NUCLEOPHILIC SUBSTITUTIONS ON THE CARBONYL GROUP—
THE CARBOXYLIC ACID FAMILY

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The carbonyl compounds, aldehydes and ketones, were the focus of the preceding chapter. We saw that much of the chemistry of these compounds can be correlated with the electrophilic character of the carbonyl carbon atom.

Compounds of another class, generally known as the carboxylic acid family, also contain carbonyl groups. They differ from aldehydes and ketones in that the carbonyl group is bonded to at least one heteroatom: an oxygen, nitrogen, or halogen atom. These important substances are widely distributed in nature. Carboxylic acids are the products of oxidative decomposition of organic materials: esters occur as fruit fragrances and amides as the backbone of protein structure. Two other important members of this group, acid halides and anhydrides, are not naturally occurring compounds.

Again, the carbonyl group is the key to the chemistry of compounds in the carboxylic acid family. It is receptive to attack by nucleophiles, and it accounts for the enhanced acidity of the α-hydrogen atoms in many of these substances.

Yet there is an important difference between the chemistry of the carbonyl compounds (aldehydes and ketones) and that of the members of the carboxylic acid family. Aldehydes and ketones undergo nucleophilic additions to the unsaturated carbonyl group and produce relatively stable saturated adducts. Nucleophilic additions to the carbonyl group of carboxylic acids and their derivatives lead to unstable intermediates which react further to regenerate the carbon-oxygen double bond. We will see that much of the chemistry associated with compounds of the carboxylic acid family is the interconversion of one member into another. The processes involve nucleophilic substitution on the carbonyl group:

\[ \text{Nu}^- + R-\text{C} = \text{O} \rightarrow R-\text{C} = \text{O} \text{Nu} + \text{L}^- \]
8-1 REACTIVITY IN THE CARBOXYLIC ACID FAMILY

A. Substitution versus addition

In chap. 7 we learned that nucleophilic addition to the carbonyl carbon atom of an aldehyde or ketone is a reversible process. Completion of the reaction depends on the formation of a stable adduct or subsequent conversion of the initial adduct to a stable compound.

\[
\text{Nu}^- + \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{C}}} \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{O}}} \rightarrow \text{Nu}-\overset{\cdot}{\overset{\cdot}{\overset{\cdot}{C}}} \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{O}}} \text{ or subsequent product}
\]

We can also conceive of a process resembling the reverse reaction in which a group other than the entering nucleophile departs from the original carbonyl carbon atom. The consequence of such a sequence is formation of a new compound by a process which has retained the carbonyl group.

\[
\text{Nu}^- + \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{O}}} \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{C}}} \rightarrow \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{O}}} \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{C}}} \text{Nu}^- + \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{L}}} ^-
\]

The product is the result of nucleophilic substitution on the carbonyl group. Put in different words, the nucleophile has been acylated. Acylation is the process whereby an acyl group \(R-C=O\) is transferred from one atom (or group) to another. It is an important reaction of the carboxylic acid family of compounds.

B. The nature of the leaving group

Nucleophilic substitution on a carbonyl group requires the loss of a group other than the entering nucleophile. The leaving group (L) departs with the electron pair by which it was originally bonded to the carbonyl group. The stability of a leaving group can therefore be related to the basicity of the group (sec. 6-1). Weak bases (the conjugate bases of strong acids) are good leaving groups; for they are able to accommodate the electron pair effectively.

If nucleophilic substitution were to take place with aldehydes or ketones, the leaving group would be a hydride or a carbocation. These anions are very unstable, since they are the conjugate bases of very weak acids (Table 6-1).

\[
\text{Nu}^- + \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{C}}} \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{O}}} \rightarrow \text{Nu}^- \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{C}}} \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{H}}} \text{ Unfavorable} \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{C}}} \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{O}}} \text{Nu}^- + \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{L}}} ^-
\]

An aldehyde
Nucleophilic Substitutions on the Carbonyl Group—The Carboxylic Acid Family

By contrast, compounds of the carboxylic acid family have better leaving groups. In some cases the leaving group is a relatively stable anion. An example is chloride, the conjugate base of the strong acid HCl.

\[ \text{Nu}^- + \text{R} - \text{C} = \text{O} \rightleftharpoons \text{Nu} - \text{R} - \text{C} = \text{O} \rightleftharpoons \text{Nu} - \text{R} - \text{C} = \text{O}^- + \text{Cl}^- \]

In other examples protonation enhances the ability of a group to depart.

\[ \text{R} - \text{C} = \text{O} + \text{H}^+ \rightleftharpoons \text{R} - \text{C} = \text{O}^- \rightleftharpoons \text{R} - \text{C} = \text{O}^- + \text{H}_2\text{O} \]

\[ \text{HNu} + \text{R} - \text{C} = \text{O} \rightleftharpoons \text{Nu} + \text{R} - \text{C} = \text{O} \rightleftharpoons \text{Nu} + \text{R} - \text{C} = \text{O}^- + \text{H}_2\text{O} \]

**Problem 8-1**

For each of the following reactions of compounds in the carboxylic acid family: (i) circle the acyl group of reactant and product, (ii) underline the atom or group which will become the leaving group and (iii) draw a square around the nucleophile.

a. \[ \text{CH}_3\text{C}=\text{O} + \text{H}_2\text{O} \rightleftharpoons \text{CH}_3\text{C} = \text{O} + \text{CH}_3\text{OH} \]

b. \[ \text{CH}_3\text{CH}_2\text{C}=\text{O} + \text{CH}_3\text{OH} \rightleftharpoons \text{CH}_3\text{CH}_2\text{C} = \text{O} + \text{HCl} \]

c. \[ \text{CH}_3\text{NH}_2 + \text{CH}_3\text{C}=\text{O} \rightleftharpoons \text{CH}_3\text{NH}_2 + \text{CH}_3\text{C}=\text{O} + (\text{CH}_3)_2\text{CH}=\text{O} \]

d. \[ \text{CH}_3\text{CH}_2\text{C}=\text{O} + \text{CH}_3\text{OH} \rightleftharpoons \text{CH}_3\text{CH}_2\text{C} = \text{O} + \text{CH}_3\text{CH}_2\text{OH} \]

Throughout our studies of organic chemistry we will see that leaving groups play a very important role in directing the course of reactions. The substitution of one group or atom for another is the pathway for a large number of reactions which we will consider in this and subsequent chapters. Table 8-1 summarizes the
leaving characteristics of some of the groups encountered in nucleophilic substitution on carbonyl groups.

The reactivity of compounds in the carboxylic acid family toward nucleophiles can be predicted, in part, by the tendency of leaving groups to depart. We find, for instance, that acyl halides and anhydrides are the most reactive carboxylic acid derivatives. Amides are the least reactive, and esters and carboxylic acids have an intermediate reactivity. The more stable the leaving group the more reactive the carboxylic acid derivative.

**PROBLEM 8-2**

Relate the leaving groups of table 8-1 to the acidity of the conjugate acids.

Another factor which has some bearing on reactivity of these compounds is the strength of the bond between the leaving group and the carbonyl carbon atom. This bond must break if substitution is to occur. Yet bond energies (sec. 3-5) indicate that a carbon-chlorine single bond is stronger than a carbon-nitrogen single bond. These data would suggest a reactivity opposite that predicted from leaving group abilities (table 8-1).

A closer examination of the functional groups reveals that bond energies may actually be consistent with the reactivity observed. Resonance interaction between the departing group and the carbonyl group can account for the strengthening of the C—L bond through significant double-bond character.

\[
\begin{align*}
\text{R} & \quad \text{O} \\
\text{R} & \quad \text{C} \quad \text{O} \\
\hline
\end{align*}
\]

Such an interaction is more important for the nitrogen atom of an amide than a halogen atom of an acyl halide. The carbon-nitrogen bond in an amide is actually stronger than would have been predicted from the strengths of C—N bonds in saturated molecules.

