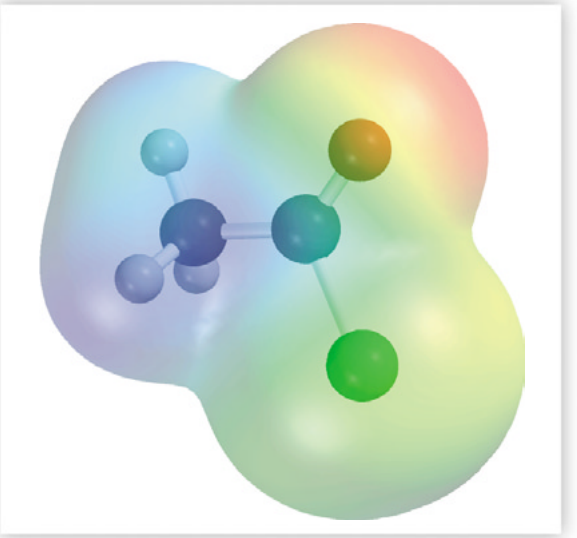


CHAPTER 20

CARBOXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL SUBSTITUTION

This chapter differs from preceding ones in that it deals with several related classes of compounds rather than just one. Included are

1. Acyl chlorides, $RC(=O)Cl$
2. Carboxylic acid anhydrides, $RC(=O)OC(=O)R$
3. Esters of carboxylic acids, $RC(=O)OR'$
4. Carboxamides, $RC(=O)NH_2$, $RC(=O)NHR'$, and $RC(=O)NR'_2$

These classes of compounds are classified as **carboxylic acid derivatives.** All may be converted to carboxylic acids by hydrolysis.

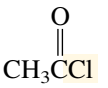
$$\underset{\text{Carboxylic acid derivative}}{RC(=O)X} + \underset{\text{Water}}{H_2O} \longrightarrow \underset{\text{Carboxylic acid}}{RC(=O)OH} + \underset{\text{Conjugate acid of leaving group}}{HX}$$

The hydrolysis of a carboxylic acid derivative is but one example of a **nucleophilic acyl substitution.** Nucleophilic acyl substitutions connect the various classes of carboxylic acid derivatives, with a reaction of one class often serving as preparation of another. These reactions provide the basis for a large number of functional group transformations both in synthetic organic chemistry and in biological chemistry.

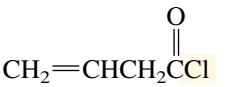
Also included in this chapter is a discussion of the chemistry of *nitriles,* compounds of the type RC≡N. Nitriles may be hydrolyzed to carboxylic acids or to amides and, so, are indirectly related to the other functional groups presented here.

20.1 NOMENCLATURE OF CARBOXYLIC ACID DERIVATIVES

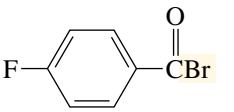
With the exception of nitriles (RC≡N), all carboxylic acid derivatives consist of an acyl group ($RC(=O)-$) attached to an electronegative atom. *Acyl groups* are named by replacing the *-ic acid* ending of the corresponding carboxylic acid by *-yl. Acyl halides* are named by placing the name of the appropriate halide after that of the acyl group.



Acetyl chloride



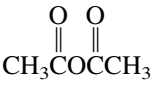
3-Butenoyl chloride



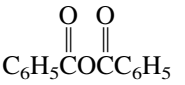
p-Fluorobenzoyl bromide

Although acyl fluorides, bromides, and iodides are all known classes of organic compounds, they are encountered far less frequently than are acyl chlorides. Acyl chlorides will be the only acyl halides discussed in this chapter.

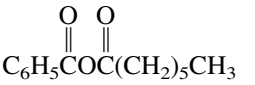
In naming *carboxylic acid anhydrides* in which both acyl groups are the same, we simply specify the acyl group and add the word "anhydride." When the acyl groups are different, they are cited in alphabetical order.



Acetic anhydride



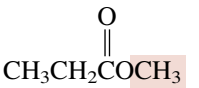
Benzoic anhydride



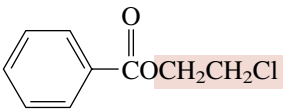
Benzoic heptanoic anhydride

The alkyl group and the acyl group of an *ester* are specified independently. Esters are named as *alkyl alkanoates.* The alkyl group R′ of $RCOR'$ is cited first, followed by the acyl portion $RC(=O)-$. The acyl portion is named by substituting the suffix *-ate* for the *-ic* ending of the corresponding acid.

Ethyl acetate



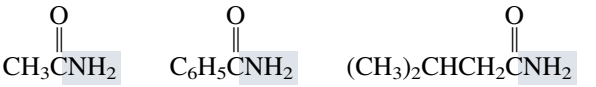
Methyl propanoate



2-Chloroethyl benzoate

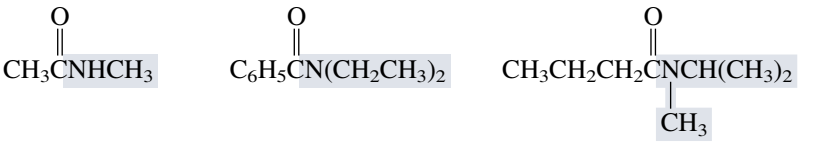
Aryl esters, that is, compounds of the type $RCOAr$, are named in an analogous way.

The names of *amides* of the type $RCNH_2$ are derived from carboxylic acids by replacing the suffix *-oic acid* or *-ic acid* by *-amide*.



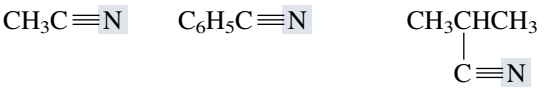
Acetamide | Benzamide | 3-Methylbutanamide

We name compounds of the type $RCNHR'$ and $RCNR'_2$ as *N*-alkyl- and *N,N*-dialkyl-substituted derivatives of a parent amide.



N-Methylacetamide | *N,N*-Diethylbenzamide | *N*-Isopropyl-*N*-methylbutanamide

Substitutive IUPAC names for *nitriles* add the suffix *-nitrile* to the name of the parent hydrocarbon chain that includes the carbon of the cyano group. Nitriles may also be named by replacing the *-ic acid* or *-oic acid* ending of the corresponding carboxylic acid with *-onitrile*. Alternatively, they are sometimes given functional class IUPAC names as alkyl cyanides.

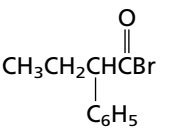


Ethanenitrile (acetonitrile) | Benzonitrile | 2-Methylpropanenitrile (isopropyl cyanide)

PROBLEM 20.1 Write a structural formula for each of the following compounds:

(a) 2-Phenylbutanoyl bromide
(b) 2-Phenylbutanoic anhydride
(c) Butyl 2-phenylbutanoate
(d) 2-Phenylbutyl butanoate
(e) 2-Phenylbutanamide
(f) *N*-Ethyl-2-phenylbutanamide
(g) 2-Phenylbutanenitrile

SAMPLE SOLUTION (a) A 2-phenylbutanoyl group is a four-carbon acyl unit that bears a phenyl substituent at C-2. When the name of an acyl group is followed by the name of a halide, it designates an *acyl halide*.



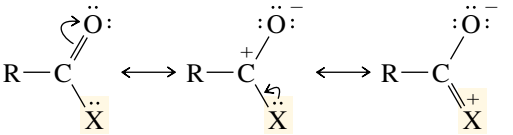
2-Phenylbutanoyl bromide

20.2 STRUCTURE OF CARBOXYLIC ACID DERIVATIVES

Figure 20.1 shows the structures and electrostatic potentials of the various derivatives of acetic acid–acetyl chloride, acetic anhydride, ethyl acetate, acetamide, and acetonitrile. Like the other carbonyl-containing compounds that we've studied, acyl chlorides, anhydrides, esters, and amides all have a planar arrangement of bonds to the carbonyl group.

An important structural feature of acyl chlorides, anhydrides, esters, and amides is that the atom attached to the acyl group bears an unshared pair of electrons that can interact with the carbonyl π system, as shown in Figure 20.2.

This electron delocalization can be represented in resonance terms by contributions from the following resonance structures:



Electron release from the substituent stabilizes the carbonyl group and decreases its electrophilic character. The extent of this electron delocalization depends on the electron-

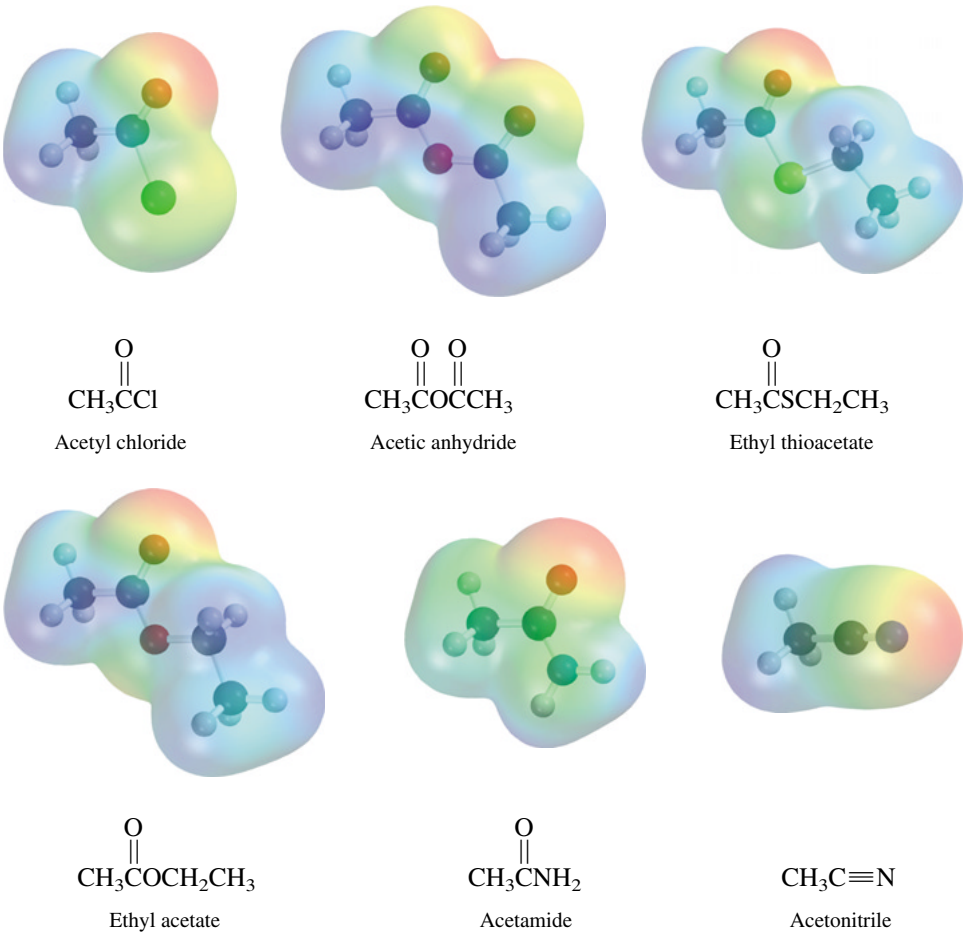
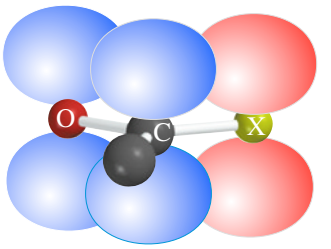


