substitution. Acyl substitution can be represented generally as follows, with \( E = \) an electrophilic group and \( Y = \) a nucleophilic group:

\[
\begin{align*}
\text{carboxylic acid derivative} & \quad \text{another carboxylic acid derivative} \\
\xrightarrow{\text{O}} \quad R\text{--C--X} + E\text{--Y} & \quad R\text{--C--Y} + E\text{--X} \\
\text{an acyl group} & \quad \text{an acyl group}
\end{align*}
\] (21.6)

The term acyl substitution comes from the fact that substitution occurs at the carbonyl carbon of an acyl group. In other words, an acyl group is transferred in Eq. 21.6 between an \( \text{--X} \) and a \( \text{--Y} \) group. The group \( \text{--X} \) might be the \( \text{--Cl} \) of an acid chloride, the \( \text{--OR} \) of an ester, and so on; this group is substituted by another group \( \text{--Y} \). This is precisely the same type of reaction as esterification of carboxylic acids (\( \text{--X} = \text{--OH}, \text{--Y} = \text{H--OCH}_3 \); Sec. 20.8A). Acyl substitution reactions of carboxylic acid derivatives are the major focus of this chapter.

Although nitriles are not carbonyl compounds, the \( \text{C==N} \) bond behaves chemically much like a carbonyl group. For example, a typical reaction of nitriles is addition.

\[
\begin{align*}
\text{Y} & \quad \text{an \( \text{C==N} \) bond} \\
\rightarrow & \quad \text{an \( \text{C==N} \) bond} \\
\text{R--C==N} + E\text{--Y} & \quad R\text{--C==N} + E\text{--Y}
\end{align*}
\] (21.7)

(Compare this reaction with addition to the carbonyl group of an aldehyde or ketone.) Although the resulting addition products are stable in some cases, in most situations they react further.

Like aldehydes and ketones, carboxylic acid derivatives undergo certain reactions involving the \( \alpha \)-carbon. The \( \alpha \)-carbon reactions of all carbonyl compounds are grouped together in Chapter 22. The reactivity of amides at nitrogen is discussed in Sec. 23.11D.

## 21.7 HYDROLYSIS OF CARBOXYLIC ACID DERIVATIVES

All carboxylic acid derivatives have in common the fact that they undergo hydrolysis (a cleavage reaction with water) to yield carboxylic acids.

### A. Hydrolysis of Esters

**Saponification of Esters**

One of the most important reactions of esters is the cleavage reaction with hydroxide ion to yield a carboxylate salt and an alcohol. The carboxylic acid itself is formed when a strong acid is subsequently added to the reaction mixture.

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{OCH}_3 & \quad \text{O} \\
\text{NO}_2 & \quad \text{NO}_2 \\
\text{methyl 3-nitrobenzoate} & \quad \text{O--C--OH} \\
+ \text{OH} & \quad \text{Na}^+ \\
\xrightarrow{20\% \text{NaOH \, 5–10 min}} & \quad \text{HCl} \\
\text{3-nitrobenzoic acid} & \quad \text{3-nitrobenzoic acid} \\
\text{(90–96% yield)} & \quad \text{(90–96% yield)}
\end{align*}
\] (21.8)
Ester hydrolysis in aqueous hydroxide is called **saponification** because it is used in the production of soaps from fats (Sec. 21.12B). Despite its association with fatty-acid esters, the term **saponification** can be used to refer to the hydrolysis in base of any carboxylic acid derivative.

The mechanism of ester saponification involves the reaction of the nucleophilic hydroxide ion at the carbonyl carbon to give a tetrahedral addition intermediate from which an alkoxide ion is expelled.

\[
\begin{align*}
\text{RC(O)}\text{OCH}_3 + \text{OH}^- &\rightarrow \text{RC(O)}\text{O}^- \text{CH}_3 + \text{H}_2\text{O} \quad (21.9a) \\
\text{tetrahedral addition intermediate}
\end{align*}
\]

The alkoxide ion, after expulsion as a leaving group (methoxide in Eq. 21.9a), reacts with the acid to give the carboxylate salt and the alcohol.

\[
\begin{align*}
\text{RC(O)}\text{O}^- + \text{H}+ &\rightarrow \text{RC(O)}\text{OH} + \text{OCH}_3^- \quad (21.9b) \\
pK_a &= 4.5 & pK_a &= 15
\end{align*}
\]