In subsequent sections of this chapter we will explore the preparation and characteristic reactions of compounds in the carboxylic acid family. We will see that there is considerable similarity to the chemistry of aldehydes and ketones.
The differences can be attributed to the presence of potential leaving groups which lead to substitution rather than addition.

8-2 ACYL HALIDES AND ANHYDRIDES

Acyl halides (often called acid halides) and anhydrides are the most reactive of the carboxylic acid derivatives. That is not surprising, since halide and carboxylate are good leaving groups. Both are relatively stable anions, so a catalyst is not usually required for reaction.

\[ R-C(\overset{\circ}{O})_2CH_2 + \text{Nu}^- \rightarrow R-C(\overset{\circ}{O})_2CH_2^+ + \text{Nu} \]

\[ R-C(\overset{\circ}{O})_2CH_2 + \text{Nu}^- \rightarrow R-C(\overset{\circ}{O})_2CH_2^+ + \text{Nu} \]

Acyl halides are normally more reactive than anhydrides. We can attribute that, in part, to the leaving group. Departure of a halide ion, the conjugate base of a very strong acid (pK_a < 1), is expected to be more favorable than loss of a carboxylate anion (pK_a of a carboxylic acid ≈ 5).

Acyl halides and anhydrides are seldom end products of syntheses. Their utility is as reactive intermediate reagents within a synthetic sequence.

A. Preparation of acyl halides

Acyl chlorides are the only acyl halides generally used. The bromides and iodides are more difficult to handle and more expensive to prepare, and they offer little synthetic advantage over chlorides.

Acyl chlorides are normally prepared from carboxylic acids through substitution of chloride for the hydroxy group. Hydroxide, a poor leaving group, must be converted to a good leaving group in order to prepare the more reactive acyl chloride. Thiocyanyl chloride or the phosphorus halides, PCl_5 or PCl_3, are the reagents usually employed for the reaction, 

\[ \text{CH}_3\text{C}(\overset{\circ}{O})_2\text{C}H_2 + \text{SOCl}_2 \rightarrow \text{CH}_3\text{C}(\overset{\circ}{O})_2\text{C}H_2\text{Cl} + \text{SO}_2 + \text{HCl} \]

去过酸 (Ethanoic acid)  过硫酰氯 (Thionyl chloride)  过氯酸 (Acetyl chloride)  (Ethanoic chloride)

98%

\[ \text{CH}_3\text{C}(\overset{\circ}{O})_2\text{C}(\overset{\circ}{O})_2\text{C}H_2 + \text{SOCl}_2 \rightarrow \text{CH}_3\text{C}(\overset{\circ}{O})_2\text{C}(\overset{\circ}{O})_2\text{C}H_2\text{Cl} + \text{SO}_2 + \text{HCl} \]

过戊酸 (Butyric acid)  过硫酰氯 (Thionyl chloride)  过氯酸 (Butyryl chloride)  (Butyric chloride)  98%
b. The reaction is often carried out by using only about 10 percent of the stoichiometric quantity of DMF in SOCl₂. Why is this possible?

c. Propose a step-by-step mechanism for the preparation of trifluoracetyl chloride from dimethylformamidinium chloride and trifluoroacetic acid.

**PROBLEM 8-5**

A synthetically useful method for the preparation of some acid chlorides is an exchange reaction. Thus acetyl chloride (bp 51°C) can be prepared by mixing acetic acid (bp 118°C) and benzoyl chloride (bp 198°C). The benzoyl chloride is converted to benzoic acid (bp 250°C) in the process. What experimental technique can be used to favor recovery of the desired product?

\[ \text{CH}_3\text{CO}_2\text{H} + \text{C}_6\text{H}_5\text{COCl} \rightarrow \text{CH}_3\text{COCl} + \text{C}_6\text{H}_5\text{CO}_2\text{H} \]

(bp 118°C) \hspace{1cm} \text{(bp 51°C)} \hspace{1cm} \text{(bp 198°C)} \hspace{1cm} \text{(bp 250°C)}

**B. Preparation of acid anhydrides**

Anhydrides of carboxylic acids are commonly prepared through reaction of an acyl chloride with the corresponding carboxylic acid. Pyridine is often used as a base to enhance the nucleophilicity of the carboxylic acid and react with the HCl which forms.

\[ \text{CH}_3\text{CH}_2\text{OH} + \text{CH}_3\text{CH}_2\text{Cl} \rightarrow \text{CH}_3\text{CH}_2\text{OC}(\text{CH}_3)\text{CO}_2\text{CH}_3 + \text{C}_5\text{H}_5\text{NCl}^- \]

Pentanoic anhydride

(Pentanoic anhydride)

Pyridinium hydrochloride

(Pyridinium chloride)

\[ \text{CH}_3\text{CH}_2\text{OH} + \text{CH}_3\text{CH}_2\text{Cl} \rightarrow \text{CH}_3\text{CH}_2\text{OC}(\text{CH}_3)\text{CO}_2\text{CH}_3 + \text{C}_5\text{H}_5\text{NCl}^- \]

Heptanoic anhydride

(Heptanoic anhydride)

Pyridinium hydrochloride

(Pyridinium chloride)

**PROBLEM 8-6**

Suggest a mechanism for the preparation of propanoic anhydride from propanoic acid and propanoyl chloride in the presence of pyridine.

Dehydration is another general method for preparing anhydrides, since the compounds are formally composed of two molecules of carboxylic acid from which one molecule of water has been removed. Because acyl halides and anhydrides readily react with water (sec. 8-3B), they are often employed as the dehydrating agent. Acetic anhydride is commonly used in the preparation of higher-molecular-weight anhydrides in a process known as anhydride exchange. Acetic anhydride is relatively inexpensive, and the hydrolysis product, acetic acid, has a lower
Each reagent first converts the hydroxy group of the carboxylic acid into a derivative which can be considered as a mixed organic-inorganic anhydride (sec. 8-2B). The original hydroxy oxygen atom is incorporated into a good leaving group. Nucleophilic addition of chloride and departure of the good leaving group follows an addition-elimination sequence typical of compounds in the carboxylic acid family.

\[
\begin{align*}
\text{R-OH} + \text{SOCl}_2 & \rightarrow \text{R-Cl} + \text{HCl} \\
\end{align*}
\]

Thionyl chloride, though less reactive than the phosphorus halides, is the simplest reagent to use. It is a liquid (bp 75°), and so it functions as both solvent and reagent in the preparation of acyl chlorides. The carboxylic acid is usually added to thionyl chloride; the gaseous products (SO\(_2\) and HCl) are allowed to evade; and then excess reagent is removed by distillation.

**PROBLEM 8-3** Butanoyl bromide can be prepared from butanoic acid and phosphorus tribromide. Propose a mechanism for the reaction.

The use of thionyl chloride in the presence of dimethylformamide (DMF) is a newer preparative method for the formation of acyl chlorides which appears to be better than the older procedures. The actual reagent is dimethylformamidinium chloride. The carboxylic acid reacts with this reagent; then chloride adds to the carbonyl group and dimethylformamide is displaced.

\[
\begin{align*}
\text{SOCl}_2 + \text{CH}_3\text{COOH} & \rightarrow \text{CH}_3\text{COCl} + \text{SO}_2 \\
\text{Thionyl chloride} &\quad \text{Dimethylformamidinium chloride} \\
\text{N(CH}_3\text{)_2} &\quad \text{N(CH}_3\text{)_2} \text{Cl}^- \\
\end{align*}
\]

**PROBLEM 8-4** a Why would you expect dimethylformamidinium chloride to be a good reagent for the preparation of acid chlorides?
boiling point than most other carboxylic acids. The equilibrium reaction can be made to favor product formation by distilling the acetic acid from the reaction mixture.

\[
2C_2H_4CO_2H + (CH_2CO_2)O \xrightarrow{\Delta} (C_2H_6CO_2)O + 2CH_3CO_2H
\]

Benzoin acid (mp 122°) Acetic anhydride Benzoin anhydride (bp 160°) Acetic acid (bp 118°)

Interestingly, direct dehydration by heating two molecules of carboxylic acid is not a successful method for the preparation of acyclic anhydrides. However, five- and six-membered cyclic anhydrides are often prepared by this direct dehydration procedure.

\[
\begin{align*}
\text{CO}_2\text{H} & \xrightarrow{\Delta} \text{H}_2\text{O} \\
\text{CO}_2\text{H} & \\
\text{Maleic acid} \quad \text{Maleic anhydride} \quad >95\% \\
\text{(Z-Butenedioic acid) [cis]} &
\end{align*}
\]

PROBLEM 8.7

a. Explain why five- and six-membered cyclic anhydrides might be expected to form more readily than acyclic anhydrides.

