8.10**

Predict the major products of each of the following reactions.

a) \[ \text{Reaction structure} \quad \xrightarrow{1) \text{LiAlH}_4} \quad \xrightarrow{2) \text{H}_3\text{O}^+} \]

b) \[ \text{Reaction structure} \]
Sample Solution

a)
8.6 Carbon Nucleophiles

Section 7.8 introduces organometallic reagents as a major source of carbon nucleophiles in reactions that involve carbonyl groups and shows how they react with aldehydes and ketones. This section discusses organometallic reactants in reactions with the carbonyl group of carboxylic acids and their derivatives. With these reactions, chemists commonly use Grignard and organolithium reagents. Both reagents react readily with members of the carboxylic acid family.

The reactions of organometallic reagents with carboxylic acids and carboxylic acid derivatives illustrate the concept of selectivity in organic reactions. When organometallic reagents react with carboxylic acids and carboxylic acid derivatives, they form one of two possible products depending on the organometallic reagent and the substrate. Organomagnesium compounds and organolithium compounds react with carboxylic acid derivatives to form alcohols.

\[
\text{RC} + \text{RC} \xrightarrow{\text{RC} \text{MgX}} \xrightarrow{\text{RC} \text{Li}} \text{O} + \text{OH} + \text{HO}
\]

Organolithium compounds, but not Grignard reagents, react with carboxylic acids to form aldehydes or ketones.

\[
\text{RC} \xrightarrow{\text{RC} \text{Li}} \text{O} + \text{OH} \xrightarrow{\text{RC} \text{Li}} \text{RCR'}
\]

Of the reactions that form alcohols, the ones involving acyl halides and anhydrides have limited synthetic utility due to their rapid reaction rates. Depending on the structure of the substrate, the reactions also tend to give many undesirable side reactions.
Esters react with Grignard reagents in much the same way that they react with metal hydrides. To see this similarity, compare the following reactions:

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{COCH}_2\text{CH}_3 \xrightarrow{\text{1)} \text{LiAlH}_4/\text{ether}} \text{CH}_3\text{CH}_2\text{CH}_2\text{C}^{-}\text{H} + \text{CH}_3\text{CH}_2\text{OH} \\
\text{1-Butanol} (92%)
\]

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{COCH}_2\text{CH}_3 \xrightarrow{\text{1)} \text{CH}_3\text{MgBr}} \text{CH}_3\text{CH}_2\text{CH}_2\text{C}^{-}\text{CH}_3 + \text{CH}_3\text{CH}_2\text{OH} \\
\text{2-Methyl-2-pentanol} (85%)
\]

The first is the reaction of an ester, ethyl butanoate, with lithium aluminum hydride. This reaction produces 1-butanol via the addition of two hydrides to the carbonyl carbon. The second reaction involves the same ester, ethyl butanoate, but it is treated with a Grignard reagent, methyl magnesium bromide. This reaction produces 2-methyl-2-pentanol by adding two methyl groups to the carbonyl carbon.

The mechanisms for both reactions are very similar. For example, compare the following reaction for the ester and Grignard reaction with the mechanism for the ester and hydride reaction shown in Section 8.5. The first step in the ester Grignard reaction is the addition of the nucleophilic carbon to the carbonyl group forming a tetrahedral intermediate.

The ethoxy group is the best leaving group because it is a weaker base than the alkyl groups. Thus, the intermediate loses the ethoxy group and forms 2-pentanone.
As with the hydrides, the reaction does not stop here. The 2-pentanone then reacts with another mole of the Grignard reagent to form the alkoxide which, after acidification, produces the final alcohol product. Ketones are much more reactive than the starting esters towards reaction with a Grignard reagent. Thus, the 2-pentanone reacts as soon as it forms. It usually is impossible to isolate the ketone intermediate.

Following are two other examples of this reaction.

Solved Exercise 8.3
Consider the structures of the following tertiary alcohols. Some cannot be prepared by a Grignard reagent reaction with an ester. Which ones cannot? For those that can be prepared from an ester, what ester and Grignard reagent should be used?