The equilibrium in this reaction lies far to the right because the carboxylic acid is a much stronger acid than methanol. Le Châtelier’s principle operates: The reaction in Eq. 21.9b removes the carboxylic acid from the equilibrium in Eq. 21.9a as its salt and thus drives the hydrolysis to completion. Hence, **saponification is effectively irreversible**. Although an excess of hydroxide ion is often used as a matter of convenience, many esters can be saponified with just one equivalent of \(\text{-OH}\). Saponification can also be carried out in an alcohol solvent, even though an alcohol is one of the products of the reaction. If saponification were reversible, an alcohol could not be used as the solvent because the equilibrium would be driven toward starting materials.

**Acid-Catalyzed Ester Hydrolysis** Because esterification of an acid with an alcohol is a reversible reaction (Sec. 20.8A), esters can be hydrolyzed to carboxylic acids in aqueous solutions of strong acids. In most cases, this reaction is slow and must be carried out with an excess of water, in which most esters are insoluble. Saponification, followed by acidification, is a much more convenient method for hydrolysis of most esters because it is faster, it is irreversible, and it can be carried out not only in water but also in a variety of solvents—even alcohols.

As expected from the principle of microscopic reversibility (Sec. 4.9B), the mechanism of acid-catalyzed hydrolysis is the exact reverse of the mechanism of acid-catalyzed esterification (Sec. 20.8A). The ester is first protonated by the acid catalyst:

\[
\begin{align*}
\text{RC(O)}\text{OCH}_3 + \text{H}+ &\rightarrow \text{RC(O)}\text{O}^+ \text{CH}_3 \\
\text{RC(O)}\text{OCH}_3 &\rightarrow \text{RC(O)}\text{OCH}_3 + \text{H}_2\text{O} \quad (21.10a)
\end{align*}
\]
As in other acid-catalyzed reactions at the carbonyl group, protonation makes the carbonyl carbon more electrophilic by making the carbonyl oxygen a better acceptor of electrons. Water, acting as a nucleophile, reacts at the carbonyl carbon and then loses a proton to give the tetrahedral addition intermediate:

![Diagram of tetrahedral addition intermediate]

(21.10b)

Protonation of the leaving oxygen converts it into a better leaving group. Loss of this group gives a protonated carboxylic acid, from which a proton is removed to give the carboxylic acid itself.

Let's summarize the important differences between acid-catalyzed ester hydrolysis and ester saponification. First, in acid-catalyzed hydrolysis, the carbonyl carbon can react with the relatively weak nucleophile water because the carbonyl oxygen is protonated. In base, the carbonyl oxygen is not protonated; hence, a much stronger base than water—namely, hydroxide ion—is required to react at the carbonyl carbon. Second, acid catalyzes ester hydrolysis, but base is not a catalyst because it is consumed by the reaction in Eq. 21.9b. Finally, acid-catalyzed ester hydrolysis is reversible, but saponification is irreversible, again because of the ionization in Eq. 21.9b.

Ester hydrolysis and saponification are both examples of acyl substitution (Sec. 21.6). Specifically, the mechanisms of these reactions are classified as nucleophilic acyl substitution mechanisms. In a nucleophilic acyl substitution reaction, the substituting group reacts as a nucleophile at the carbonyl carbon. As in the reactions of aldehydes and ketones (Fig. 19.8, p. 909), nucleophiles approach the carbonyl carbon from above or below the plane of the carbonyl group (Fig. 21.5), first interacting with the \( \pi^* \) (antibonding) molecular orbital of the carbonyl group. As the result of this reaction, a tetrahedral addition intermediate is formed. The leaving group is expelled from this intermediate, departing from above or below the plane of the new carbonyl group. In saponification, the nucleophile is \( \sim \text{OH} \), and in acid-catalyzed hydrolysis, the nucleophile is water; in both cases, the \( \sim \text{OR} \) group of the ester is displaced. With the exception of the reactions of nitriles, most of the reactions in the remainder of this chapter are nucleophilic acyl substitution reactions. They follow the same pattern as saponification, the only substantial difference being the identity of the nucleophiles and the leaving groups.
Hydrolysis and Formation of Lactones

Because lactones are cyclic esters, they undergo the reactions of esters, including saponification. Saponification converts a lactone completely into the carboxylate salt of the corresponding hydroxy acid. Upon acidification, the hydroxy acid forms. However, if a hydroxy acid is allowed to stand in acidic solution, it comes to equilibrium with the corresponding lactone. The formation of a lactone from a hydroxy acid is nothing more than an intramolecular esterification (an esterification within the same molecule) and, like esterification, the lactonization equilibrium is acid-catalyzed.