FIGURE 20.1 The structures and electrostatic potential maps of various derivatives of acetic acid. These models may be viewed on *Learning By Modeling.*

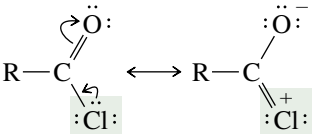


X = OH; carboxylic acid
X = Cl; acyl chloride
X = OCR; acid anhydride
X = OR; ester
X = NR_2; amide

FIGURE 20.2 The three σ bonds originating at the carbonyl carbon are coplanar. The *p* orbital of the carbonyl carbon, its oxygen, and the atom by which group X is attached to the acyl group overlap to form an extended π system through which the π electrons are delocalized.

donating properties of the substituent X. Generally, the less electronegative X is, the better it donates electrons to the carbonyl group and the greater its stabilizing effect.

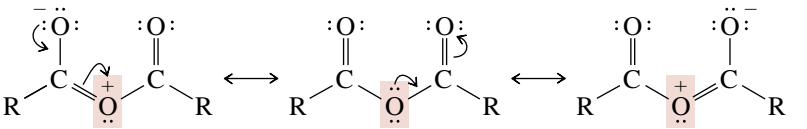
Resonance stabilization in acyl chlorides is not nearly as pronounced as in other derivatives of carboxylic acids:



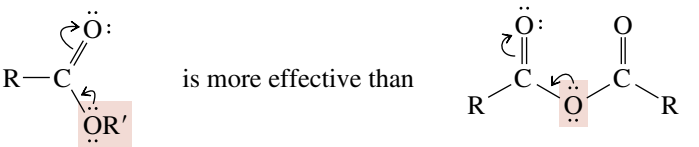
Weak resonance stabilization

Because the carbon–chlorine bond is so long—typically on the order of 180 pm for acyl chlorides—overlap between the 3*p* orbitals of chlorine and the π orbital of the carbonyl group is poor. Consequently, there is little delocalization of the electron pairs of chlorine into the π system. The carbonyl group of an acyl chloride feels the normal electron-withdrawing inductive effect of a chlorine substituent without a significant compensating electron-releasing effect due to lone-pair donation by chlorine. This makes the carbonyl carbon of an acyl chloride more susceptible to attack by nucleophiles than that of other carboxylic acid derivatives.

Acid anhydrides are better stabilized by electron delocalization than are acyl chlorides. The lone-pair electrons of oxygen are delocalized more effectively into the carbonyl group. Resonance involves both carbonyl groups of an acid anhydride.

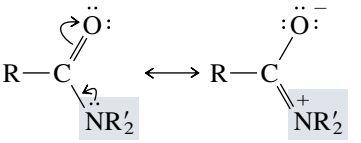


The carbonyl group of an ester is stabilized more than is that of an anhydride. Since both acyl groups of an anhydride compete for the oxygen lone pair, each carbonyl is stabilized less than the single carbonyl group of an ester.



Ester — is more effective than — Acid anhydride

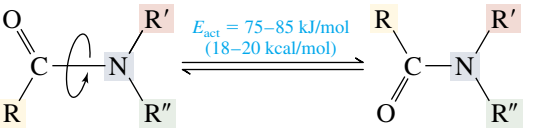
Esters are stabilized by resonance to about the same extent as carboxylic acids but not as much as amides. Nitrogen is less electronegative than oxygen and is a better electron-pair donor.



Very effective
resonance stabilization

Amide resonance is a powerful stabilizing force and gives rise to a number of structural effects. Unlike the pyramidal arrangement of bonds in ammonia and amines, the bonds to nitrogen in amides lie in the same plane. The carbon–nitrogen bond has considerable double-bond character and, at 135 pm, is substantially shorter than the normal 147-pm carbon–nitrogen single-bond distance observed in amines.

The barrier to rotation about the carbon–nitrogen bond in amides is 75 to 85 kJ/mol (18–20 kcal/mol).



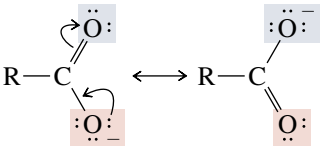
Recall that the rotational barrier in ethane is only 12 kJ/mol (3 kcal/mol).

This is an unusually high rotational energy barrier for a single bond and indicates that the carbon–nitrogen bond has significant double-bond character, as the resonance picture suggests.

PROBLEM 20.2 The ^{1}H NMR spectrum of *N,N*-dimethylformamide shows a separate signal for each of the two methyl groups. Can you explain why?

Electron release from nitrogen stabilizes the carbonyl group of amides and decreases the rate at which nucleophiles attack the carbonyl carbon. Nucleophilic reagents attack electrophilic sites in a molecule; if electrons are donated to an electrophilic site in a molecule by a substituent, then the tendency of that molecule to react with external nucleophiles is moderated.

An extreme example of carbonyl group stabilization is seen in carboxylate anions:



The negatively charged oxygen substituent is a powerful electron donor to the carbonyl group. Resonance in carboxylate anions is more effective than resonance in carboxylic acids, acyl chlorides, anhydrides, esters, and amides.

Table 20.1 summarizes the stabilizing effects of substituents on carbonyl groups to which they are attached. In addition to a qualitative ranking, quantitative estimates of the relative rates of hydrolysis of the various classes of acyl derivatives are given. A weakly stabilized carboxylic acid derivative reacts with water faster than does a more stabilized one.

Most methods for their preparation convert one class of carboxylic acid derivative to another, and the order of carbonyl group stabilization given in Table 20.1 bears directly on the means by which these transformations may be achieved. A reaction that converts one carboxylic acid derivative to another that lies below it in the table is practical; a reaction that converts it to one that lies above it in the table is not. This is another way of saying that *one carboxylic acid derivative can be converted to another if the reaction*

TABLE 20.1 Relative Stability and Reactivity of Carboxylic Acid Derivatives

Carboxylic acid derivative		Stabilization	Relative rate of hydrolysis*
Acyl chloride	RCCl (O)	Very small	10^{11}
Anhydride	RCOCR (O, O)	Small	10^{7}
Ester	RCOR′ (O)	Moderate	1.0
Amide	RCNR′$_2$ (O)	Large	$< 10^{-2}$
Carboxylate anion	RCO$^-$ (O)	Very large	

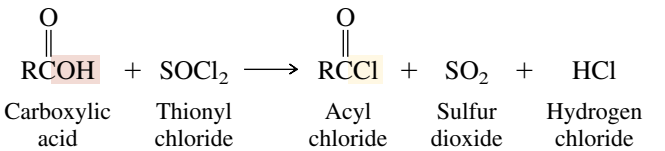
*Rates are approximate and are relative to ester as standard substrate at pH 7.

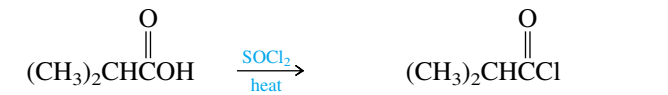
leads to a more stabilized carbonyl group. Numerous examples of reactions of this type will be presented in the sections that follow. We begin with reactions of acyl chlorides.

20.3 NUCLEOPHILIC SUBSTITUTION IN ACYL CHLORIDES

One of the most useful reactions of acyl chlorides was presented in Section 12.7. Friedel–Crafts acylation of aromatic rings takes place when arenes are treated with acyl chlorides in the presence of aluminum chloride.

Acyl chlorides are readily prepared from carboxylic acids by reaction with thionyl chloride (Section 12.7).



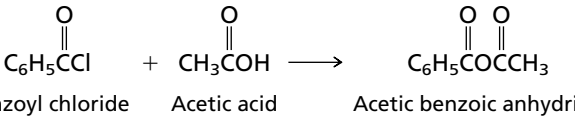


On treatment with the appropriate nucleophile, an acyl chloride may be converted to an acid anhydride, an ester, an amide, or a carboxylic acid. Examples are presented in Table 20.2.