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

Acetic anhydride is an economically important product of the chemical industry. One commercial method for its preparation involves addition of acetic acid to the very reactive carbonyl group of a compound known as ketene.

\[
\text{CH}_3\text{CO}_2\text{H} + \text{CH}_2=\text{C}=\text{O} \rightarrow \text{CH}_2=\text{C}(-\text{O})\text{O} \text{CCH}_3 \xrightarrow{\Delta} \text{CH}_2=-\text{C}(-\text{O})\text{O} \text{CCH}_3
\]

Acetic acid Ketene Acetic anhydride

Most anhydrides used in synthetic chemistry are symmetrical; that is, they are composed of the fragments of two identical molecules of carboxylic acid. Unsymmetrical (mixed) anhydrides, which commonly involve an organic and an inorganic acid fragment, are often found as intermediates in preparative reactions (sec. 8-2A). The mixed anhydrides of phosphoric acid play an important role in many biological processes (sec. 8-9B).

PROBLEM 8.8

Draw the structural formulas for the organic product(s) in each of the following reactions.

a. \( \text{C}_4\text{H}_8\text{CH}_2\text{COCl} + \text{C}_6\text{H}_5\text{CH}_2\text{CO}_2\text{Na}^+ \rightarrow \)

b. Phenylacetic acid + thionyl chloride \( \rightarrow \)

c. 3-Methyl-1,5-pentanedioic acid (\( \beta \)-methylglutaric acid) + acetic anhydride \( \xrightarrow{\Delta} \)
8-3 OXYGEN OR SULFUR AS THE NUCLEOPHILE—ESTERS AND CARBOXYLIC ACIDS

Some of the earliest investigations into the nature of chemical equilibria involved experiments on the interconversions of esters and carboxylic acids. These reactions, proceeding in opposite directions, are nucleophilic substitutions on carboxyl groups by oxygen nucleophiles.

Esterification of a carboxylic acid involves substitution of hydroxy by an alkoxy group. The ester is converted back to the carboxylic acid by substitution of the alkoxy by a hydroxy group.

\[
\begin{align*}
\text{R-COOH} \quad \text{+ R'OH} & \quad \text{+ H₂O} \\
\text{R-COOR'} & \quad \text{An ester}
\end{align*}
\]

A. Substitution by alcohols

Reaction of a carboxylic acid with an alcohol in the presence of an acid catalyst is one of the standard methods for preparing an ester. The reaction, known as the Fischer esterification, is a simple route to esters from readily available starting materials.

\[
\text{CH₃CO₂H} + \text{C₂H₅OH} \xrightarrow{\text{H}^+} \text{CH₃CO₂C₂H₅} + \text{H₂O}
\]

Acetic acid Ethanol Ethyl acetate (Ethyl ethanoate)

\[
K = \frac{[\text{CH₃CO₂C₂H₅}][\text{H₂O}]}{[\text{CH₃CO₂H}][\text{C₂H₅OH}]} \approx 4
\]

Equilibrium constants for esterification are often relatively small in magnitude. For example, the reaction of acetic acid and ethanol has an equilibrium constant of about 4. If the reaction is to be synthetically useful, some technique must be employed to increase the quantity of ester formed. Two approaches are common. In one, the water is removed as the reaction proceeds. In the other, an excess of one reagent is used.
If the Fischer esterification is carried out by using equimolar quantities of acetic acid and ethanol, what will be the concentration of ethyl acetate at equilibrium?

What will be the ethyl acetate concentration at equilibrium if 10 moles of ethanol is used with 1 mol of acetic acid?

The commercial preparation of ethyl acetate from acetic acid and ethanol involves distilling the low-boiling ester (bp 77°) from the reaction as it is formed. The distillate is actually a ternary azetrope (a constant-boiling mixture) boiling at 70° and consisting of 83% ethyl acetate, 8% ethanol, and 9% water. The latter two components are readily removed by an extraction process, and then the ethyl acetate is recycled for further esterification.

A wide variety of esters can be formed by the Fischer method, such as sulfuric, hydrochloric, and p-toluene sulfonic acids, which are common catalysts.

\[
\begin{align*}
\text{BrCH}_2\text{CO}_2\text{H} + \text{C}_2\text{H}_5\text{OH} & \xrightarrow{\text{H}_2\text{SO}_4} \text{BrCH}_2\text{CO}_2\text{C}_2\text{H}_5 + \text{H}_2\text{O} \\
\text{K} \cdot \text{C}_2\text{H}_5\text{CO}_2\text{CCOO}_2\text{K} + 2\text{C}_2\text{H}_5\text{OH} & \xrightarrow{\text{H}_2\text{SO}_4} \text{H}_2\text{CO}_2\text{CCOO}_2\text{C}_2\text{H}_5 + 2\text{H}_2\text{O} \\
\text{HO}_2\text{CCO}_2\text{H} + 2\text{C}_2\text{H}_5\text{OH} & \xrightarrow{\text{H}_2\text{SO}_4} \text{H}_2\text{CO}_2\text{CCOO}_2\text{C}_2\text{H}_5 + \text{H}_2\text{O} \\
\text{CH}_2\text{CO}_2\text{H} + \text{C}_2\text{H}_5\text{OH} & \xrightarrow{\text{H}_2\text{SO}_4} \text{CH}_2\text{CO}_2\text{C}_2\text{H}_5 + \text{H}_2\text{O}
\end{align*}
\]

When the carboxylic acid and hydroxy groups are present in the same molecule, a lactone (cyclic ester) may form. Lactonization occurs readily with \(\gamma\) - and \(\delta\)-hydroxy acids, which form unstrained five- and six-membered rings (sec. 4-3).

\[
\text{HOCH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H} \xrightarrow{\text{H}^+} \text{\gamma-Hydroxybutyric acid (4-Hydroxybutyric acid)}
\]

Esterification and the reverse reaction, ester hydrolysis (sec. 8-38), have been extensively studied in order to elucidate the mechanism of this reversible process. In an important experiment in the development of a mechanistic description for the reaction, isotopically labeled alcohol was used to demonstrate that the alcohol
oxygen atom actually becomes bonded to the carboxy carbon atom. Benzoic acid was treated with $^{18}$O-labeled methanol in the presence of an acid catalyst. The methyl benzoate which was produced contained the $^{18}$O label, and the water contained only unlabeled oxygen atoms.

\[
\text{C}_6\text{H}_5\text{CO}_2\text{H} + \text{CH}_3\text{CH}_2\text{OH} \xrightleftharpoons{H^+} \text{C}_6\text{H}_5\text{CO}_2\text{CH}_3 + \text{H}_2\text{O}
\]

Benzoic acid \hspace{1cm} Methanol\textsuperscript{$^{18}$O} \hspace{1cm} Methyl benzoate\textsuperscript{$^{18}$O}

Another series of experiments established that the rate of esterification decreases as crowding near the carboxy group increases.

\[
\text{CH}_3\text{CO}_2\text{H} > (\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}) > 
\]

These data, along with the experimental observation that acid catalyzes the rate of ester formation, are consistent with nucleophilic addition of the alcohol to the protonated carboxy group. A tetrahedral adduct is formed. We developed a similar mechanism for the addition of oxygen nucleophiles to aldehydes and ketones (sec. 7-3). In the case of esterification the tetrahedral adduct cannot be isolated, and it leads, by loss of water, to the product.

\[
\text{CH}_3\text{CO}_2\text{H} + \text{H}^+ \rightleftharpoons \text{CH}_3\text{CH}_2\text{OH} \rightleftharpoons \text{CH}_3\text{CH}_2\text{O} - \text{H}_2\text{O} \rightleftharpoons \text{CH}_3\text{CH}_2\text{O} + \text{H}_2\text{O}^+
\]

**PROBLEM 8-10**

Compare the tetrahedral adducts in ester and hemiacetal formation. Why does one reaction proceed by addition and the other by substitution?