As the examples in Eqs. 21.12 and 21.13 illustrate, lactones containing five- and six-membered rings are favored at equilibrium over their corresponding hydroxy acids. Although lactones with ring sizes smaller than five or larger than six are well known, they are
less stable than their corresponding hydroxy acids. Consequently, the lactonization equilibria for these compounds favor instead the hydroxy acids.

\[
\text{acid catalyst} \quad \stackrel{\rightleftharpoons}{\text{O}} \quad \text{O} + \text{H}_2\text{O} \quad (\text{almost no lactone present at equilibrium}) \quad (21.14)
\]

B. Hydrolysis of Amides

Amides can be hydrolyzed to carboxylic acids and ammonia or amines by heating them in acidic or basic solution.

\[
\begin{align*}
\text{Ph} & \quad \text{O} \quad \text{CH}_2\text{CH}_2\text{CH}_2\text{C} \quad \text{NH}_2 + \text{H}_2\text{O} & \quad \text{Ph} & \quad \text{O} & \quad \text{CH}_2\text{CH}_2\text{CH}_2\text{C} \quad \text{OH} + \text{NH}_4^+ \text{HSO}_4^- \\
\text{2-phenylbutanamide} & \quad (55 \text{ wt } \% \text{ H}_2\text{SO}_4, \text{ heat, 2 h}) & \quad 2\text{-phenylbutanoic acid} & \quad (88–90\% \text{ yield})
\end{align*}
\]

In acid, protonation of the ammonia or amine product drives the hydrolysis equilibrium to completion. The amine can be isolated, if desired, by addition of base to the reaction mixture following hydrolysis, as in the following example.

\[
\begin{align*}
\text{NH} & \quad \text{C} \quad \text{CH}_3 & \quad \text{protonated amine} & \quad \text{NH}_2 & \quad \text{Br} \quad \text{CH}_3 & \quad \text{Br} & \quad \text{H}_2\text{O} \quad \text{Cl}^- \\
\text{Ph} & \quad \text{Br} & \quad \text{CH}_3 & \quad \text{HCl} \quad \text{H}_2\text{O} & \quad \text{NH}_3 & \quad \text{Cl}^- & \quad \text{OH} & \quad \text{H}_2\text{O} \quad \text{Cl}^- \\
\text{60–67\% yield)
\end{align*}
\]

The hydrolysis of amides in base is analogous to the saponification of esters. In base, the reaction is driven to completion by formation of the carboxylic acid salt.

\[
\begin{align*}
\text{NH} & \quad \text{C} \quad \text{NO}_2 & \quad \text{O} \quad \text{30\% KOH, heat} \quad \text{CH}_3\text{OH/H}_2\text{O} & \quad \text{NH}_2 & \quad \text{NO}_2 \quad \text{O} \quad \text{K}^+ \\
\text{OCH}_3 & \quad \text{OCH}_3 & \quad \text{(95–97\% yield)}
\end{align*}
\]

The conditions for both acid- and base-promoted amide hydrolysis are considerably more severe than the corresponding reactions of esters. That is, amides are considerably \textit{less reactive} than esters. The relative reactivities of carboxylic acid derivatives are discussed in Sec. 21.7E.

The mechanisms of amide hydrolysis are typical nucleophilic acyl substitution mechanisms; you are asked to explore this point in Problem 21.10.
21.10 Show in detail curved-arrow the hydrolysis mechanism of N-methylbenzamide (a) in acidic solution; (b) in aqueous NaOH. Assume that each mechanism involves a tetrahedral addition intermediate.

21.11 Give the structures of the hydrolysis products that result from each of the following reactions. Be sure to show the product stereochemistry in part (b).