PROBLEM 20.3 Apply the knowledge gained by studying Table 20.2 to help you predict the major organic product obtained by reaction of benzoyl chloride with each of the following:

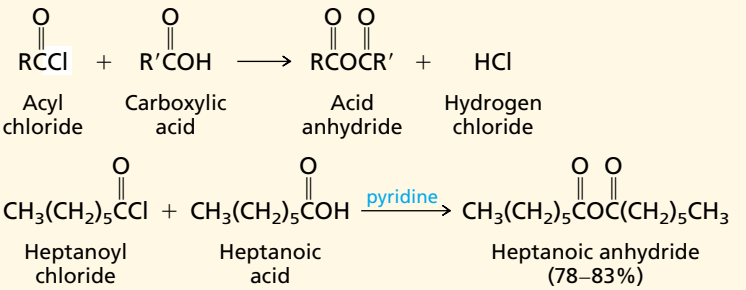
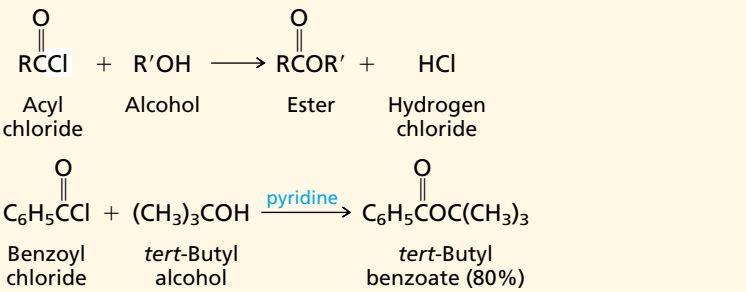
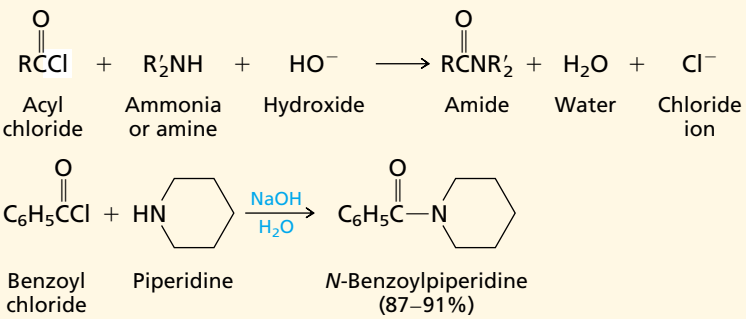
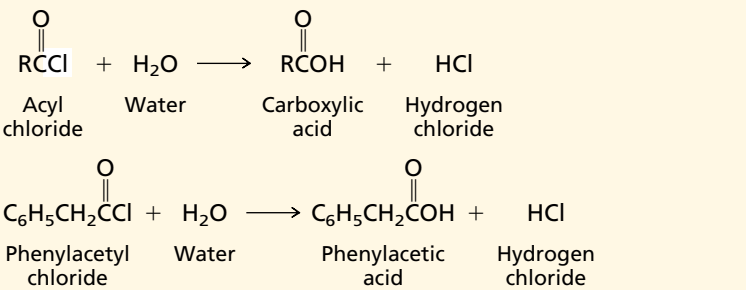
(a) Acetic acid
(b) Benzoic acid
(c) Ethanol
(d) Methylamine, CH_3NH_2
(e) Dimethylamine, $(CH_3)_2NH$
(f) Water

SAMPLE SOLUTION (a) As noted in Table 20.2, the reaction of an acyl chloride with a carboxylic acid yields an acid anhydride.

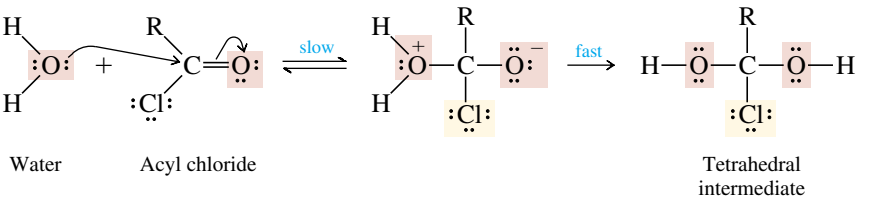


The product is a mixed anhydride. Acetic acid acts as a nucleophile and substitutes for chloride on the benzoyl group.

TABLE 20.2 Conversion of Acyl Chlorides to Other Carboxylic Acid Derivatives

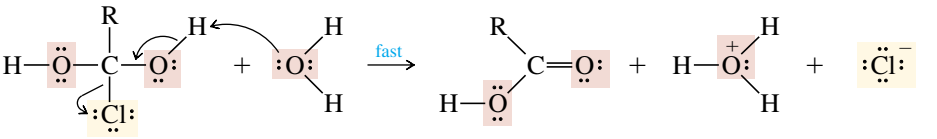
Reaction (section) and comments	General equation and specific example
Reaction with carboxylic acids (Section 20.4) Acyl chlorides react with carboxylic acids to yield acid anhydrides. When this reaction is used for preparative purposes, a weak organic base such as pyridine is normally added. Pyridine is a catalyst for the reaction and also acts as a base to neutralize the hydrogen chloride that is formed.	
Reaction with alcohols (Section 15.8) Acyl chlorides react with alcohols to form esters. The reaction is typically carried out in the presence of pyridine.	
Reaction with ammonia and amines (Section 20.13) Acyl chlorides react with ammonia and amines to form amides. A base such as sodium hydroxide is normally added to react with the hydrogen chloride produced.	
Hydrolysis (Section 20.3) Acyl chlorides react with water to yield carboxylic acids. In base, the acid is converted to its carboxylate salt. The reaction has little preparative value because the acyl chloride is nearly always prepared from the carboxylic acid rather than vice versa.	

First stage: Formation of the tetrahedral intermediate by nucleophilic addition of water to the carbonyl group



Water Acyl chloride Tetrahedral intermediate

Second stage: Dissociation of the tetrahedral intermediate by dehydrohalogenation



Tetrahedral intermediate Water Carboxylic acid Hydronium ion Chloride ion

FIGURE 20.3 Hydrolysis of acyl chloride proceeds by way of a tetrahedral intermediate. Formation of the tetrahedral intermediate is rate-determining.

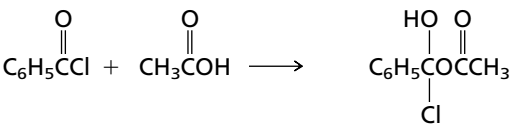
The mechanisms of all the reactions cited in Table 20.2 are similar to the mechanism of hydrolysis of an acyl chloride outlined in Figure 20.3. They differ with respect to the nucleophile that attacks the carbonyl group.

In the first stage of the mechanism, water undergoes nucleophilic addition to the carbonyl group to form a tetrahedral intermediate. This stage of the process is analogous to the hydration of aldehydes and ketones discussed in Section 17.6.

The tetrahedral intermediate has three potential leaving groups on carbon: two hydroxyl groups and a chlorine. In the second stage of the reaction, the tetrahedral intermediate dissociates. Loss of chloride from the tetrahedral intermediate is faster than loss of hydroxide; chloride is less basic than hydroxide and is a better leaving group. The tetrahedral intermediate dissociates because this dissociation restores the resonance-stabilized carbonyl group.

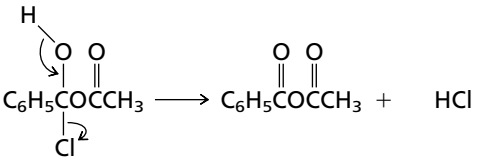
PROBLEM 20.4 Write the structure of the tetrahedral intermediate formed in each of the reactions given in Problem 20.3. Using curved arrows, show how each tetrahedral intermediate dissociates to the appropriate products.

SAMPLE SOLUTION (a) The tetrahedral intermediate arises by nucleophilic addition of acetic acid to benzoyl chloride.



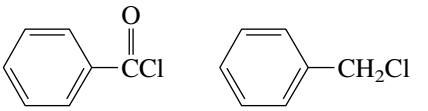
Benzoyl chloride Acetic acid Tetrahedral intermediate

Loss of a proton and of chloride ion from the tetrahedral intermediate yields the mixed anhydride.



Tetrahedral intermediate | Acetic benzoic anhydride | Hydrogen chloride

Nucleophilic substitution in acyl chlorides is much faster than in alkyl chlorides.

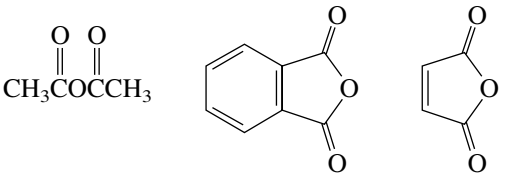


	Benzoyl chloride	Benzyl chloride
Relative rate of hydrolysis (80% ethanol–20% water; 25°C)	1,000	1

The sp^2-hybridized carbon of an acyl chloride is less sterically hindered than the sp^3-hybridized carbon of an alkyl chloride, making an acyl chloride more open toward nucleophilic attack. Also, unlike the S_N2 transition state or a carbocation intermediate in an S_N1 reaction, the tetrahedral intermediate in nucleophilic acyl substitution has a stable arrangement of bonds and can be formed via a lower energy transition state.

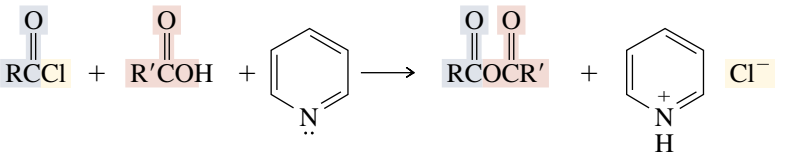
20.4 PREPARATION OF CARBOXYLIC ACID ANHYDRIDES

After acyl halides, acid anhydrides are the most reactive carboxylic acid derivatives. Three of them, acetic anhydride, phthalic anhydride, and maleic anhydride, are industrial chemicals and are encountered far more often than others. Phthalic anhydride and maleic anhydride have their anhydride function incorporated into a ring and are referred to as *cyclic anhydrides.*



Acetic anhydride | Phthalic anhydride | Maleic anhydride

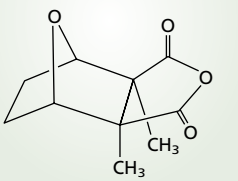
The customary method for the laboratory synthesis of acid anhydrides is the reaction of acyl chlorides with carboxylic acids (Table 20.2).