**PROBLEM 8-11**

\( a \) Use hybrid orbital considerations to explain the observation that the oxygen atom of an alcohol is more basic than the carboxyl oxygen atom in an aldehyde or ketone.

\( b \) Explain the fact that the carboxyl oxygen atom of an ester is more basic than the alkoxy oxygen of an ester.

\[
\begin{align*}
\text{R} - \text{C} = \text{O} & \xrightleftharpoons{K_1} \text{R} - \text{C} = \text{O} \\
\text{OR}^* & \xrightleftharpoons{K_2} \text{R} - \text{C} = \text{O} \\
\text{OR}^* & \xrightleftharpoons{H^+} \text{R} - \text{C} = \text{O} \\
K_1 > K_2
\end{align*}
\]
Formation of an ester from a carboxylic acid and an alcohol may be experimentally inconvenient, once isolation of the desired product from the equilibrated reaction mixture can require complicated purification procedures. It is often desirable to convert the carboxylic acid to a reactive acyl halide or anhydride so that reaction with an alcohol is an essentially irreversible process.

The requisite acyl chloride can be prepared in advance (sec. 8-2A) and then utilized for ester formation as needed. Another common approach is to treat the carboxylic acid with thionyl chloride and then add the alcohol without isolating the acyl chloride. A base, usually a tertiary amine, is generally employed to take up the HCl which is generated.

\[
(CH_3)_2C=O + SOCl_2 \rightarrow (CH_3)_2COCl
\]

Pivalic acid

(2,2-Dimethylpropanoic acid)

Thionyl chloride

Pivaloyl chloride

(2,2-Dimethylpropanoyl chloride)

\[
(CH_3)_2CO,H_4 + \text{Ethyl pivalate} \rightarrow (CH_3)_3CO,H_4
\]

Ethyl pivalate

(Ethyl 2,2-Dimethylpropanoate)

95%

\[
\begin{align*}
\text{CH}_2\text{COC}l & + \text{CH}_3\text{C}l \to \text{C}_6\text{H}_5\text{NCH}_2\text{Cl} \to \text{CH}_3\text{CO,C(CH}_3)_3 \\
\text{Acyl chloride} & \quad \text{t-butyl alcohol} \quad \text{2-Methyl-2-propanol} \quad \text{1-butyl acetate} \\
\text{C}_6\text{H}_5\text{CH}=\text{CHC}l & + \text{C}_6\text{H}_5\text{OH} + \text{SOCl}_2 \to \text{C}_6\text{H}_5\text{CH}=\text{CHCO,C,H}_4 \\
\text{Cinnamic acid} & \quad \text{Phenol} \quad \text{Phenyl cinnamate} \quad \text{(Phenyl 3-phenylpropanoate)} \quad 78%
\end{align*}
\]

Anhydrides, though less reactive than acyl chlorides, are often suitable for the preparation of esters. One portion of the molecule acylates the alcohol, and the other half of the anhydride is recovered as a carboxylic acid. When the anhydride is part of a cyclic structure, reaction with 1 mol of alcohol opens the ring and forms a half-acid-half-ester.

\[
(CH_3CO)O + (CH_3)2COH \xrightarrow{\text{ZnCl}_2} \text{CH}_3\text{CO,C(CH}_3)_3 + \text{CH}_3\text{CO,H}
\]

Acetic anhydride

n-butyl alcohol

n-butyl acetate

Acetic acid

90%

\[
\text{Suarcyic anhydride} + \text{CH}_3\text{OH} \rightarrow \text{H}_2\text{O,CCH}_2\text{CHCO,C,H}_3
\]

Sucinic anhydride

Methanol

Methyl hydrogen succinate

(Monomethyl succinate)

90%

* The word "hydrogen" in the name indicates that one of the carboxy groups remains in the product.
PROBLEM 8.12
Provide a structural formula and name for the major organic product in each of the following reactions.

a. \( \text{CH}_3\text{CH}_2\text{CHCO}_2\text{H} + \text{C}_2\text{H}_5\text{OH} \xrightarrow{\text{H}^+} \)

b. \( \text{C}_2\text{H}_5\text{CO}_2\text{H} + 5\text{SOCl}_2 \)

c. \( \text{O} \quad \text{O} \quad \text{O} \quad + \text{C}_2\text{H}_5\text{OH} \rightarrow \)

d. \( \text{CH}_3\text{COCl} + (\text{CH}_3)_2\text{CHOH} \rightarrow \)

e. \( \text{C}_4\text{H}_9\text{CO}_2\text{Na}^+ + \text{C}_2\text{H}_5\text{COCl} \rightarrow \)

f. \( \text{C}_2\text{H}_5\text{COCl} + \text{C}_2\text{H}_5\text{OH} \rightarrow \)

PROBLEM 8.13
Propose a mechanism for each of the following methods for the preparation of propyl acetate.

\( \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} + \text{CH}_3\text{CO}_2\text{H} \xrightarrow{\text{H}^+} \text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_3 \)

\( \text{CH}_3\text{CH}_2\text{OH} + \text{CH}_3\text{COCl} \xrightarrow{\text{R}^+} \text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3 \)

Equilibration of an alcohol with an ester containing a different alkoxy group is a method for converting one ester to another. The process, known as transesterification, is normally catalyzed by an acid.

\( \text{CH}_3\text{CH}=\text{CHCO}_2\text{H} + \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} \xrightarrow{\text{CH}_3\text{CH}=\text{CHCO}_2\text{H}} \text{CH}_3\text{CH}=\text{CHCO}_2\text{CH}_2\text{CH}_3 \)

(Methyl propionate) (1-Butanol)

\( \text{CH}_2=\text{CHCO}_2\text{C}_2\text{H}_5 + \text{CH}_3\text{OH} \)

(Methyl propionate) (Butyl acetate)

\( \text{CH}_2=\text{CHCO}_2\text{C}_2\text{H}_5 + \text{CH}_3\text{OH} \rightarrow \text{CH}_3\text{CO}_2\text{C}_2\text{H}_5 + \text{CH}_3\text{OH} \)

Butyl acetate (Methanol) 94%

PROBLEM 8.14
The equilibrium constants for transesterification are usually near unity. What are two experimental techniques that might be used to ensure a high yield of butyl acetate from methyl acetate and 1-butanol?
The importance of the esterification reaction has led to many clever methods for manipulating the equilibria so as to maximize product yield. Acetate esters can be prepared in high yield by utilizing isopropenyl acetate as the source of the acetyl group:

\[
\text{CH}_3\text{C}_\text{O} + \text{CH}_2\text{OH} \xrightarrow{\text{H}_2\text{SO}_4} \text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3
\]

Isopropenyl acetate

Glycol (1,2,3-Propanetriol)

\[
\text{CH}_3\text{CO}_2\text{CH}_3 + 3 \left(\text{CH}_2=\text{C} \right)\text{H}_2\text{OH} \to \text{CH}_3\text{C}_\text{O} + 3\text{CH}_3\text{C}_\text{O}\text{H}
\]

Glycerol triacetate

\[
\text{Acetone}
\]

The reaction is another example of transesterification, but in this case the alcohol being displaced is the unstable enol of acetone. As the enol departs, it tautomerizes to the keto form (acetone), and the reaction becomes essentially irreversible.