1) \[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} \\
\end{align*}
\]

2) \[
\begin{align*}
\text{PhCH}_2\text{CH}_2\text{OH} \\
\end{align*}
\]

3) \[
\begin{align*}
\text{CH}_3\text{C}_6\text{H}_{11}\text{OH} \\
\end{align*}
\]

4) \[
\begin{align*}
\text{CH}_3\text{OH} \\
\end{align*}
\]

5) \[
\begin{align*}
\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH} \\
\end{align*}
\]

6) \[
\begin{align*}
\text{CH}_3\text{C}_6\text{H}_{11}\text{CH}(\text{OH})\text{CH}_2\text{CH}_2\text{OH} \\
\end{align*}
\]

Solution

Two of the substituents must be the same to produce a tertiary alcohol by a Grignard reagent reacting with an alcohol. Alcohols 1, 4, and 5 can be synthesized in this way because they have two identical substituents.

Prepare compound 1 by reaction of propyl magnesium bromide with methyl butanoate.

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

Prepare compound 4 by reaction of methyl magnesium bromide with methyl propanoate.
Exercise 8.11

Organolithium reagents react with esters in a similar manner to Grignard reagents. Predict the product formed from the reaction of ethyl lithium with methyl benzoate. Write a mechanism for this reaction.

Some organometallic reagents react with carboxylic acids to form aldehydes and ketones. However, with Grignard reagents, the reaction is not very effective. The reaction proceeds very rapidly, producing a carboxylate salt that is insoluble in solution. The reaction usually stops at this point. Even in the presence of a large excess of Grignard reagent, only small amounts of the alkyl group add to the carbonyl group.

\[
\text{RCOH} + \text{R'MgBr} \rightarrow \text{RCO}^+ \text{MgBr} + \text{R'H}
\]

Because of the rapidity of this reaction, a Grignard reagent cannot react with another functional group when a carboxylic acid is present, even if the additional functional group is more reactive.

On the other hand, an organolithium reagent is more nucleophilic than a Grignard reagent. Thus, it is much more successful in taking a reaction with a carboxylic acid to the completion of the aldehyde or ketone formation. When mixed, the carboxylic acid and organolithium reagent immediately react to form a lithium salt much like the Grignard reagent.
However, the reaction doesn't stop there. The organolithium compound has sufficient reactivity to add to the carbonyl group to form a dianion. An organolithium reagent is sufficiently reactive to react with a negatively charged species.

After protonation, the dilithium salt forms an unstable hydrate of a ketone, which rapidly loses water to form a ketone.

A reaction between a carboxylic acid and an organolithium reagent is very useful, as it directly converts the carbonyl group of a carboxylic acid to the carbonyl group of a ketone. This is a useful reaction in that it can readily form an unsymmetrical ketone.

The above conversion of a carboxylic acid to a ketone works well with all carboxylic acids except those with some other functional group that reacts with the lithium reagent. The following are two examples of organolithium and carboxylic acid reactions.
Amides also react with organometallic compounds. When the amide has two alkyl groups on the nitrogen, the reaction forms a ketone.

\[
\text{O} \quad \text{1) CH}_3\text{CH}_2\text{Li} \quad \text{O} \\
\text{CH}_3\text{CN(CH}_3)_2 \quad \text{2) H}_3\text{O}^{\ominus} \\
\text{CH}_3\text{CCH}_2\text{CH}_3 \quad \text{2-Butanone} \quad (74\%)
\]

The presence of one or more hydrogens on the nitrogen complicates the reaction, because they are sufficiently acidic to react with both Grignard reagents and organolithium reagents, thus preventing the reaction from forming the ketone.

**Solved Exercise 8.4**

Fatty acids are long chain carboxylic acids found in a variety of biochemical sources. Most fatty acids contain an even number of carbon atoms. Those containing an odd number of carbon atoms are relatively rare. Propose a synthesis of pentadecanoic acid from myristic acid (tetradecanoic acid). (Needed information from Chapter 12: Reacting 1-tetradecanol with concentrated HBr accomplishes the synthesis of 1-bromotetradecane.)