Acyl chloride | Carboxylic acid | Pyridine | Carboxylic acid anhydride | Pyridinium chloride

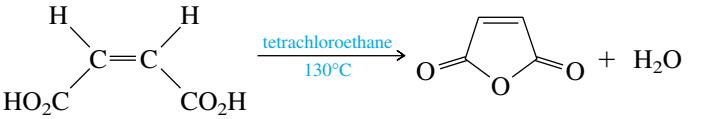
This procedure is applicable to the preparation of both symmetrical anhydrides (R and R′ the same) and mixed anhydrides (R and R′ different).

Acid anhydrides rarely occur naturally. One example is the putative aphrodisiac *cantharidin,* obtained from a species of beetle.



PROBLEM 20.5 Benzoic anhydride has been prepared in excellent yield by adding one molar equivalent of water to two molar equivalents of benzoyl chloride. How do you suppose this reaction takes place?

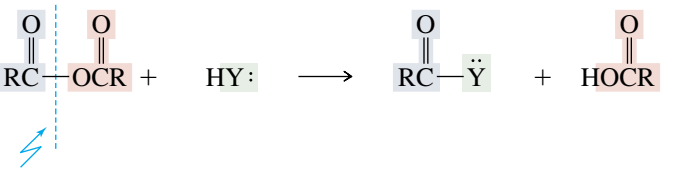
Cyclic anhydrides in which the ring is five- or six-membered are sometimes prepared by heating the corresponding dicarboxylic acids in an inert solvent:



Maleic acid — Maleic anhydride (89%) — Water

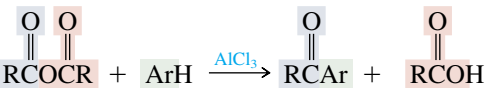
20.5 REACTIONS OF CARBOXYLIC ACID ANHYDRIDES

Nucleophilic acyl substitution in acid anhydrides involves cleavage of a bond between oxygen and one of the carbonyl groups. One acyl group is transferred to an attacking nucleophile; the other retains its single bond to oxygen and becomes the acyl group of a carboxylic acid.

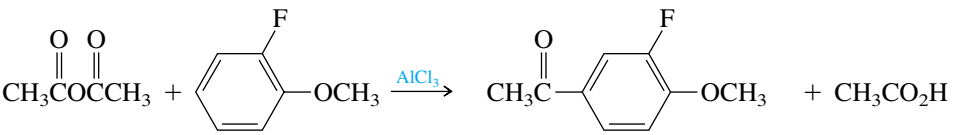


Bond cleavage occurs here in an acid anhydride. — Nucleophile — Product of nucleophilic acyl substitution — Carboxylic acid

One reaction of this type, Friedel–Crafts acylation (Section 12.7), is already familiar to us.



Acid anhydride — Arene — Ketone — Carboxylic acid



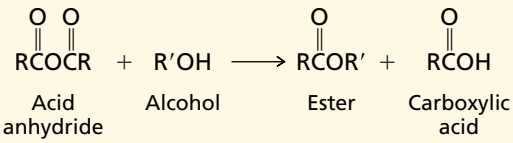
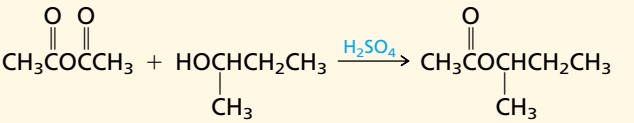
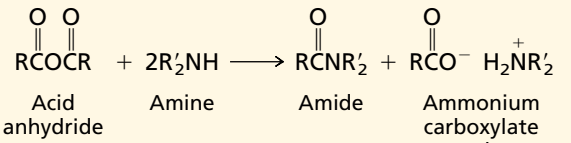
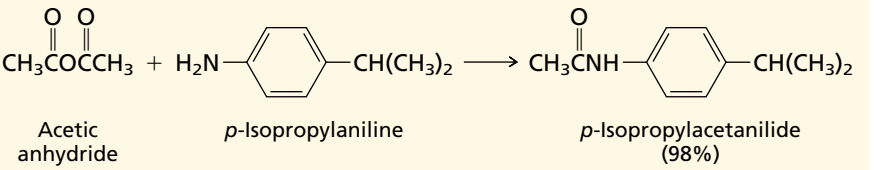
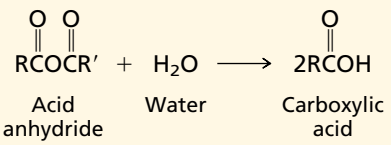
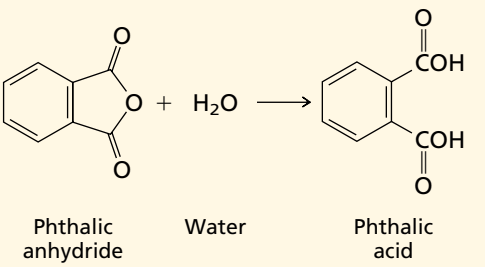
Acetic anhydride — *o*-Fluoroanisole — 3-Fluoro-4-methoxyacetophenone (70–80%) — Acetic acid

An acyl cation is an intermediate in Friedel–Crafts acylation reactions.

PROBLEM 20.6 Write a structural formula for the acyl cation intermediate in the preceding reaction.

Conversions of acid anhydrides to other carboxylic acid derivatives are illustrated in Table 20.3. Since a more highly stabilized carbonyl group must result in order for nucleophilic acyl substitution to be effective, acid anhydrides are readily converted to carboxylic acids, esters, and amides but not to acyl chlorides.

TABLE 20.3 Conversion of Acid Anhydrides to Other Carboxylic Acid Derivatives

Reaction (section) and comments	General equation and specific example
Reaction with alcohols (Section 15.8) Acid anhydrides react with alcohols to form esters. The reaction may be carried out in the presence of pyridine or it may be catalyzed by acids. In the example shown, only one acetyl group of acetic anhydride becomes incorporated into the ester; the other becomes the acetyl group of an acetic acid molecule.	 
Reaction with ammonia and amines (Section 20.13) Acid anhydrides react with ammonia and amines to form amides. Two molar equivalents of amine are required. In the example shown, only one acetyl group of acetic anhydride becomes incorporated into the amide; the other becomes the acetyl group of the amine salt of acetic acid.	 
Hydrolysis (Section 20.5) Acid anhydrides react with water to yield two carboxylic acid functions. Cyclic anhydrides yield dicarboxylic acids.	 

PROBLEM 20.7 Apply the knowledge gained by studying Table 20.3 to help you predict the major organic product of each of the following reactions:

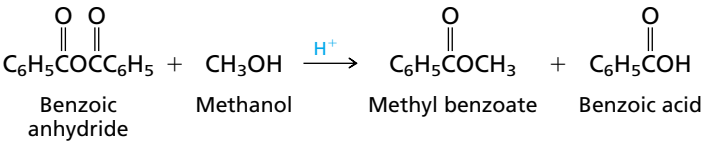
(a) Benzoic anhydride + methanol $\xrightarrow{H^+}$

(b) Acetic anhydride + ammonia (2 mol) ⟶

(c) Phthalic anhydride + $(CH_3)_2NH$ (2 mol) ⟶

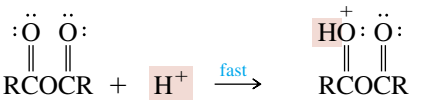
(d) Phthalic anhydride + sodium hydroxide (2 mol) ⟶

SAMPLE SOLUTION (a) Nucleophilic acyl substitution by an alcohol on an acid anhydride yields an ester.

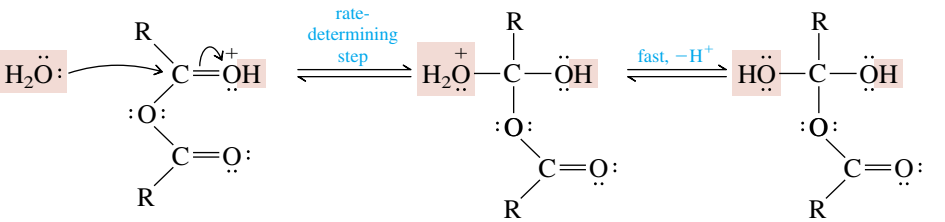


The first example in Table 20.3 introduces a new aspect of nucleophilic acyl substitution that applies not only to acid anhydrides but also to acyl chlorides, esters, and amides. Nucleophilic acyl substitutions can be catalyzed by acids.

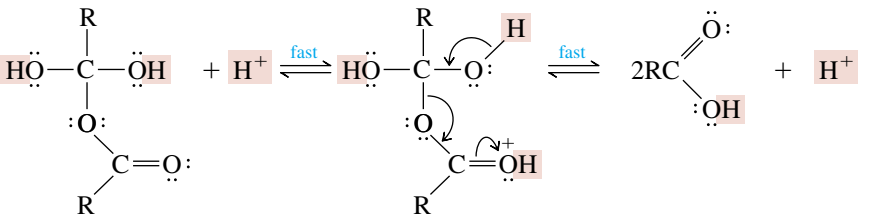
We can see how an acid catalyst increases the rate of nucleophilic acyl substitution by considering the hydrolysis of an acid anhydride. Formation of the tetrahedral intermediate is rate-determining and is the step that is accelerated by the catalyst. The acid anhydride is activated toward nucleophilic addition by protonation of one of its carbonyl groups:



The protonated form of the acid anhydride is present to only a very small extent, but it is quite electrophilic. Water (and other nucleophiles) add to a protonated carbonyl group much faster than they do to a neutral one. Thus, the rate-determining nucleophilic addition of water to form a tetrahedral intermediate takes place more rapidly in the presence of an acid than in its absence.



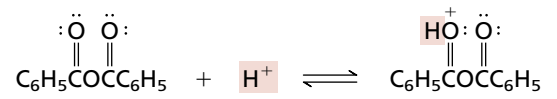
Acids also catalyze the dissociation of the tetrahedral intermediate. Protonation of its carbonyl oxygen permits the leaving group to depart as a neutral carboxylic acid molecule, which is a less basic leaving group than a carboxylate anion.