**PROBLEM 8-15** Isopropenyl acetate is readily prepared commercially by the reaction of ketene \((\text{CH}_3\text{C}=\text{O})\) and acetone. Propose a mechanism for this reaction.

**B. Substitution by water**

All carboxylic acid derivatives are hydrolyzed (cleaved by water) to produce carboxylic acids. Low-molecular-weight acyl halides and anhydrides react violently, so they must be stored and utilized under anhydrous conditions. The reaction is seldom used synthetically, since acyl halides and anhydrides are almost always prepared from the carboxylic acids (sec. 8-2).

\[
\text{CH}_3\text{C}_\text{O}_2\text{Cl} + \text{H}_2\text{O} \to \text{CH}_3\text{CO}_2\text{H} + \text{HCl}
\]

Acetyl chloride

Acetic acid

\[
\text{HO}_2\text{C}_\text{C}\text{O}_2\text{H} + \text{H}_2\text{O} \to \text{HO}_2\text{C}_\text{C}\text{H}_2\text{C}_\text{O}_2\text{H}
\]

Gluconic anhydride

Gluconic acid (1,5-Pentanedicarboxylic acid)

Although many higher-molecular-weight acyl halides and anhydrides seem relatively stable toward water, they are in fact also quite reactive. Their deceptively low reactivity is due to their low solubility in water. Reaction can occur only at the interface between the two immiscible reactants.

Esters and amides react slowly with water. The addition of an acid or base is almost always employed in order to attain suitable rates of reaction.
Ester hydrolysis is the reverse of the formation of an ester from an alcohol and an acid. Thermodynamics require that the sequence of steps involved in the forward reaction must be the same (in the reverse order) as the sequence of steps in the reverse reaction when reaction conditions are identical. This is often stated as the principle of microscopic reversibility.

Numerous studies of ester hydrolysis have provided information relative to the mechanism of esterification. We proposed (sec. 8-3A) that a tetracoordinate intermediate is involved in the esterification sequence. Yet this intermediate is not capable of being isolated and identified. Might the reaction involve a tetracoordinate transition state rather than an intermediate?

A hydrolysis experiment has provided support for the intermediate. The reactant was ethyl benzoate labeled with $^{18}$O in the carbonyl group. As hydrolysis proceeded, samples were removed and chemically unchanged ester was isolated. It was found that the unlabeled oxygen atoms from the water were being incorporated into the ester. The only reasonable way that could occur is by the involvement of an intermediate which reverts to ester faster than it is converted to the carboxylic acid.

**PROBLEM 8-16**

Set up a mechanistic scheme to show how exchange of water with $^{18}$O-labeled ethyl benzoate is consistent with a tetracoordinate intermediate in ester hydrolysis (and esterification).

The rates of hydrolysis of esters are increased by acid or base, but there is an important difference. Acid is a catalyst (i.e., it is regenerated), whereas base is a
reactant (one mole of base is consumed per mole of ester hydrolyzed). Furthermore, acid-catalyzed hydrolysis is an equilibrium reaction with an equilibrium constant near unity. In contrast, base-promoted hydrolysis is essentially irreversible because formation of the carboxylate anion is energetically quite favorable.

\[
\text{R-CO}_2\text{R}' + \text{H}_2\text{O} \rightleftharpoons \text{R-CO}_2\text{H} + \text{R'OH}
\]

\[
\text{R-CO}_2\text{R}' + \text{HO}^- \xrightleftharpoons[\text{H}_2\text{O}]^{\text{+}} \text{R-CO}_2^- + \text{R'OH}
\]

**PROBLEM 8-17**

a. Propose a mechanism for the hydrolysis of ethyl benzoate in aqueous sodium hydroxide.

b. Why is esterification of a carboxylic acid in aqueous base (the reverse of the base-promoted hydrolysis of an ester) not a favorable reaction?

**PROBLEM 8-18**

The *haloform reaction* is used as a qualitative test for methyl ketones. A ketone is usually treated with iodine in an aqueous base medium. The reaction involves halogenation of the methyl ketone followed by substitution of hydroxide for the good leaving group, triiodomethyl carbanion.

\[
\text{C}_4\text{H}_6\text{C}_3\text{CH}_3 + \text{I}_2 \xrightarrow{\text{NaOH/H}_2\text{O}} \text{C}_4\text{H}_6\text{CO}_2\text{Na}^+ + \text{HCl}_2
\]

*a* Propose a step-by-step mechanism for the haloform reaction of acetophenone.

*b* Do you expect acetaldehyde to undergo the haloform reaction?

*c* Halogen and aqueous sodium hydroxide form an oxidizing solution (NaOX) which accounts for the haloform reaction of certain alcohols such as ethanol, 2-propanol, and 2-butanol. Write the chemical equation for the haloform reaction of 2-butanol using NaOH/H₂O/I₂.

Hydrolysis of amides is very similar to the hydrolysis of esters, though it is generally slower. Reactions are carried out in basic or acidic media.

\[
\text{CH}_2\text{O}+\text{NHCCCH}_3 + \text{KOH} \xrightarrow{\Delta \text{H}_2\text{O/Methanol}} \text{4-Methoxycarbonyl-2-nitroaniline}
\]

\[
\text{CH}_2\text{O}+\text{NH}_2 + \text{CH}_3\text{CO}_2\text{K}^+ \xrightarrow{97\% \text{Potassium acetate}} \text{4-Methoxycarbonyl-2-nitroaniline}
\]

\[
\text{HO}_2\text{C(CH}_3)_2\text{CO}_2\text{NH}_2 + \text{H}_2\text{O} \xrightarrow{\text{HCl}} \text{HO}_2\text{C(CH}_3)_2\text{CO}_2\text{H} + \text{NH}_4\text{Cl}
\]

Glutaramide

Glutaric acid

94%
Amide hydrolysis has limited synthetic application as a method for producing carboxylic acids. In the laboratory, amides are normally prepared from carboxylic acids or their derivatives (sec. 8-4), so there is little advantage in converting amides back to carboxylic acids. We will, however, encounter some rather sophisticated degradative techniques for hydrolysis of the amide bonds of peptides and proteins (chap. 16).

One synthetically important application of amide hydrolysis occurs during the conversion of nitriles to carboxylic acids. Nitriles are readily prepared from substances other than compounds of the carboxylic acid family (secs. 7-2A, 9-8B). The addition of water to a nitrile produces an amide (sec. 7-9A) which is subsequently hydrolyzed to a carboxylic acid. The conversion under acidic or basic conditions is usually carried out at elevated temperatures without isolating the amide.

$$\text{C}_{6}\text{H}_{5}\text{C}_2\text{H}_4\text{CH}_2\text{CN} + 2\text{H}_2\text{O} \xrightarrow{\text{NaOH}/\text{H}_2\text{O}} \text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$$

$\text{3-benzyl-2-methylpentanenitrile}$

$$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CONH}_2 \rightarrow \text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{Na}^+ \xrightarrow{\text{H}^+} \text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$$

$\text{Not isolated}$

$\text{3-Benzyl-3-methylpentanoic acid}$

$$\text{C}_3\text{H}_7\text{CN} + 2\text{H}_2\text{O} \xrightarrow{\text{H}_2\text{SO}_4} \text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$$

$\text{3-Methylbenzanilide}$

$\text{2-Methylbenzoic acid}$

**Problem 8-19**

Suggest a mechanism for the hydrolysis of benzamide in

a. Aqueous acid

b. Aqueous base

### C. Soaps and Detergents

The basic hydrolysis of esters is known as saponification. The name originated from the ancient method for producing soap. Animal fats, which are triesters of the alcohol glycerol (triglycerides, sec. 17-1), were hydrolyzed by heating in an aqueous base. Potash (potassium carbonate) extracted from wood ashes was usually the base employed. Modern soapmaking utilizes aqueous sodium hydroxide (caustic soda or lye) for the hydrolysis of fats.
OXYGEN OR SULFUR AS THE NUCLEOPHILE—ESTERS AND CARBOXYLIC ACIDS

RCOCH₂

RCO₂H + 3NaOH → 3RCO₂Na⁺ + 3H₂O

RCO₂H₂

A triglyceride

A soap

Glycerol

A soap is the sodium or potassium salt of a long-chain carboxylic acid (R = C₁₃₋₁₇). The carboxylic acids derived from natural fats are known as fatty acids. An economically important industry is based on the recovery of animal fat from meat processing and subsequent conversion of the fat to soap or chemical raw materials.