**Solution**

This exercise requires that you propose a synthesis of a carboxylic acid by adding a carbon atom to the original molecule. The Grignard synthesis of a carboxylic acid is the best method to accomplish this purpose.

\[
\text{CH}_3\text{(CH}_2)_{13}\text{Br} \quad \text{1) Mg, ether} \quad \text{CH}_3\text{(CH}_2)_{13}\text{COH} \\
\text{1-Bromotetradecane} \quad \text{2) CO}_2 \quad \text{Pentadecanoic acid} \\
\text{3) H}_3\text{O}^{\ominus}
\]
Because you are told that 1-bromotetradecane is synthesized from 1-tetradecanol, completion of the synthesis requires making 1-tetradecanol. This is accomplished by reducing the original acid with LiAlH₄.

\[
\text{CH}_3\text{(CH}_2\text{)}_{12}\text{COH} \xrightarrow{1) \text{LiAlH}_4} \text{CH}_3\text{(CH}_2\text{)}_{12}\text{CH}_2\text{OH} \xrightarrow{2) \text{H}_3\text{O}^+} \text{CH}_3\text{(CH}_2\text{)}_{12}\text{CH}_2\text{Br}
\]

(Tetradecanoic acid (Myristic acid) 1-Tetradecanol 1-Bromotetradecane)

You could obtain a better yield of product by first synthesizing the ethyl ester of myristic acid and then reducing the ester with LiAlH₄. To review the reasons for this, see Section 8.5.

**Exercise 8.12**

Predict the major products of each of the following reactions.

a) 

\[
\text{CH}_3\text{O} \quad \xrightarrow{1) \text{MgBr}} \quad \text{CH}_3\text{O} \quad \xrightarrow{2) \text{H}_3\text{O}^+} \quad \text{OCH}_2\text{CH}_3
\]

b) 

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{COCH}_2\text{CH}_3 \xrightarrow{1) \text{CH}_3\text{CH}_2\text{CHCH}_2\text{Li}} \xrightarrow{2) \text{H}_3\text{O}^+} \text{CH}_3
\]

c) 

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{COCH}_3 \xrightarrow{1) \text{CH}_3\text{MgBr}} \xrightarrow{2) \text{H}_3\text{O}^+} \text{CH}_3\text{O}
\]

d)
8.7 Nitriles

Chemists often consider nitriles (RC≡N) carboxylic acid derivatives because, in terms of reactivity, a nitrile greatly resembles a carbonyl group. Nitriles readily hydrolyze to form amides or carboxylic acids and carboxylic acid derivatives. Also, nitriles are easy to synthesize (Chapter 12). Thus, the hydrolysis of nitriles is one of the primary methods that chemists use to prepare carboxylic acids and carboxylic acid derivatives.

When forming a carboxylic acid from a nitrile, chemists hydrolyze the nitrile by adding water to it along with either an acid or
a base catalyst. If they use mild reaction conditions, the hydrolysis stops at the amide. If they use more vigorous conditions, the amide hydrolyzes and forms the carboxylic acid. More vigorous reaction conditions include higher concentrations of the acid or the base and the addition of heat.

\[
\begin{align*}
\text{RCN} + \text{H}_2\text{O} &\rightarrow \text{RCNH}_2 + \text{H}_2\text{O} \\
\text{RCN} + \text{H}_2\text{O} &\rightarrow \text{RCNH}_2 + \text{H}_2\text{O} \\
\text{RCN} &\rightarrow \text{RCNH}_2 + \text{H}_2\text{O} \\
\text{RCN} &\rightarrow \text{RCNH}_2 + \text{H}_2\text{O} \\
\end{align*}
\]

To hydrolyze the nitrile with a base, the mechanism begins with a nucleophilic attack of the hydroxide ion on the electrophilic carbon of the nitrile group.

\[
\begin{align*}
\text{RCN} + \text{HO}^- &\rightarrow \text{RCNH}_2 + \text{H}_2\text{O} \\
\text{RCN} &\rightarrow \text{RCNH}_2 + \text{H}_2\text{O} \\
\end{align*}
\]