(a) 
\[\text{(CH}_3\text{)}_2\text{CH-}^\text{N} + \text{H}_2\text{O} \xrightarrow{\text{NaOH}}\]

(b) 
\[\text{NH}_2\text{O, H}_2\text{O}^+, \text{heat} \xrightarrow{\text{NaOH}}\]

C. Hydrolysis of Nitriles

Nitriles are hydrolyzed to carboxylic acids and ammonia by heating them in strongly acidic or strongly basic solution.

\[
\text{PhCH}_2\text{C} \equiv \text{N} + 2\text{H}_2\text{O} + \text{H}_2\text{SO}_4 \xrightarrow{\text{heat} 3\text{ h}} \text{PhCH}_2\text{CO}_2\text{H} + \text{NH}_4^+ \text{HSO}_4^- \quad (21.18) \\
\text{phenylacetonitrile} \quad \text{phenylacetic acid} \quad (78\% \text{ yield})
\]

\[
\text{1-cyclohexene carbonitrile} + \text{KOH} + \text{H}_2\text{O} \xrightarrow{\text{heat} 17\text{ h}} \text{1-cyclohexene carboxylic acid} + \text{NH}_3 \quad (79\% \text{ yield})
\]

Nitriles hydrolyze more slowly than esters and amides. Consequently, the conditions required for the hydrolysis of nitriles are more severe.

The mechanism of nitrile hydrolysis in acidic solution involves, first, protonation of the nitrogen (Sec. 21.5):

\[
\text{R-} \equiv \text{N} : + \overset{\text{O}}{\text{H}}_2 \quad \xleftrightarrow{\text{R-} \equiv \text{N} - \text{H} + :\overset{\text{O}}{\text{H}}_2} \quad (21.20a)
\]

This protonation makes the nitrile carbon much more electrophilic, just as protonation of a carbonyl oxygen makes a carbonyl carbon more electrophilic. A nucleophilic reaction of water at the nitrile carbon and loss of a proton gives an intermediate called an imidic acid.

\[
\text{R-} \equiv \overset{\text{N}}{\text{H}} + \overset{\text{O}}{\text{H}}_2 \quad \xrightarrow{\text{R-} \equiv \text{N} - \text{H} + :\overset{\text{O}}{\text{H}}_2} \quad \text{an imidic acid} \quad (21.20b)
\]
An imidic acid is the nitrogen analog of an enol (Sec. 14.5A). That is, an imidic acid is to an amide as an enol is to a ketone.

\[
\begin{align*}
\text{imidic acid} & \quad \text{amide} \\
R-C=\text{NH} & \quad R-C=\text{NH}_2 \\
\text{enol} & \quad \text{ketone} \\
R-C=\text{CH}_2 & \quad R-C=\text{CH}_3
\end{align*}
\]

Just as enols are converted spontaneously into aldehydes or ketones, an imidic acid is converted under the reaction conditions into an amide:

\[
\text{imidic acid} \quad \overset{\text{H}_2\text{O}^+}{\longrightarrow} \quad \text{amide}
\]

(21.20c)

Because amide hydrolysis is faster than nitrile hydrolysis, the amide formed in Eq. 21.20c does not survive under the vigorous conditions of nitrile hydrolysis and is therefore hydrolyzed to a carboxylic acid and ammonium ion, as discussed in Sec. 21.7B. Thus, the ultimate product of nitrile hydrolysis in acid is a carboxylic acid.

Notice that nitriles behave mechanistically much like carbonyl compounds. Compare, for example, the mechanism of acid-promoted nitrile hydrolysis in Eqs. 21.20a and b with that for the acid-catalyzed hydration of an aldehyde or ketone (Sec. 19.7A). In both mechanisms, an electronegative atom is protonated (nitrogen of the C≡N bond, or oxygen of the C=O bond), and water then reacts as a nucleophile at the carbon of the resulting cation.

The parallel between nitrile and carbonyl chemistry is further illustrated by the hydrolysis of nitriles in base. The nitrile group, like a carbonyl group, reacts with basic nucleophiles and, as a result, the electronegative nitrogen assumes a negative charge. Proton transfer gives an imidic acid (which, like a carboxylic acid, ionizes in base).

\[
\text{imidic acid} \quad \overset{\text{OH}^-}{\longrightarrow} \quad \text{ionized imidic acid}
\]

(21.21a)

As in acid-promoted hydrolysis, the imidic acid reacts further to give the corresponding amide, which, in turn, hydrolyzes under the reaction conditions to the carboxylate salt of the corresponding carboxylic acid (Sec. 21.7B).

\[
\text{imidic acid} \quad \overset{\text{H}_2\text{O}^+}{\longrightarrow} \quad \text{amide}
\]

(21.21b)
D. Hydrolysis of Acid Chlorides and Anhydrides

Acid chlorides and anhydrides react *rapidly* with water, even in the absence of acids or bases.