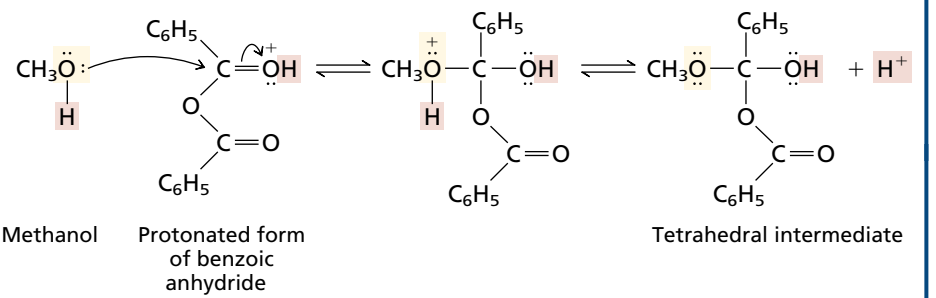
This pattern of increased reactivity resulting from carbonyl group protonation has been seen before in nucleophilic additions to aldehydes and ketones (Section 17.6) and in the mechanism of the acid-catalyzed esterification of carboxylic acids (Section 19.14). Many biological reactions involve nucleophilic acyl substitution and are catalyzed by enzymes that act by donating a proton to the carbonyl oxygen, the leaving group, or both.

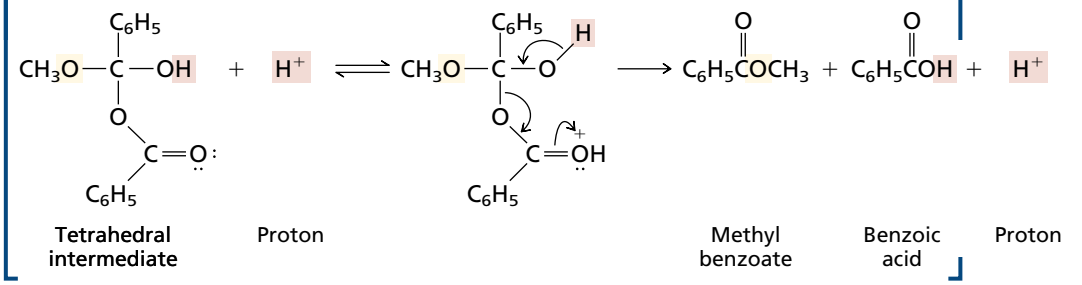
PROBLEM 20.8 Write the structure of the tetrahedral intermediate formed in each of the reactions given in Problem 20.7. Using curved arrows, show how each tetrahedral intermediate dissociates to the appropriate products.

SAMPLE SOLUTION (a) The reaction given is the acid-catalyzed esterification of methanol by benzoic anhydride. The first step is the activation of the anhydride toward nucleophilic addition by protonation.



The tetrahedral intermediate is formed by nucleophilic addition of methanol to the protonated carbonyl group.

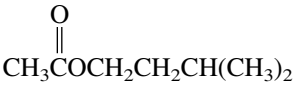




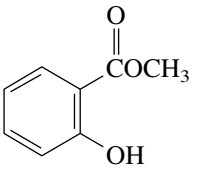
Acid anhydrides are more stable and less reactive than acyl chlorides. Acetyl chloride, for example, undergoes hydrolysis about 100,000 times more rapidly than acetic anhydride at 25°C.

20.6 SOURCES OF ESTERS

Many esters occur naturally. Those of low molecular weight are fairly volatile, and many have pleasing odors. Esters often form a significant fraction of the fragrant oil of fruits and flowers. The aroma of oranges, for example, contains 30 different esters along with 10 carboxylic acids, 34 alcohols, 34 aldehydes and ketones, and 36 hydrocarbons.



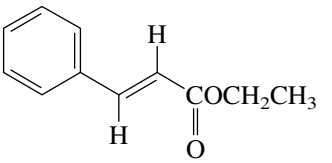
3-Methylbutyl acetate
(contributes to characteristic odor of bananas)



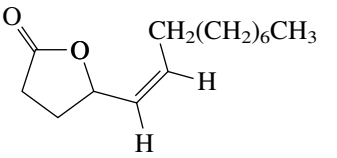
Methyl salicylate
(principal component of oil of wintergreen)

3-Methylbutyl acetate is more commonly known as isoamyl acetate.

Among the chemicals used by insects to communicate with one another, esters occur frequently.



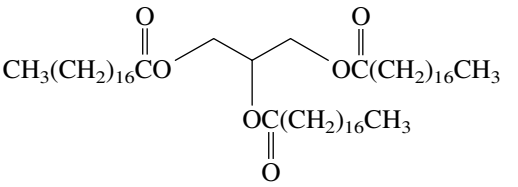
Ethyl cinnamate
(one of the constituents of the sex pheromone of the male oriental fruit moth)



(*Z*)-5-Tetradecen-4-olide
(sex pheromone of female Japanese beetle)

Notice that (*Z*)-5-tetradecen-4-olide is a cyclic ester. Recall from Section 19.15 that cyclic esters are called *lactones* and that the suffix *-olide* is characteristic of IUPAC names for lactones.

Esters of glycerol, called *glycerol triesters, triacylglycerols,* or *triglycerides,* are abundant natural products. The most important group of glycerol triesters includes those in which each acyl group is unbranched and has 14 or more carbon atoms.



Tristearin, a trioctadecanoyl ester of glycerol found in many animal and vegetable fats

A molecular model of tristearin is shown in Figure 26.2.

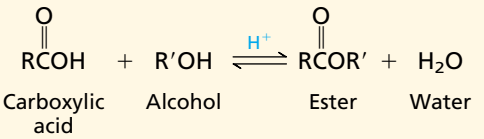
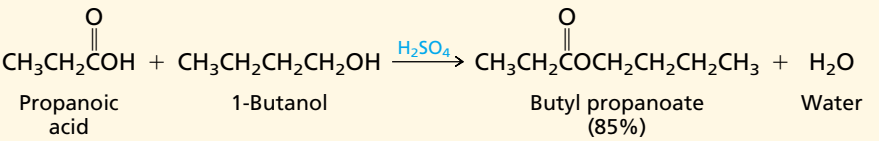
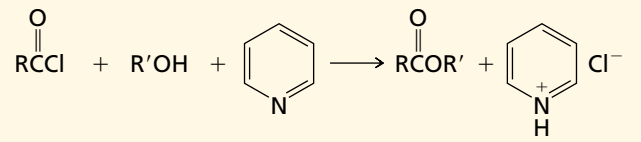
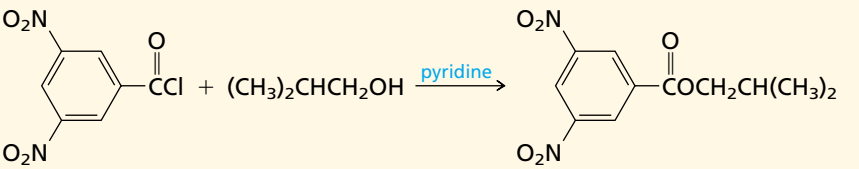
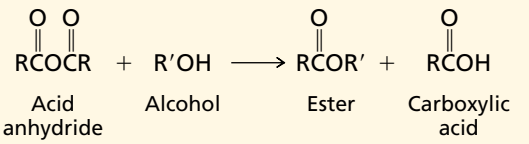
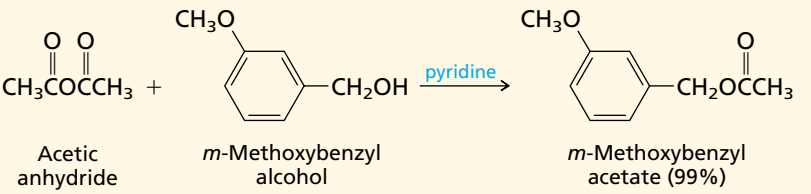
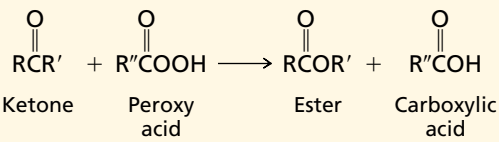
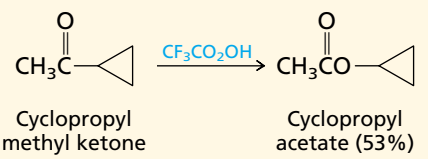
Fats and **oils** are naturally occurring mixtures of glycerol triesters. Fats are mixtures that are solids at room temperature; oils are liquids. The long-chain carboxylic acids obtained from fats and oils by hydrolysis are known as **fatty acids.**

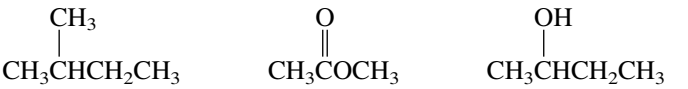
The chief methods used to prepare esters in the laboratory have all been described earlier, and are summarized in Table 20.4.

20.7 PHYSICAL PROPERTIES OF ESTERS

Esters are moderately polar, with dipole moments in the 1.5 to 2.0-D range. Dipole–dipole attractive forces give esters higher boiling points than hydrocarbons of similar shape and molecular weight. Because they lack hydroxyl groups, however, ester molecules cannot form hydrogen bonds to each other; consequently, esters have lower boiling points than alcohols of comparable molecular weight.

TABLE 20.4 Preparation of Esters

Reaction (section) and comments	General equation and specific example
From carboxylic acids (Sections 15.8 and 19.14) In the presence of an acid catalyst, alcohols and carboxylic acids react to form an ester and water. This is the Fischer esterification.	 
From acyl chlorides (Sections 15.8 and 20.3) Alcohols react with acyl chlorides by nucleophilic acyl substitution to yield esters. These reactions are typically performed in the presence of a weak base such as pyridine.	 
From carboxylic acid anhydrides (Sections 15.8 and 20.5) Acyl transfer from an acid anhydride to an alcohol is a standard method for the preparation of esters. The reaction is subject to catalysis by either acids (H_2SO_4) or bases (pyridine).	 
Baeyer–Villiger oxidation of ketones (Section 17.16) Ketones are converted to esters on treatment with peroxy acids. The reaction proceeds by migration of the group R′ from carbon to oxygen. It is the more highly substituted group that migrates. Methyl ketones give acetate esters.	 