This product then rapidly picks up a proton from a molecule of water to produce an unstable isoamide and regenerates the hydroxide catalyst.

\[
\begin{align*}
\text{RCN} + \text{HO}^- &\rightarrow \text{RCNH}_2 + \text{H}_2\text{O} \\
\text{RCN} &\rightarrow \text{RCNH}_2 + \text{H}_2\text{O} \\
\end{align*}
\]

Because isoamides are unstable, they rapidly \textit{isomerize} to form the amide. They isomerize by transferring a proton from the oxygen to the nitrogen. This transfer is accompanied by the shift of the π bond.

\[
\begin{align*}
\text{RCNH}_2 + \text{H}_2\text{O} &\rightarrow \text{RCNH}_2 + \text{H}_2\text{O} \\
\text{RCNH}_2 &\rightarrow \text{RCNH}_2 \\
\end{align*}
\]

\textit{To isomerize a compound means to change the molecular structure from one atomic sequence to another.}
The equilibrium here is far to the right. Chemists call this rapid interconversion of functional groups a **tautomerism**.

When an acid is the catalyst, the reaction begins with protonation of the nitrile nitrogen.

This reaction has an unfavorable equilibrium because the nitrogen is not very basic, so it does not protonate easily. Base strength depends on the ability of the atom to donate a pair of electrons, and that ability depends on which orbital holds the electrons. With a nitrile, an $sp$ hybrid orbital holds the nonbonding electrons of the nitrogen. As discussed in Chapter 1, an $sp$ hybrid orbital is closer to the nucleus than a $p$ orbital, an $sp^2$, or an $sp^3$ hybrid orbital. Thus, an electron pair in an $sp$ orbital is closer to the nucleus than an electron pair in an $sp^2$ orbital or an $sp^3$ orbital and is less available to act as a base. After the nitrile nitrogen is protonated, water adds via a nucleophilic addition to the carbon of the nitrile. Then, the intermediate loses a proton and tautomerizes to form the amide.

Because the nonbonding electron pair is in the $sp$ orbital, the reaction requires heat to proceed. This additional heat also increases the rate of hydrolysis of the amide. The increased rate of amide hydrolysis makes isolating the amide from the acid-catalyzed reaction very difficult.
Hydride addition to nitriles is a method that chemists use to synthesize primary amines. As the reaction proceeds, it moves through two successive additions of hydride from lithium aluminum hydride to the carbon of the nitrile.

The strength of lithium aluminum hydride as a hydride nucleophile makes possible the second hydride reaction with the negatively charged imine intermediate. Finally, addition of water to the dianion hydrolyzes it to the primary amine.

In another type of reaction, nitriles react with Grignard reagents and organolithium reagents to produce ketones. When the reaction involves an organometallic reagent and a nitrile, only one molecule of the organometallic reagent reacts with the nitrile. Neither a Grignard reagent nor an organolithium reagent is sufficiently nucleophilic to react with the intermediate iminium ion \((\text{C}≡\text{N}^-)\) formed in the reaction, thus allowing protonation of the iminium ion to form an imine. The imine then hydrolyzes to form a ketone.
Exercise 8.13

Predict the major products of each of the following reactions.

a) 

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CHCN} \xrightarrow{1) \text{LiAlH}_4} \xrightarrow{2) \text{H}_3\text{O}^+} \text{CH}_3\text{CCH}_3
\]

Methyl phenyl ketone (Acetophenone) (87%)

b) 

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CN} \xrightarrow{\text{H}_2\text{O}, \text{OH}} \xrightarrow{50^\circ\text{C}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CN}
\]

c) 


2) H₃O⁺

1) CH₃Li

2) H₃O⁺

d)

CH₃CH₂CH₂CH₂CN →

1) CH₃Li

2) H₃O⁺

e)

CN

O

1) LiAlH₄

2) H₃O⁺

reflux

f)

CN

CH₃CH₂CH₂CH₂CN →

1) LiAlH₄

2) H₃O⁺

Sample Solution

a)