\[
\text{Acid chloride or anhydride} + \text{H}_2\text{O} \rightarrow \text{carboxylic acid}
\]

(94% yield)

\[
\text{Ph} = \text{CH} = \text{C} = \text{Cl} + \text{H}_2\text{O} \rightarrow \text{Ph} = \text{CH} = \text{C} = \text{OH} + \text{Cl}^-(>95\% \text{ yield})
\]

However, the hydrolysis reactions of acid chlorides and anhydrides are almost never used for the preparation of carboxylic acids because these derivatives are themselves usually prepared from acids (Sec. 20.9). Rather, these reactions serve as reminders that if samples of acid chlorides and anhydrides are allowed to come into contact with moisture they will rapidly become contaminated with the corresponding carboxylic acids.

E. Mechanisms and Reactivity in Nucleophilic Acyl Substitution Reactions

As we’ve seen, all carboxylic acid derivatives can be hydrolyzed to carboxylic acids; however, the *conditions* under which the different derivatives are hydrolyzed differ considerably. Hydrolysis reactions of amides and nitriles require heat as well as acid or base; hydrolysis reactions of esters require acid or base, but require heating only briefly, if at all; and hydrolysis reactions of acid chlorides and anhydrides occur rapidly at room temperature even in the absence of acid and base. These trends in reactivity, which are observed not only in hydrolysis but in *all* nucleophilic acyl substitution reactions, can be summarized as follows:

*Reactivities of carboxylic acid derivatives in nucleophilic acyl substitution reactions:*

\[
nitriles < amides < esters, \text{ acids} << \text{anhydrides} < \text{acid chlorides}
\]

(The reactions of nitriles are additions, not substitutions, but are included for comparison.)

The practical significance of this reactivity order is that selective reactions are possible. In other words, an ester can be hydrolyzed under conditions that will leave an amide in the same molecule unaffected; likewise, nucleophilic substitution reactions on an acid chloride can be carried out under conditions that will leave an ester group unaffected.

Understanding the trends in relative reactivity requires, first, an understanding of the mechanisms by which nucleophilic acyl substitution reactions take place. (The reactivity of nitriles is considered later.) Let’s start with a reaction free-energy diagram for a generalized carbonyl substitution reaction that occurs under neutral or basic conditions. Carbonyl substitution involves...
the reaction of a nucleophile Nuc\(^{-}\) with a carbonyl compound to form a tetrahedral addition intermediate, which then breaks down with loss of a leaving group X\(^{-}\).

\[
\begin{align*}
\text{Nuc}^{-} + R-C-X &\rightarrow R-C-Nuc + \text{Nuc}^{-} + X^{-} \\
\text{tetrahedral addition intermediate}
\end{align*}
\]

(21.25)

In this generalized reaction, let’s imagine that reactants and products are of comparable stability and that the transition states for both formation and breakdown of the tetrahedral addition intermediates have the same energies. (The case in which Nuc\(^{-}\) is identical to X\(^{-}\) is the simplest example of such a case.) The reaction free-energy diagram for this case is shown in Fig. 21.6a.

**Figure 21.6** How the structure of a carbonyl compound affects the rates of its nucleophilic substitution reactions. In each case, the reactive intermediate is the tetrahedral addition intermediate (see Eq. 21.25). The transition state for the reaction of the nucleophile is shown at the same energy level in all three parts for reference. (a) A reaction free-energy diagram for a generalized reaction in which the reactants and products have the same standard free energy, and the transition states for the two steps shown in Eq. 21.25 also have the same standard free energy. (b) When a carbonyl compound (for example, an amide) is stabilized by resonance and when it contains a poor leaving group, the rates of both formation and breakdown of the tetrahedral addition intermediate are decreased, and nucleophilic substitution is slower. An increase in the stability of the carbonyl compound decreases the rate by increasing the free-energy difference between reactant and transition state. (c) When a carbonyl compound (for example, an acid chloride) is destabilized and when it contains an excellent leaving group, the rates of both formation and breakdown of the tetrahedral addition intermediate are increased, and nucleophilic substitution is faster.
Two major factors can alter this diagram and thus affect the rate of a carbonyl substitution reaction:

1. the stability of the carbonyl compound, and
2. the leaving-group ability of $X^-$

These two factors tend to track together.