CH₃(CH₂)₁₃CH=CH(CH₂)₇CO₂Na⁺ + H⁺ → CH₃(CH₂)₁₃CH=CH(CH₂)₇CO₂H

Sodium oleate

A soap

Oleic acid

(9-Octadecenoic acid)

A fatty acid

CH₃(CH₂)₁₃CO₂K⁺ + H⁺ → CH₃(CH₂)₁₃CO₂H

Potassium palmitate

A soap

Palmitic acid

(16-Hexadecenoic acid)

A fatty acid

Soaps owe their properties to the combination of a polar carboxylate group and nonpolar hydrocarbon chain within the same molecule. In an aqueous medium, large numbers of soap molecules congregate in a spherical structure known as a micelle. The polar carboxylate ends of the molecules are at the outside edge of the micelle because of their attraction for water (hydrophilic). The nonpolar hydrocarbon ends of the molecules assemble together at the center of the micelle so as to minimize any contact with water (hydrophobic).

An idealized soap micelle
A "soap solution" is actually the suspension of soap micelles in water. Soap cleaves by attracting nonpolar molecules (greases, etc.) to the nonpolar center of the micelle. The outer, polar part of the micelle is attracted to the water as the "solubilized" grease is washed away.

Soaps are classified as surfactants; that is, they are surface-active agents. Soaps lower the surface tension of water. The lowered surface tension enables a soap solution to penetrate the weave of a fabric, which thereby enhances the soap's cleansing ability.

Many types of synthetic detergents are now available for laundering and other surfactant applications. The most common types are salts of sulfonic acids (sec. 8-9A). These materials are classified as anionic detergents because the polar end of the molecule is an alkylsulfonate anion.

CH₃(CH₂)₆C₆H₄SO₄Na⁺
Sodium p-decylbenzenesulfonate
An anionic detergent

Detergents are better than soaps for use in water containing significant concentrations of calcium and magnesium ions ("hard water"). Long-chain carboxylic acids form relatively insoluble calcium and magnesium salts which separate from the aqueous phase as an ineffective "soap scum." Related sulfonic acid salts remain soluble and retain their surfactant properties.

Most synthetic detergents possess straight-chain rather than branched-chain alkyl groups. The straight chains are more readily degraded by natural processes. Such biodegradability is essential to prevent waste water systems from depositing high concentrations of "soap" into rivers and lakes.

Two other types of synthetic detergents are used for more specialized surfactant applications. Cationic detergents are based upon quaternary ammonium salt structures and are widely used in fabric softeners. Polyalcohols (polyols) and polyethers find applications as neutral detergents.

\[(\text{CH}_2\text{CH}_2\text{OH})_n\text{CH}_3\text{Cl}^-\]
N,N-Dimethyl-N,N-diolauredammonium chloride
A cationic detergent

\[(\text{CH}_2\text{O})_n\text{CH}_3\text{O}^-\]
Dodecyl β-galactoside
A neutral detergent

**Problem 8-20**
Dishwasher detergents and other strong cleaning agents often contain a strong base such as sodium hydroxide or trisodium phosphate. How does the additive enhance the cleaning ability of the detergent?

**D. Substitution by thioles**

A compound which contains a sulfur atom is normally a good nucleophile (sec. 9-3C). *This* acids, the sulfur derivatives of carboxylic acids, can be prepared through nucleophilic substitution by hydrogen sulfide on acid derivatives. Thioesters, the sulfur analogs of esters, are synthesized from thioles (mercaptans) and reactive acylating agents derived from acids.
Thioesters are generally more reactive than esters toward nucleophilic substitution. The reactivity is attributed to the better leaving-group ability of thiols (mercaptide) than that of alkoxides.

The facile cleavage of the acyl-sulfur bond provides a basis for some important biological transformations. *Coenzyme A* (CoASH) is a complex molecule which terminates in a thiol group.

Coenzyme A is often found in biological systems as a thioester. One of the functions of the coenzyme thioester is as an activating agent (sec. 17-1B). For example, acetyl coenzyme A (AcSCoA) can transfer an acetyl group to a phosphate ion (often called "inorganic phosphate"). This particular reaction is controlled by the enzyme phosphotransferase. It occurs in certain bacteria as one of the steps in the formation of adenosine triphosphate (ATP).
**Problem 8-21**

Complete each of the following equations.

a. \( \text{C}_2\text{H}_5\text{CONH}_2 + \text{H}_2\text{O} \xrightarrow{\text{H}_2\text{NCl}_2} \text{H}_2\text{O} \)

b. Methyl pivalate + 2-methyl-1-propanol (excess) \( \xrightarrow{\Delta} \text{C}_3\text{H}_7\text{CH}_2\text{SO}_3\text{H} \)

c. \( \begin{array}{c}
\text{O} \\
\text{CO}_2\text{CH}_3 \\
\text{H}_2\text{O} \\
\xrightarrow{\Delta}
\end{array} \)

d. \( \begin{array}{c}
\text{O} \\
\text{O} \\
\xrightarrow{\Delta}
\end{array} \) + \( \text{H}_2\text{O} \) (excess) \( \xrightarrow{\text{NaOH}} \)

e. Benzoyl chloride + \( \text{H}_2\text{O} \) \( \xrightarrow{\text{THF}} \)

f. \( \beta\)-Methyl-\( \gamma\)-butyrolactone + ethanol ----

**8-4 Nitrogen as the Nucleophile—Amides**

Most of the nucleophilic nitrogen compounds that we will encounter in organic chemistry are amines. Primary and secondary amines, as well as ammonia, can react with carboxylic acids and their derivatives to produce amides.

\[ \text{R}-\begin{array}{c}
\text{C}^\text{O} \\
\text{t}
\end{array} + \text{NH}_2 \xrightarrow{\text{4 HL}} \text{R}-\begin{array}{c}
\text{C}^\text{O} \\
\text{N} \\
\end{array} \]

But amines are also bases, and therefore they readily react with carboxylic acids in acid-base reactions which lead to ammonium salts.

\[ \text{CH}_3\text{CO}_2\text{H} + \text{NH}_3 \rightarrow \text{CH}_3\text{CO}_2\text{NH}_4 \]

Acetic acid Ammonia Ammonium acetate

\[ \text{C}_6\text{H}_5\text{CH}_2\text{CO}_2\text{H} + \text{CH}_3\text{NH}_2 \rightarrow \text{C}_6\text{H}_5\text{CH}_2\text{CO}_2\text{NH}_3\text{CH}_3 \]

Phenylacetic acid Methylamine Phenyldiamine

Salt formation is a rapid, exothermic process, and the ammonium salts which are obtained are commonly high-melting, stable solids. A high temperature is usually required to dehydrate the ammonium salt and form the corresponding amide. This type of thermally promoted amide formation is used commercially for the preparation of the polyamide nylon (sec. 20-3C).

\[ \text{CH}_3\text{CO}_2\text{NH}_3 \xrightarrow{150^\circ} \text{H}_2\text{O} \rightarrow \text{CH}_3\text{CONH}_2 \]

Ammonium acetate Acetamide 90%
PROBLEM

8-22

The ammonium salt of a carboxylic acid can be converted to the corresponding amide by heating the salt to 150–200℃.

a How is it possible that the ammonium ion, a nonnucleophilic species, can function as the reagent which ultimately adds an amino group to the carbonyl carbon atom?

b Suggest a mechanism for the conversion of ammonium prepansoate to prepepamidate.