CH₃CH₂CH₂CH₂CN →

1) LiAlH₄

2) H₃O⁺

CH₃CH₂CH₂CH₂CH₂NH₂

CH₂CH₃

8.8 The Baeyer-Villiger Oxidation

The Baeyer-Villiger reaction, named for the two German chemists who discovered it in 1899, is useful for converting a ketone to an ester. It works best when converting a symmetrical ketone to an ester or a cyclic ketone to a lactone.
The proposed mechanism for the Baeyer-Villiger oxidation reaction involves the nucleophilic addition of trifluoroperacetic acid (CF$_3$COOOH) or persulfuric acid (H$_2$SO$_5$) to the carbonyl carbon of the ketone. After the tetrahedral intermediate forms, a carbon adjacent to the carbon—trifluoroperacetic acid bond migrates its bond from the carbon—trifluoroperacetic acid bond to an oxygen of the peracid. Simultaneous with the bond migration, the carboxylate anion departs and the ester forms.

A bond migration is the movement of a bond from one atom to another, usually adjacent, atom.

The Baeyer-Villiger reaction works well on a variety of substrates, including the following:
Unlike the symmetrical ketone used as the substrate to illustrate the mechanism of the Baeyer-Villiger reaction, both ketones used as substrates in the examples are unsymmetrical. Even though they are unsymmetrical, each reaction gives only one major product. The selectivity of the reaction occurs because different groups have a different tendency to migrate to the oxygen. Studies of the Baeyer-Villiger reaction, as well as of other reactions with groups that migrate, show that the migratory aptitude for groups is $H > \text{tert-alkyl} > \text{secondary alkyl} \sim \text{benzyl} \sim \text{phenyl} > \text{primary alkyl} > \text{methyl}$. In all cases the migration takes the electron pair along with the group that migrates. The migratory aptitude parallels the base strength of the migrating group. The more basic the group, the more difficult it is for that group to migrate. The greater the difference between the two groups of an unsymmetrical ketone, the greater the selectivity shown in the reaction product.

**Exercise 8.14**

What is the major product formed in the Baeyer-Villiger reaction of 2-methylcyclohexanone?

Industry uses the Baeyer-Villiger reaction for the synthesis of various commercially useful products. One example is the synthesis of the lactone of 6-hydroxyhexanoic acid—its common name is...
Caprolactone. Caprolactone is widely used as a starting material for some types of polyesters.

\[ \text{Caprolactone (91\%)} \]

Another industrial synthesis makes large ring lactones. Perfume manufacturers value these lactones because a number of them are commonly used for musk fragrances. A simple one, extracted from the roots of *Angelica archangelica*, shows the synthesis of musk fragrances.

\[ \text{Lactone of 15-hydroxypentadecanoic acid (84\%)} \]

### Synthesis of Caprolactone

To 2.84 mL (12 mmol) of 32\% peracetic acid solution, add 890 mg (9.1 mmol) of cyclohexanone. Stir the reaction mixture at room temperature for at least 24 hours. Add 10 mL of ethyl ether and wash the solution with 5 mL of saturated sodium bicarbonate solution three times to remove unreacted peracid as well as any acetic acid formed in the reaction. Dry the ether solution with anhydrous sodium sulfate and evaporate the ether. Fractional distillation of the product under reduced pressure produces 920 mg (89\%) of caprolactone. The bp is 96-98°C at 10mm pressure.

### Discussion Questions
1. Propose a mechanism showing the formation of the acetic acid by-product in this reaction.
2. In oxygen, caprolactone undergoes a ring opening reaction to form an acyclic polymer. A polymer is a molecule consisting of a long chain of identical subunits. In this polymer, each subunit is derived from caprolactone and is connected by an ester functional group. Propose a structure for this polymer.

Exercise 8.15

Predict the major products of each of the following reactions

a) ![Image of a reaction with CH₃COOH]

b) ![Image of a reaction with CF₃COOH]

c) ![Image of a reaction with benzene COOH]

d) ![Image of a reaction with CF₃COOH]

Sample Solution
c)
A significant activity of organic chemists, and organic chemistry students, is proposing reasonable reaction mechanisms. When chemists discover a new reaction or identify an unexpected reaction product, they propose a mechanism for the transformation of the starting materials to the products. When chemists want to synthesize a previously unsynthesized molecule, or when they want to synthesize a molecule by an untried route, they propose reaction mechanisms to establish an experimental route for these syntheses. Whenever possible, they propose the reaction mechanism for a new reaction by finding an analogy with a known reaction or reaction mechanism.