Let’s examine two extreme cases to understand the effect of these factors on reaction rate. First, consider the reaction of a nucleophile (for example, $^-$OH) with an amide. This situation is depicted in Fig. 21.6b. An amide is stabilized by the resonance interaction of the unshared electron pair of the nitrogen with the carbonyl group, as follows:

$$\begin{align*}
\text{amide} & \quad \overset{\text{O}^-}{\text{R}} - \text{C} = \text{NH}_2 \\
\text{amide anion} & \quad \overset{\text{O}^-}{\text{R}} - \text{C} = \text{NH}_2
\end{align*}$$

(21.26)

This stabilization increases the energy difference between the amide and the tetrahedral addition intermediate, in which this resonance interaction is not present. The leaving group in this case is the amide anion, $^-$NH$_2$, which is a poor leaving group because it is a very strong base; the $pK_a$ of its conjugate acid (H$^+$NH$_2$) is about 32. The difficulty in expelling a very basic leaving group is reflected in a higher free-energy barrier for the second step, breakdown of the tetrahedral addition intermediate. As a result, the second step is rate-limiting.

Remember that reactivity is governed by the standard free energy of activation $\Delta G^\ddagger$, which is the difference in the standard free energies of the rate-limiting transition state and the reactants (Sec. 4.8C). Also recall that reactions with larger $\Delta G^\ddagger$ are slower than reactions with smaller $\Delta G^\ddagger$. For amide hydrolysis, the standard free energy of activation is the difference between the standard free energy of the rate-limiting transition state—the transition state for breakdown of the tetrahedral intermediate—and that of the starting amide. As Fig. 21.6b shows, this is a much greater $\Delta G^\ddagger$ than in Fig. 21.6a. Hence, amide hydrolysis is a particularly slow reaction and therefore requires harsh reaction conditions to proceed at a reasonable rate.

You may have noticed that the products of the reaction in Fig. 21.6b are less stable than the reactants. This is a direct reflection of the fact that the leaving group is much more basic than the nucleophile. Don’t forget that a subsequent and very rapid step of amide hydrolysis is not shown in this diagram—namely, ionization of the carboxylic acid product and protonation of the amide ion:

$$\begin{align*}
\text{a carboxylate ion} & \quad \overset{\text{O}^-}{\text{R}} - \text{C} = \text{NH}_2 \\
\text{an amine} & \quad \overset{\text{O}^-}{\text{R}} - \text{C} = \text{NH}_2
\end{align*}$$

(21.27)

It is this last, very favorable, equilibrium that drives base-promoted amide hydrolysis to completion.

Notice particularly the role of reactant stabilization in reducing the reaction rate. Recall that this is also an important factor in the relative reactivities of aldehydes and ketones (Sec. 19.7C). Notice also that the electron-donating ability—the Lewis basicity—of the amide nitrogen is really at the heart of both the reactant-stabilization and the leaving-group effects. Its ability to donate electrons by resonance governs the reactant-stabilization effect, and its strong Brønsted basicity makes the nitrogen a poor leaving group. Amides in which this resonance interaction is absent are actually very reactive! (See the sidebar on pp. 1002–1003.)
The saponification of esters can be analyzed much like the base-promoted hydrolysis of amides. Esters are also stabilized by the resonance interaction between the carboxylate oxygen and the carbonyl group. This places a positive charge on the carboxylate oxygen:

\[
\begin{align*}
\begin{array}{c}
\text{O} \\
\text{R} \quad \text{C} \quad \text{RR'} \\
\end{array}
& \quad \leftrightarrow \quad
\begin{array}{c}
\text{O} \\
\text{R} \quad \text{C} \quad \text{R'} \\
\end{array}
\end{align*}
\]

Because oxygen is more electronegative than nitrogen, this resonance interaction is less important in an ester than it is in an amide; hence, esters are stabilized less by resonance than amides are. Thus, the carbonyl stabilization effect in an ester is less pronounced than it is in an amide. Now consider the leaving group: an alkoxide ion is much less basic than an amide ion; hence, the increase in the energy barrier resulting from leaving group basicity is less pronounced in an ester as well. Esters, then, are more reactive than amides.