2-Methylbutane: mol wt 72, bp 28°C | Methyl acetate: mol wt 74, bp 57°C | 2-Butanol: mol wt 74, bp 99°C

Esters can participate in hydrogen bonds with substances that contain hydroxyl groups (water, alcohols, carboxylic acids). This confers some measure of water solubility on low-molecular-weight esters; methyl acetate, for example, dissolves in water to the extent of 33 g/100 mL. Water solubility decreases as the carbon content of the ester increases. Fats and oils, the glycerol esters of long-chain carboxylic acids, are practically insoluble in water.

20.8 REACTIONS OF ESTERS: A REVIEW AND A PREVIEW

The reaction of esters with Grignard reagents and with lithium aluminum hydride, both useful in the synthesis of alcohols, were described earlier. They are reviewed in Table 20.5.

Nucleophilic acyl substitutions at the ester carbonyl group are summarized in Table 20.6. Esters are less reactive than acyl chlorides and acid anhydrides. Nucleophilic acyl substitution in esters, especially ester hydrolysis, has been extensively investigated from a mechanistic perspective. Indeed, much of what we know concerning the general topic

TABLE 20.5 Summary of Reactions of Esters Discussed in Earlier Chapters

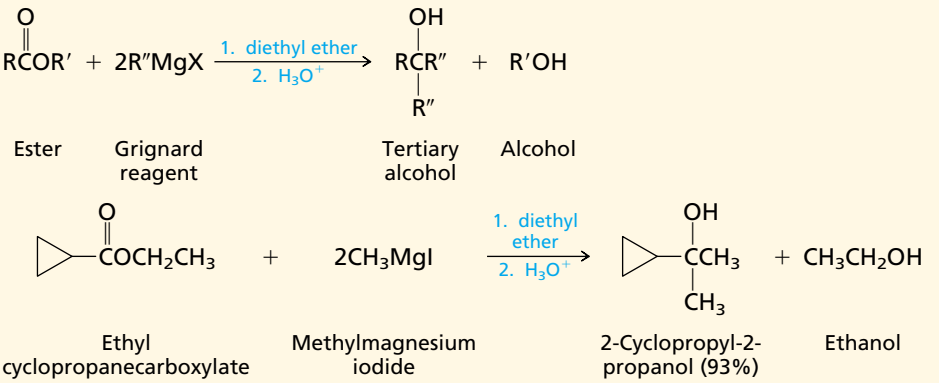
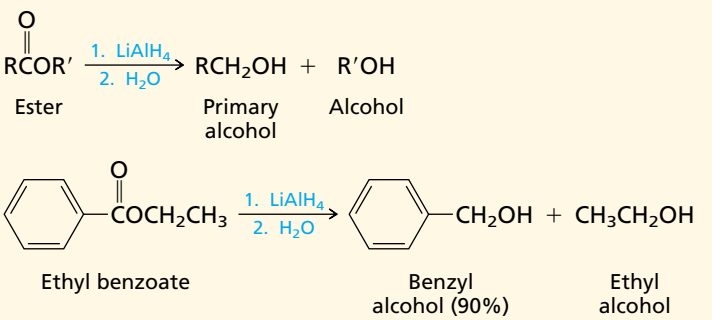
Reaction (section) and comments	General equation and specific example
Reaction with Grignard reagents (Section 14.10) Esters react with two equivalents of a Grignard reagent to produce tertiary alcohols. Two of the groups bonded to the carbon that bears the hydroxyl group in the tertiary alcohol are derived from the Grignard reagent.	 Ester; Grignard reagent; Tertiary alcohol; Alcohol. Ethyl cyclopropanecarboxylate; Methylmagnesium iodide; 2-Cyclopropyl-2-propanol (93%); Ethanol
Reduction with lithium aluminum hydride (Section 15.3) Lithium aluminum hydride cleaves esters to yield two alcohols.	 Ester; Primary alcohol; Alcohol. Ethyl benzoate; Benzyl alcohol (90%); Ethyl alcohol

TABLE 20.6 Conversion of Esters to Other Carboxylic Acid Derivatives

Reaction (section) and comments	General equation and specific example
Reaction with ammonia and amines (Section 20.13) Esters react with ammonia and amines to form amides. Methyl and ethyl esters are the most reactive.	$RCOR' + R''_2NH \longrightarrow RCNR''_2 + R'OH$ Ester · Amine · Amide · Alcohol $FCH_2COCH_2CH_3 + NH_3 \xrightarrow{H_2O} FCH_2CNH_2 + CH_3CH_2OH$ Ethyl fluoroacetate · Ammonia · Fluoroacetamide (90%) · Ethanol
Hydrolysis (Sections 20.9 and 20.10) Ester hydrolysis may be catalyzed either by acids or by bases. Acid-catalyzed hydrolysis is an equilibrium-controlled process, the reverse of the Fischer esterification. Hydrolysis in base is irreversible and is the method usually chosen for preparative purposes.	$RCOR' + H_2O \longrightarrow RCOH + R'OH$ Ester · Water · Carboxylic acid · Alcohol $O_2N\text{-}C_6H_4\text{-}COCH_3 \xrightarrow{1.\ H_2O,\ NaOH;\ 2.\ H^+} O_2N\text{-}C_6H_4\text{-}COH + CH_3OH$ Methyl *m*-nitrobenzoate · *m*-Nitrobenzoic acid (90–96%) · Methanol

of nucleophilic acyl substitution comes from studies carried out on esters. The following sections describe those mechanistic studies.

20.9 ACID-CATALYZED ESTER HYDROLYSIS

Ester hydrolysis is the most studied and best understood of all nucleophilic acyl substitutions. Esters are fairly stable in neutral aqueous media but are cleaved when heated with water in the presence of strong acids or bases. The hydrolysis of esters in dilute aqueous acid is the reverse of the Fischer esterification (Sections 15.8 and 19.14):

$$RCOR' + H_2O \underset{}{\overset{H^+}{\rightleftharpoons}} RCOH + R'OH$$

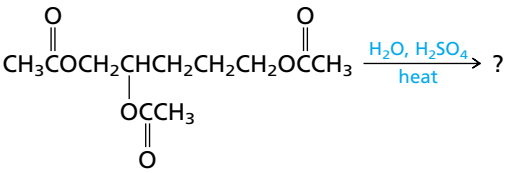
Ester · Water · Carboxylic acid · Alcohol

When esterification is the objective, water is removed from the reaction mixture to encourage ester formation. When ester hydrolysis is the objective, the reaction is carried out in the presence of a generous excess of water.

$$C_6H_5CH(Cl)COCH_2CH_3 + H_2O \xrightarrow[\text{heat}]{HCl} C_6H_5CH(Cl)COH + CH_3CH_2OH$$

Ethyl 2-chloro-2-phenylacetate · Water · 2-Chloro-2-phenylacetic acid (80–82%) · Ethyl alcohol

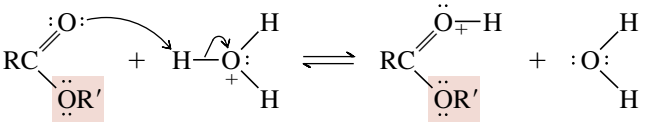
PROBLEM 20.9 The compound having the structure shown was heated with dilute sulfuric acid to give a product having the molecular formula $C_5H_{12}O_3$ in 63–71% yield. Propose a reasonable structure for this product. What other organic compound is formed in this reaction?



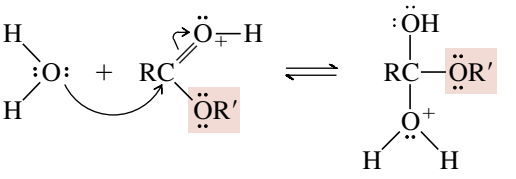
The mechanism of acid-catalyzed ester hydrolysis is presented in Figure 20.4. It is precisely the reverse of the mechanism given for acid-catalyzed ester formation in Section 19.14. Like other nucleophilic acyl substitutions, it proceeds in two stages. A tetrahedral intermediate is formed in the first stage, and this tetrahedral intermediate dissociates to products in the second stage.

A key feature of the first stage is the site at which the starting ester is protonated. Protonation of the carbonyl oxygen, as shown in step 1 of Figure 20.4, gives a cation that is stabilized by electron delocalization. The alternative site of protonation, the alkoxy oxygen, gives rise to a much less stable cation.

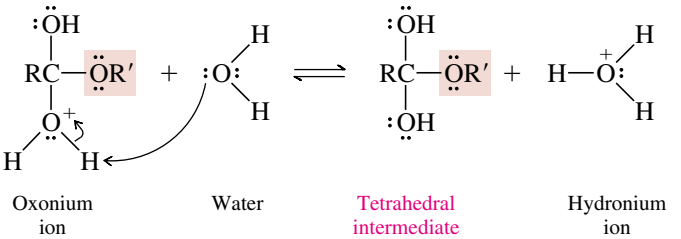
Step 1: Protonation of the carbonyl oxygen of the ester



Step 2: Nucleophilic addition of water to protonated form of ester



Step 3: Deprotonation of the oxonium ion to give the neutral form of the tetrahedral intermediate

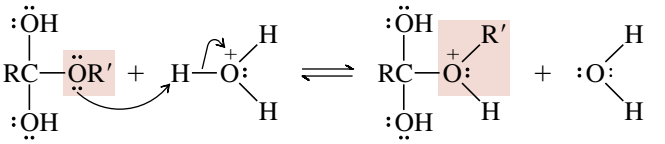


—Cont.

FIGURE 20.4 The mechanism of acid-catalyzed ester hydrolysis. Steps 1 through 3 show the formation of the tetrahedral intermediate. Dissociation of the tetrahedral intermediate is shown in steps 4 through 6.