In Chapter 6, you surveyed the major types of mechanisms and in Chapters 7 and 8 you examined two of them in some detail. In this section, you will see how to actually use mechanisms by investigating a case study that involves mechanisms. As a part of this case study, you will examine a proposed mechanism for a reaction not covered previously in this book.

Before looking at the case study, an important principle for you to consider is that almost all the reactions covered in this book fit under the classification of acid-base reactions. Thus, answering the following two questions: 1) “Where is the acid?” and 2) “Where is the base?” allows you to more readily propose a mechanism for a particular reaction. Use the following sequence when proposing a mechanism for a reaction. Identify the atoms that probably act as the acid and the base. Use your information about how acids and bases interact and plan a step-by-step way that this acid and base would likely react together.

For example, look at an acid-base reaction that you are already familiar with—the acid-catalyzed hydrolysis of a nitrile. Answer the questions: Where is the acid? Where is the base? The $\text{H}^+$ is the acid because it is electron deficient. The nitrogen of the nitrile is the base because it has a pair of nonbonding electrons. How does this acid and base react together? First, the $\text{H}^+$ protonates the nitrogen.

8.9 Solving Mechanistic Problems
Then, because the protonation step enhanced the electrophilicity of the carbon atom, the nucleophile (water) attacks the nitrile carbon.

The product of this attack then loses a proton from the oxygen to form a neutral compound. This product is an isoamide, which is a tautomer of an amide.

Now consider the case study. The experimental evidence described here is the actual work done by John T. Edward and Sin Cheong Wong at McGill University (*J. Am. Chem. Soc.*, 1979, 101, 1807). This work involved an acid-catalyzed hydrolysis of thioacetanilide.

Edward and Wong found that this reaction gives two different product mixtures and that the determining factor, as to which product mixture they obtained, depended on the sulfuric acid concentration. With a 48% concentration of sulfuric acid, 100% of the product was an aniline and thioacetic acid mixture.

With a 3% concentration of sulfuric acid, more than half the product was acetanilide and hydrogen sulfide. The remaining product was aniline and thioacetic acid, showing that only part of the reaction followed the above pathway.
As they changed the concentration of sulfuric acid, they found that the ratio between these two reactions changed predictably. They also found that when they increased the temperature, they increased the amount of product (aniline and thioacetic acid) from the first reaction.

With this data and with your knowledge of acid-base theory and reaction mechanisms, you are ready to propose a mechanism. Following the above sequence, decide which is the acid and which is the base. The acid is sulfuric acid and the base is either the nitrogen or sulfur of the thioacetanilide. Because the nitrogen is donating electron density to the carbon of the thiocarbonyl group it is less basic than the sulfur. Then, using reasoning by analogy, propose a mechanistic sequence similar to the hydrolysis of an amide for the first reaction. This sequence begins with the protonation of the sulfur in the thiocarbonyl group, followed by nucleophilic attack by the oxygen of water and loss of a proton to give a tetrahedral intermediate.

The tetrahedral intermediate has three possible protonation sites: the nitrogen, the sulfur, or the oxygen. Of these three, both sulfur and oxygen are weaker bases than nitrogen. In addition, protonation of the oxygen leads to the reverse reaction of the sequence shown above. Thus, protonation occurs on the nitrogen.

The protonation of the nitrogen atom of the tetrahedral intermediate makes the aniline molecule a good leaving group. This step forms thioacetic acid.
The second reaction follows the same mechanistic pathway until it reaches the same tetrahedral intermediate, but at low acid concentrations, little protonation occurs. Because the \( \text{SH} \) is the conjugate base of a stronger acid than either of the other leaving groups, the loss of the \( \text{SH} \) group (\( pK_a \) of \( \text{H}_2\text{S} \) is 7) is a lower energy path than the loss of either \( \text{OH} \) (\( pK_a \) of \( \text{H}_2\text{O} \) is 15.7) or \( \text{PhNH}^- \) (\( pK_a \) of \( \text{PhNH}_2 \) is 25).