Five- and six-membered lactams (cyclic amides) readily form from suitable compounds possessing an amino and a carboxylate group. We again have examples of favorable intramolecular reactions (sec. 7-3A) leading to unstrained rings.

\[
\text{NH}_2
\]

\[
\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H} \xrightarrow{\Delta} \text{CH}_3\text{NHC} = \text{C}=\text{O}
\]

4-Aminopentanoic acid

4-Methylbutyrolactam

≥100%

The most common method for preparing amides is the reaction of acyl halides with ammonia or amines and the interchange between esters and amines. The former procedure requires an extra mole of amine or some other base to take up the acid that is produced.

\[
\text{(CH}_3\text{)}_2\text{CHCO}_2\text{H} + \text{SOCl}_2 \rightarrow \text{(CH}_3\text{)}_2\text{CHCOCICl}
\]

2-Methylpropanoic acid

Thionyl chloride

2-Methylpropanoyl chloride

\[
\text{(CH}_3\text{)}_2\text{CHCONH}_2 + \text{NH}_4\text{Cl}^- \rightarrow \text{(CH}_3\text{)}_2\text{CHCONH}_2\text{Cl}^{-}
\]

2-Methylpropanamide

≥85%

\[
\text{COCl} + 2\text{(CH}_3\text{)}_2\text{NH} \rightarrow \text{CON(CH}_3)_2 + \text{(CH}_3\text{)}_2\text{NH}_2\text{Cl}^{-}
\]

Cyclohexanecarboxylic chloride

Dimethylamine (N-Methylethanamine)

X-N- Dimethyl-cyclohexanecarboxamide

≥99%
PROBLEM 8-23

Why are amide yields low when equimolar quantities of amine and acyl chloride react?

The nitrogen analogs of anhydrides are imides. They are prepared by exchange of ammonia or amines with anhydrides or by reaction of amides with carboxylic acids.

\[
\text{Phthalic anhydride} + \text{NH}_3 \text{ (excess)} \xrightarrow{\text{H}_2\text{O}} \text{Phthalimide} \]

\[
\text{HO}_2\text{CCH}_2\text{C}_6\text{H}_4\text{CONH}_2 \xrightarrow{\Delta} \text{NH} + \text{H}_2\text{O} \]

Gutarimide

Gutarimide 68% (8%)

PROBLEM 8-24

Write chemical equations for the conversion of pentanoic acid to

a. Sodium pentanoate
b. Pentanoyl chloride
c. N-Methylpentanamide
d. Ammonium pentanoate
e. Methyl pentanate.

PROBLEM 8-25

Fill in the structures missing in the following synthetic sequence.

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

An excellent method for preparing amides from amine and carboxylic acids utilizes N,N'-dicyclohexylcarbodiimide (DCC) as an activating reagent. Yields are
usually high and conditions sufficiently mild to allow use of this expensive reagent for many complex peptide syntheses (sec. 16-2D).

\[
\text{CH}_3\text{CO}_2\text{H} + \text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{NH}_2 + \frac{\text{Acetic acid}}{} \xrightarrow{\text{THF}, 0^\circ} \text{C}_6\text{H}_5\text{N} = \text{C} - \text{NC}_6\text{H}_5
\]

\[
\xrightarrow{\text{DCC}} \text{N}_2\text{N}'\text{-Dicyclohexylcarbodiimide} \quad \text{N}_2\text{N}'\text{-Dicyclohexylurea}
\]

Conversion of the carbodiimide to a urea during the sequence is a hydration reaction. But DCC is doing more than functioning as a dehydrating agent. The carboxylic acid adds to the diimide carbon atom to produce an unstable intermediate. This intermediate is an activated carboxylic acid derivative which is reactive toward nucleophilic substitution.
A combination of many of the reactions of carboxylic acid derivatives is utilized in the process known as enantiomer resolution (sec. 4-4E). Recall that the enantiomers of an individual compound have identical physical properties and cannot be separated by the usual laboratory methods (sec. 4-4A). But diastereomers are separable stereoisomers (sec. 4-4E). Conversion of enantiomers to diastereomers can provide a method of separation.

A common method for resolving racemic alcohols is to convert the alcohols to half acid–half esters through reaction with a cyclic anhydride (sec. 8-3A). The free carboxylate group is then used as a "handle" for connection to a naturally occurring optically active amine such as brucine. The ammoxidation salt resulting from reaction of the acid with this amine is a mixture of diastereomers which may be separated, usually by fractional crystallization. Separation of the diastereomers accomplishes separation of the original alcohol enantiomers. Regeneration of the half acid–half ester from each diastereomer by acidification followed by hydrolysis of the esters produces the individual alcohol enantiomers. The resolution of 2-octanol is outlined in Fig. 8-1.

![Diagram of enantiomer resolution process]

**FIGURE 8-1**

The enantiomer resolution of 2-octanol.

**PROBLEM 8-26**

a. What important aspect of the ester hydrolysis mechanism receives support from the formation of optically pure alcohol in the resolution sequence?

b. The structural formula of the alkaloid brucine is depicted below. Draw a formula for brucine 2-octyl phthalate.
8-5 HYDRIDE AS THE NUCLEOPHILE—REDUCTION

We encountered the complex metal hydrides, lithium aluminum hydride and sodium borohydride, during our study of aldehydes and ketones (sec. 7-4A). It should not be surprising to learn that these same substances are useful hydride donors toward other types of carboxyl groups. An important contribution to their synthetic utility relates to the markedly different reactivity of the two hydride donors. Lithium aluminum hydride reacts with a broad range of compounds, whereas sodium borohydride is much less reactive and is therefore quite selective.

The course of reactions of hydride donors with compounds of the carboxylic acid family depends on the nature of the reactant and reagent. Acyl halides, anhydrides, esters, and carboxylic acids tend to undergo reduction to primary alcohols. However, proper choice of the reaction conditions and hydride source may permit an aldehyde to be isolated. Amides lead to amines or in certain cases to aldehydes. The usual reaction of a hydride donor with a compound of the carboxylic acid family is reduction.

A. Reactions with acyl halides, anhydrides, esters, and carboxylic acids

The four members of the carboxylic acid family are considered together because they follow similar reaction pathways. Consider their reactions with lithium aluminum hydride. Reduction of each leads to a primary alcohol.

\[
\begin{align*}
2\text{Cl}_2\text{C}=\text{C}O \quad + \quad \text{LiAlH}_4 & \quad \xrightarrow{\text{3} \text{H}_2\text{O}} \quad 2\text{Cl}_2\text{CCH}_2\text{OH} \\
\text{Trichloroacetyl chloride} & \\
(\text{C}_4\text{H}_4\text{CO})_2\text{O} \quad + \quad \text{LiAlH}_4 & \quad \xrightarrow{\text{3} \text{H}_2\text{O}} \quad 2\text{C}_6\text{H}_5\text{CH}_2\text{OH} \\
\text{Benzoic anhydride} & \text{Benzyl alcohol} 45\% \\
2\text{CH}_3\text{CH}≡\text{CH}\text{CH}_2\text{CO}_2\text{H} \quad + \quad \text{LiAlH}_4 & \quad \xrightarrow{\text{3} \text{H}_2\text{O}} \quad 2\text{CH}_3\text{CH}≡\text{CHCH}_2\text{CH}_2\text{OH} \quad + \quad 2\text{CH}_3\text{OH} \\
\text{Methyl 3-pentenoate} & \text{Neopentyl alcohol} 75\% \\
4(\text{C}_2\text{H}_5\text{CO})_2\text{H} \quad + \quad 3\text{LiAlH}_4 & \quad \xrightarrow{\text{3} \text{H}_2\text{O}} \quad 4(\text{C}_2\text{H}_5)_2\text{CCH}_2\text{OH} \\
\text{Phosphoric acid} \text{(1,2-Dimethoxyethane) acid)} & \\
\end{align*}
\]
8-10 SUMMARY

A. The chemistry of the carboxylic acid family

The concept of the polar carboxyl group provides a basis for understanding the chemistry of carboxylic acids and their derivatives. Reactions are initiated by the addition of a nucleophile to the carboxyl carbon atom. But unlike aldehydes and ketones, compounds of the carboxylic acid family undergo nucleophilic substitution rather than addition.