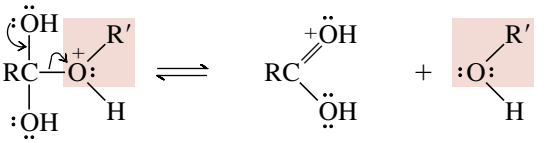
FIGURE 20.4 (*Continued*)

Step 4: Protonation of the tetrahedral intermediate at its alkoxy oxygen



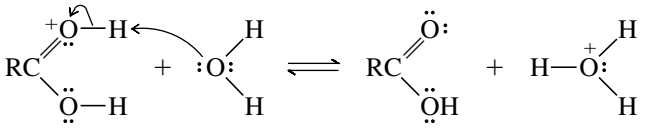
Tetrahedral intermediate | Hydronium ion | Oxonium ion | Water

Step 5: Dissociation of the protonated form of the tetrahedral intermediate to an alcohol and the protonated form of the carboxylic acid



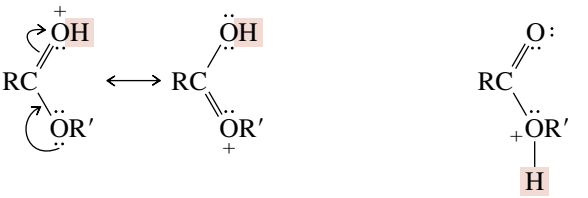
Oxonium ion | Protonated form of carboxylic acid | Alcohol

Step 6: Deprotonation of the protonated carboxylic acid



Protonated form of carboxylic acid | Water | Carboxylic acid | Hydronium ion

Protonation of carbonyl oxygen ***Protonation of alkoxy oxygen***



Positive charge is delocalized. Positive charge is localized on a single oxygen.

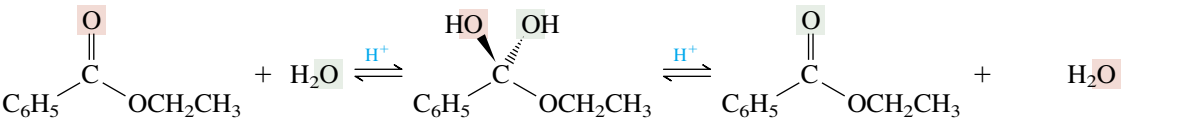
Protonation of the carbonyl oxygen, as emphasized earlier in the reactions of aldehydes and ketones, makes the carbonyl group more susceptible to nucleophilic attack. A water molecule adds to the carbonyl group of the protonated ester in step 2. Loss of a proton from the resulting oxonium ion gives the neutral form of the tetrahedral intermediate in step 3 and completes the first stage of the mechanism.

Once formed, the tetrahedral intermediate can revert to starting materials by merely reversing the reactions that formed it, or it can continue onward to products. In the second stage of ester hydrolysis, the tetrahedral intermediate dissociates to an alcohol and a carboxylic acid. In step 4 of Figure 20.4, protonation of the tetrahedral intermediate at

its alkoxy oxygen gives a new oxonium ion, which loses a molecule of alcohol in step 5. Along with the alcohol, the protonated form of the carboxylic acid arises by dissociation of the tetrahedral intermediate. Its deprotonation in step 6 completes the process.

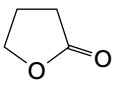
PROBLEM 20.10 On the basis of the general mechanism for acid-catalyzed ester hydrolysis shown in Figure 20.4, write an analogous sequence of steps for the specific case of ethyl benzoate hydrolysis.

The most important species in the mechanism for ester hydrolysis is the tetrahedral intermediate. Evidence in support of the existence of the tetrahedral intermediate was developed by Professor Myron Bender on the basis of isotopic labeling experiments he carried out at the University of Chicago. Bender prepared ethyl benzoate, labeled with the mass-18 isotope of oxygen at the carbonyl oxygen, then subjected it to acid-catalyzed hydrolysis in ordinary (unlabeled) water. He found that ethyl benzoate, recovered from the reaction before hydrolysis was complete, had lost a portion of its isotopic label. This observation is consistent only with the reversible formation of a tetrahedral intermediate under the reaction conditions:



The two OH groups in the tetrahedral intermediate are equivalent, and so either the labeled or the unlabeled one can be lost when the tetrahedral intermediate reverts to ethyl benzoate. Both are retained when the tetrahedral intermediate goes on to form benzoic acid.

PROBLEM 20.11 In a similar experiment, unlabeled 4-butanolide was allowed to stand in an acidic solution in which the water had been labeled with ^{18}O. When the lactone was extracted from the solution after 4 days, it was found to contain ^{18}O. Which oxygen of the lactone do you think became isotopically labeled?

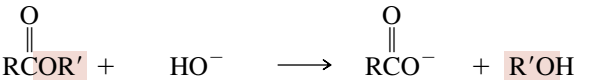


4-Butanolide

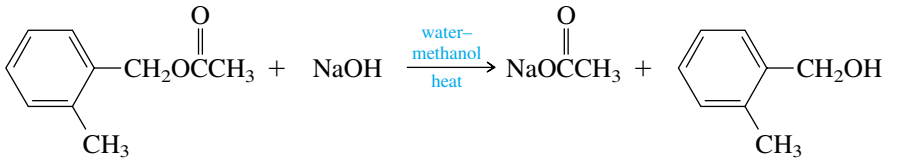
20.10 ESTER HYDROLYSIS IN BASE: SAPONIFICATION

Unlike its acid-catalyzed counterpart, ester hydrolysis in aqueous base is *irreversible.*

Since it is consumed, hydroxide ion is a reactant, not a catalyst.

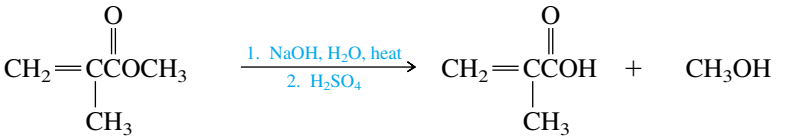


This is because carboxylic acids are converted to their corresponding carboxylate anions under these conditions, and these anions are incapable of acyl transfer to alcohols.



o-Methylbenzyl acetate | Sodium hydroxide | Sodium acetate | *o*-Methylbenzyl alcohol (95–97%)

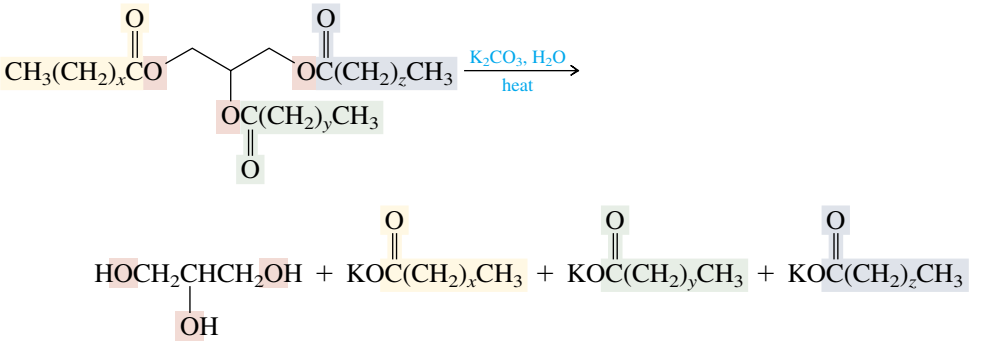
To isolate the carboxylic acid, a separate acidification step following hydrolysis is necessary. Acidification converts the carboxylate salt to the free acid.



Methyl 2-methylpropenoate (methyl methacrylate) | 2-Methylpropenoic acid (87%) (methacrylic acid) | Methyl alcohol

Ester hydrolysis in base is called **saponification,** which means "soap making." Over 2000 years ago, the Phoenicians made soap by heating animal fat with wood ashes. Animal fat is rich in glycerol triesters, and wood ashes are a source of potassium carbonate. Basic cleavage of the fats produced a mixture of long-chain carboxylic acids as their potassium salts.

Procedures for making a variety of soaps are given in the May 1998 issue of the *Journal of Chemical Education,* pp. 612–614.

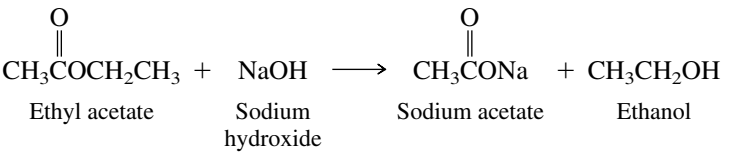


Glycerol | Potassium carboxylate salts

Potassium and sodium salts of long-chain carboxylic acids form micelles that dissolve grease (Section 19.5) and have cleansing properties. The carboxylic acids obtained by saponification of fats are called *fatty acids.*

PROBLEM 20.12 *Trimyristin* is obtained from coconut oil and has the molecular formula $C_{45}H_{86}O_6$. On being heated with aqueous sodium hydroxide followed by acidification, trimyristin was converted to glycerol and tetradecanoic acid as the only products. What is the structure of trimyristin?

In one of the earliest kinetic studies of an organic reaction, carried out in the 19th century, the rate of hydrolysis of ethyl acetate in aqueous sodium hydroxide was found to be first order in ester and first order in base.

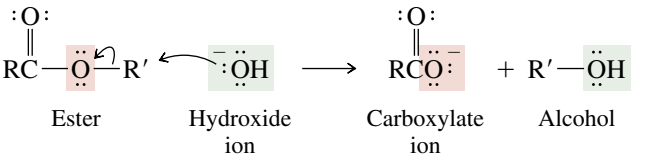


$$\text{Rate} = k[\text{CH}_3\text{COCH}_2\text{CH}_3][\text{NaOH}]$$

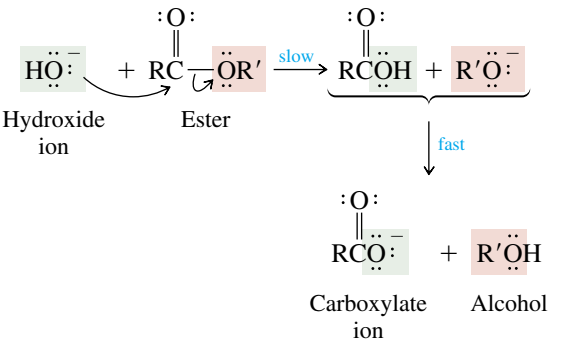
Overall, the reaction exhibits second-order kinetics. Both the ester and the base are involved in the rate-determining step or in a rapid step that precedes it.