This pathway is exactly the reverse of the pathway for the initial formation of the tetrahedral intermediate, except that the sulfur leaves.

The only remaining question is, why does the change in acid concentration lead to different products? At low acid concentrations, only a small amount of protonation of the tetrahedral intermediate
occurs. The group that leaves is the most stable anion. In this case, the leaving group is the $\text{SH}^-$ anion.

Increasing the acid concentration increases the likelihood that the tetrahedral intermediate will accept more than one proton from the acid. Then the question becomes, which protonated group is the better leaving group? The nitrogen, as well as the sulfur, and possibly the oxygen, are protonated at the higher acid concentrations. Preferential protonation on the nitrogen leads to a resonance-stabilized leaving group, which causes the carbon—nitrogen bond to break more easily.

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**Key Ideas from Chapter 8**

- A nucleophilic substitution at the carbonyl group is identical to a nucleophilic addition to the carbonyl group, except that in the nucleophilic substitution, the nucleophile has some leaving group attached to the carbonyl carbon.

- A leaving group is an atom or group that departs from the substrate in a reaction.

- Leaving groups for nucleophilic substitutions on the carbonyl group generally include halides, carboxylate ions, hydroxides, alkoxide or amide ions or their conjugate acids.

- The mechanism for a nucleophilic substitution at the carbonyl group begins with an attack by the nucleophile at the carbonyl carbon. The substitution then proceeds through a tetrahedral intermediate, which loses the leaving group. Acid catalysis is common and the reaction takes place via a protonated carbonyl group.

- Hydrolysis of an ester is the reaction of the ester with water. Esterification is the reaction of a carboxylic acid and an alcohol. These reactions are the inverse of one another. The catalyst for this reaction is either an acid or a base. Usually, a base is the catalyst for the hydrolysis reaction, and an acid is the catalyst for the esterification reaction.

- Ester formation or hydrolysis is an equilibrium process in acid, but not in base. The basic hydrolysis is catalytic for the hydroxide ion. However, once the carboxylic acid is formed, it reacts with the hydroxide ion in solution.
Amide hydrolysis follows the same pathway as esterification. However, amide formation requires a primary or secondary amine instead of the alcohol required by the esterification.

A reaction of a carboxylic acid with SOCl₂, PCl₃, or PCl₅ generally produces an acyl halide.

A reaction of an acyl halide with a carboxylic acid, or an anhydride exchange, synthesizes an acid anhydride.

A reduction of a carboxylic acid derivative occurs by using LiAlH₄ as the reducing agent. All carboxylic acid derivatives, except the amides, produce alcohols from the carboxylate portion of the molecules. Amides produce amines.

All carboxylic acid derivatives react with organolithium compounds. Depending on the leaving group, the reaction produces either a ketone or a tertiary alcohol. Carboxylic acids produce ketones; esters produce tertiary alcohols.

Chemists usually consider nitriles as a part of the carboxylic acid family. Hydrolysis of a nitrile produces either an amide or a carboxylic acid. Hydrolysis proceeds either via an acid or a base catalysis.

A reaction between a nitrile with a hydride donor produces a primary amine.

A reaction between a nitrile and either a Grignard reagent or an organolithium compound produces a ketone.

The Baeyer-Villiger reaction synthesizes an ester from a ketone. The reaction involves migration of a group with its electrons from the carbon to an oxygen. The migratory aptitude for migrating groups is H > tert-alkyl > secondary alkyl ~ benzyl ~ phenyl > primary alkyl > methyl.

When solving a mechanism problem, look for an analogy among the mechanisms that you already know. Then draw the curved arrows to show the movement of electrons as the molecules react.

If you can not find a clear analogy among the mechanisms you know, search for the most strongly acidic and basic atoms. Then using only previously studied methods, draw the curved arrows to show electron movement.