Let’s now go to the other end of the reactivity spectrum: acid chlorides. This case is depicted in Fig. 21.6.c. The resonance interaction between a chlorine unshared electron pair and the carbonyl group is rather ineffective because it requires the overlap of a chlorine \(3p\) orbital with a carbon \(2p\) orbital. Because this overlap is very poor (Fig. 16.7, p. 771), acid chlorides are stabilized much less by resonance than esters or amides are. What’s more, the polar effect of the chlorine also destabilizes the carbonyl compound through an unfavorable interaction of the carbon–chlorine bond dipole with the partial positive charge on the carbonyl carbon:

Acid chlorides, then, are destabilized relative to amides or esters, and this destabilization reduces the standard free-energy difference between an acid chloride and its transition state.

Now consider the leaving-group effect in the hydrolysis of an acid chloride. Because chloride ion is a very weak base, it is an excellent leaving group. Its leaving-group ability is reflected in a decrease in the transition-state energy for the breakdown of the tetrahedral addition intermediate. In fact, this transition-state energy is decreased so much that the first step—reaction with the nucleophile—becomes rate-limiting. The overall result implied by Fig. 21.6.c is that acid chloride hydrolysis should have a much smaller \(\Delta G^\circ\) than ester or amide hydrolysis. This means that acid chloride hydrolysis should be much faster than amide or ester hydrolysis, as observed.

The resonance stabilization of an anhydride is more important than that in an acid chloride (why?) but less important than that of an ester because of the repulsion between the positive charge on the carboxylate oxygen and the partial positive charge on the carbonyl carbon:

\[
\begin{align*}
\begin{array}{c}
\text{O} \\
\text{R} \quad \text{C} \quad \text{O} \\
\end{array}
& \quad \leftrightarrow \quad
\begin{array}{c}
\text{O} \\
\text{R} \quad \text{C} \quad \text{R} \\
\end{array}
\end{align*}
\]

Hence, from the point of view of reactant stabilization, an anhydride should be more reactive than an ester, but less reactive than an acid chloride. The leaving group in an anhydride is a carboxylate anion—the conjugate base of a carboxylic acid, which has a \(pK_a\) typically in the 4–5 range. This leaving group is considerably more basic than a chloride ion, but considerably
less basic than an alkoxide ion. Hence, an analysis of leaving-group ability also places anhydrides between acid chlorides and esters in reactivity, and this is what is observed.

The following two important principles about nucleophilic carbonyl substitution have emerged from this discussion:

1. Stabilization of the carbonyl compound decreases reactivity; destabilization of the carbonyl compound increases reactivity.
2. Higher basicity of the leaving group decreases reactivity; lower basicity increases reactivity.

To summarize:

\[
\begin{array}{cccccc}
\text{R—C—X} & \text{amides} & \text{esters, carboxylic acids} & \text{anhydrides} & \text{acid chlorides} \\
\text{X} = & \text{—NH}_2 & \text{—OR, —OH} & \text{—O—C—R} & \text{—Cl} \\
\end{array}
\]

increasing stabilization of the carbonyl compound
increasing leaving-group basicity
therefore
increasing reactivity

Although this detailed analysis has been carried out for reactions that involve a negatively charged nucleophile, the same conclusions are obtained from an analysis of acid-catalyzed reactions.

What about nitriles? Reactions of nitriles in base are slower than those of other acid derivatives because nitrogen is less electronegative than oxygen and accepts additional electrons less readily. Reactions of nitriles in acid are slower because of their extremely low basicities. It is the protonated form of a nitrile that reacts with nucleophiles in acid solution, but so little of this form is present (Sec. 21.5) that the rate of the reaction is very small.

**PROBLEMS**

21.12 Use an analysis of resonance effects and leaving-group basicities to explain why acid-catalyzed hydrolysis of esters is faster than acid-catalyzed hydrolysis of amides.

21.13 Which should be faster: base-promoted hydrolysis of an acid fluoride or base-promoted hydrolysis of an acid chloride? Explain your reasoning.

21.14 Complete the following reactions.

(a) \[\text{N=C—CH}_2—\text{C—OCH}_3 + \text{—OH (1 equiv.)} \xrightarrow{\text{H}_2\text{O/H}_3\text{O}^-} \]

(b) \[\text{F—C=O—C}_2\text{H}_5 + \text{—OH} \xrightarrow{\text{H}_2\text{O}} \xrightarrow{\text{H}_2\text{O}^+} \]

(c) \[\text{H}_2\text{N—C—NH}_2 + \text{H}_2\text{O} \xrightarrow{\text{heat, H}_2\text{O}^+} \xrightarrow{\text{H}_2\text{O}} \]