Substitution takes place because compounds of the carboxylic acid family contain potentially good leaving groups. A leaving group departs from the initially formed tetrahedral adduct to regenerate the carbon-oxygen double bond. The overall process is acylation of the nucleophile.

\[
\text{Nu}^- + \text{Nu}^+ \rightarrow \text{Nu}^- \rightarrow \text{Nu}^+ + \text{Nu}^- \rightarrow \text{Nu}^+ \rightarrow \text{Nu}^+
\]

Nucleophiles are, or can readily be converted to, leaving groups. Thus many reactions involve substitution of one leaving group for another. The changes account for the interconversion of members of the carboxylic acid family (fig. 8-3).

**FIGURE 8-3**

interconversions of carboxy derivatives (order of reaction is the reverse at top).

- SOCl₂
- Ph₃PO₃
- R'COOH
- R'COOR

<table>
<thead>
<tr>
<th>Reactions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂O + R'COOH</td>
<td>R'COOH + H₂O</td>
</tr>
<tr>
<td>R'COOH + OH⁻</td>
<td>R'COO⁻ + OH⁺</td>
</tr>
<tr>
<td>R'COOH + H⁺</td>
<td>R'COOH⁺</td>
</tr>
<tr>
<td>R'COOH⁺ + OH⁻</td>
<td>R'COO⁻ + H₂O</td>
</tr>
<tr>
<td>R'COOH + H₂O₂</td>
<td>R'COO⁻ + H₂O₂⁻</td>
</tr>
</tbody>
</table>

**Legend:**
- R'COOH: Carboxylic acid
- R'COO⁻: Anion of carboxylic acid
- R': Organic substituent
In some cases substitution is made effectively irreversible by a second addition of the same nucleophile. Reactions with hydride donors and organometallic reagents follow this pathway in the formation of alcohols.

$$\text{C}_3\text{H}_7\text{OH} + [\text{H}^+] \rightarrow \text{C}_3\text{H}_7\text{OH}$$

The carbonyl group of carboxylic acid derivatives enhances the acidity of hydrogen atoms connected to the adjacent carbon atom. Removal of such α-hydrogen atoms produces enolate ions which are potential nucleophiles. Reaction of an ester enolate anion with a second ester group is a synthetically important pathway to β-keto esters.

$$\text{CH}_3\text{CO}_2\text{H} + \text{CH}_2\text{CO}_2\text{H} \rightarrow \text{CH}_3\text{C}==\text{CH}_2\text{CO}_2\text{H}$$

The decarboxylation of β-keto acids (obtained from β-keto esters) extends the synthetic utility of the acylation reaction. Loss of carbon dioxide proceeds through the formation of enol intermediates.

$$\text{CH}_3\text{C}==\text{CH}_2\text{CO}_2\text{H} \rightarrow \text{CH}_3\text{C}==\text{CH}_2\text{C}==\text{CH}_2$$

Sulfuric and phosphoric acids undergo reactions which resemble those of carboxylic acids. Esters, amides, and acid halide derivatives of these acids can be prepared and used as components of various organic processes.

B. Reactions of compounds of the carboxylic acid family

Formation of carboxylic acid derivatives:

a) Acyl halides (sec. 8-2A)

$$\text{RCO}_2\text{H} + \text{SOCl}_2 \rightarrow \text{RCO}_2\text{Cl}$$

$$\text{RCO}_2\text{H} + \text{POCl}_3 \rightarrow \text{RCO}_2\text{Cl}$$
Nucleophilic Substitutions on the Carbonyl Group—The Carboxylic Acid Family

b Anhydrides (sec. 8-2B)

\[
\text{RCO}_2\text{O} + R'\text{CO}_2\text{H} \rightarrow \text{RCO}_2\text{O} + R'\text{CO}_2\text{H}
\]

2RCO_2H + (R'CO_2)O \rightarrow (RCO)_2O + 2R'CO_2H

c Esters (sec. 8-3A)

\[
\text{RCO}_2\text{H} + R'\text{OH} \xrightarrow{H^+} \text{RCO}_2\text{R}' + H_2O
\]

\[
\text{RCO}_2\text{H} + R'\text{OH} \rightarrow \text{RCO}_2\text{R}'
\]

\[
(\text{RCO}_2)O + R'\text{OH} \xrightarrow{H^+} \text{RCO}_2\text{R}' + \text{RCO}_2\text{H}
\]
d Thiocarboxylic acids (sec. 8-3D)

\[
\text{RCO}_2\text{SH} \rightarrow \text{RCO}_2\text{SH}
\]
e Thioesters (sec. 8-3D)

\[
\text{RCO}_2\text{O} + R'S\text{H} \rightarrow \text{RCO}_2\text{O} + R'S\text{H}
\]
f Amides (sec. 8-4)

\[
\text{RCO}_2\text{H} + \text{HN} \rightarrow \text{RCO}_2\text{H}
\]

\[
(\text{RCO}_2)O + \text{HN} \rightarrow \text{RCO}_2\text{H} + \text{RCO}_2\text{H}
\]

\[
\text{RCO}_2\text{H} + \text{HN} \rightarrow \text{RCO}_2\text{H} + \text{H}_2\text{O}
\]

Formation of carboxylic acids from carboxylic acid derivatives (sec. 8-33)

\[
\text{RCO}_2\text{H} + \text{H}_2\text{O} \xrightarrow{H^+ or OH^-} \text{RCO}_2\text{H}
\]

Formation of alcohols

a By hydride addition from complex metal hydrides (sec. 8-5A)

\[
\text{RCOCl} + \text{NaBH}_4 \rightarrow \text{RCH}_2\text{OH}
\]
(RCO)₂O + LiAIH₄ → 2RCH₂OH
RCO₂R' + LiAIH₄ → RCH₂OH + R'O
RCO₂H + LiAIH₄ → RCH₂OH

b By hydride addition from diborane (sec. 8-5C)
RCO₂R' + (BH₃)₂ → RCH₂OH + R'O
RCO₂H + (BH₃)₂ → RCH₂OH

c By addition of organometallic reagents (sec. 8-6A)
HCO₂R' + 2R''MgX → R''CHOH + R'O
HCO₂R' + 2R''MgX → R''CR'' + R'O
ROCOR + 3R'MgX → R''COH + 2R'O

Formation of aldehydes and ketones

a By hindered hydride addition (sec. 8-5A)
RCO₂Cl + LiAIH₄ → RCO₂H
RCO₂Cl + R₂Cd → RCR'
RCO₂H + R'Li → RCR'

Formation of amines (sec. 8-5B,C)
RCN + LiAIH₄ → RCH₂N
RCN + (BH₃)₂ → RCH₂N

The ester condensation (Claisen) reaction (sec. 8-7B,C)
2RCH₂CO₂R' + NaOR' → RCH₂CHCO₂R' + R'O