Two processes that are consistent with second-order kinetics both involve hydroxide ion as a nucleophile but differ in the site of nucleophilic attack. One of these processes is an S_N2 reaction in which hydroxide displaces carboxylate from the alkyl group of the ester. We say that this pathway involves *alkyl–oxygen cleavage,* because it is the bond between oxygen and the alkyl group of the ester that breaks. The other process involves *acyl–oxygen cleavage,* with hydroxide attacking the carbonyl group.

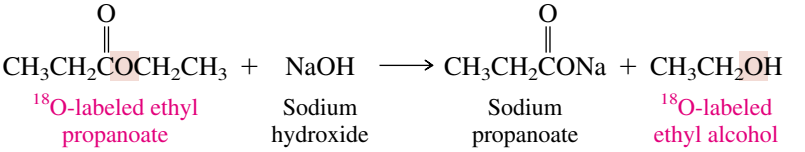
Alkyl–oxygen cleavage



Acyl–oxygen cleavage



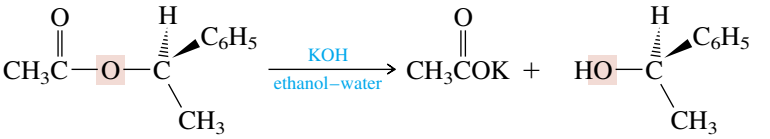
Convincing evidence that ester hydrolysis in base proceeds by the second of these two paths, namely, acyl–oxygen cleavage, has been obtained from several sources. In one experiment, ethyl propanoate labeled with ^{18}O in the ethoxy group was hydrolyzed. On isolating the products, all the ^{18}O was found in the ethyl alcohol; there was no ^{18}O enrichment in the sodium propanoate.



The carbon–oxygen bond broken in the process is therefore the one between oxygen and the acyl group. The bond between oxygen and the ethyl group remains intact.

PROBLEM 20.13 In a similar experiment, pentyl acetate was subjected to saponification with ^{18}O-labeled hydroxide in ^{18}O-labeled water. What product do you think became isotopically labeled here, acetate ion or 1-pentanol?

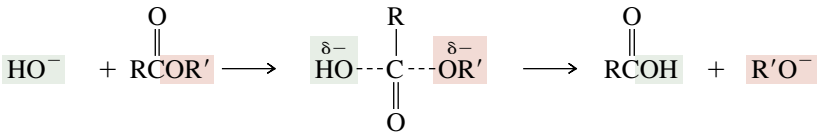
Identical conclusions in support of acyl–oxygen cleavage have been obtained from stereochemical studies. Saponification of esters of optically active alcohols proceeds with *retention of configuration.*



(*R*)-(+)-1-Phenylethyl acetate | Potassium acetate | (*R*)-(+)-1-Phenylethyl alcohol (80% yield; same optical purity as ester)

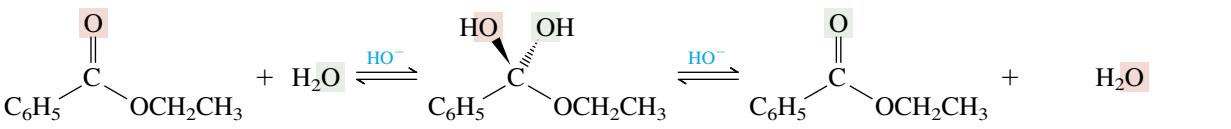
None of the bonds to the stereogenic center are broken when acyl–oxygen cleavage occurs. Had alkyl–oxygen cleavage occurred instead, it would have been accompanied by inversion of configuration at the stereogenic center to give (*S*)-(−)-1-phenylethyl alcohol.

Once it was established that hydroxide ion attacks the carbonyl group in basic ester hydrolysis, the next question to be addressed concerned whether the reaction is concerted or involves an intermediate. In a concerted reaction acyl–oxygen cleavage occurs at the same time that hydroxide ion attacks the carbonyl group.



Hydroxide ion | Ester | Representation of transition state for concerted displacement | Carboxylic acid | Alkoxide ion

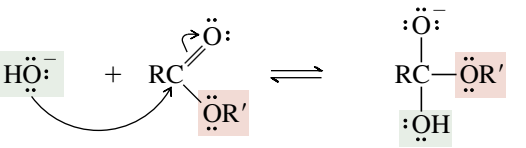
In an extension of the work described in the preceding section, Bender showed that basic ester hydrolysis was *not* concerted and, like acid hydrolysis, took place by way of a tetrahedral intermediate. The nature of the experiment was the same, and the results were similar to those observed in the acid-catalyzed reaction. Ethyl benzoate enriched in ^{18}O at the carbonyl oxygen was subjected to hydrolysis in base, and samples were isolated before saponification was complete. The recovered ethyl benzoate was found to have lost a portion of its isotopic label, consistent with the formation of a tetrahedral intermediate:



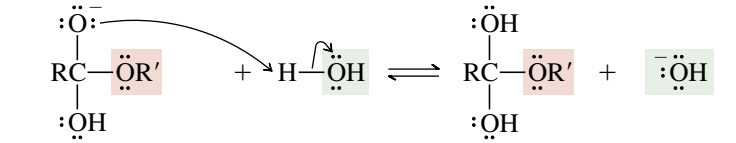
Ethyl benzoate (labeled with ^{18}O) | Water | Tetrahedral intermediate | Ethyl benzoate | Water (labeled with ^{18}O)

All these facts—the observation of second-order kinetics, acyl–oxygen cleavage, and the involvement of a tetrahedral intermediate—are accommodated by the reaction mechanism shown in Figure 20.5. Like the acid-catalyzed mechanism, it has two distinct

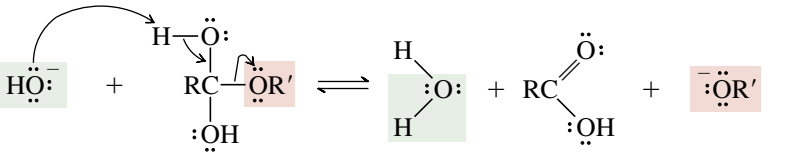
Step 1: Nucleophilic addition of hydroxide ion to the carbonyl group



Step 2: Proton transfer to anionic form of tetrahedral intermediate



Step 3: Dissociation of tetrahedral intermediate



Step 4: Proton transfer steps yield an alcohol and a carboxylate anion

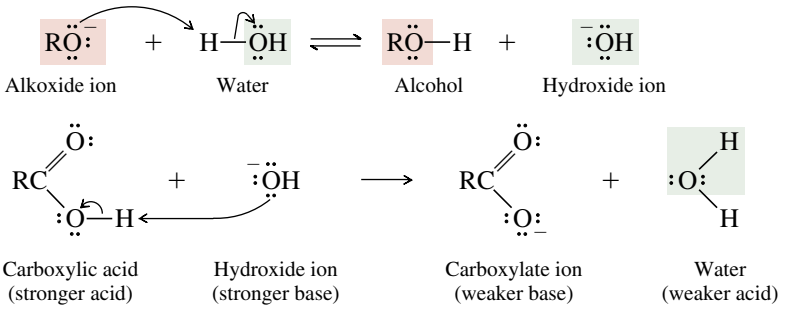


FIGURE 20.5 The mechanism of ester hydrolysis in basic solution.

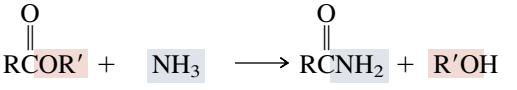
stages, namely, formation of the tetrahedral intermediate and its subsequent dissociation. All the steps are reversible except the last one. The equilibrium constant for proton abstraction from the carboxylic acid by hydroxide is so large that step 4 is, for all intents and purposes, irreversible, and this makes the overall reaction irreversible.

Steps 2 and 4 are proton-transfer reactions and are very fast. Nucleophilic addition to the carbonyl group has a higher activation energy than dissociation of the tetrahedral intermediate; step 1 is rate-determining.

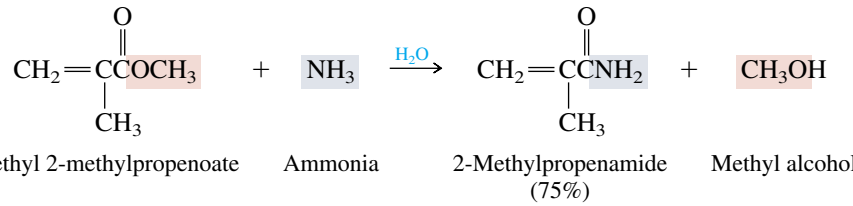
PROBLEM 20.14 On the basis of the general mechanism for basic ester hydrolysis shown in Figure 20.5, write an analogous sequence of steps for the saponification of ethyl benzoate.

20.11 REACTION OF ESTERS WITH AMMONIA AND AMINES

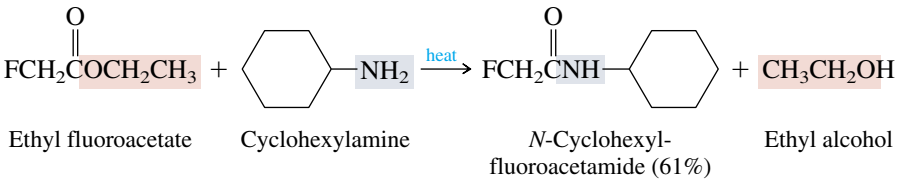
Esters react with ammonia to form amides.



Ammonia is more nucleophilic than water, making it possible to carry out this reaction using aqueous ammonia.

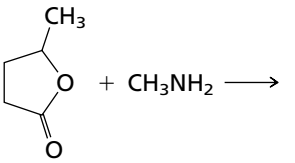


Amines, which are substituted derivatives of ammonia, react similarly:



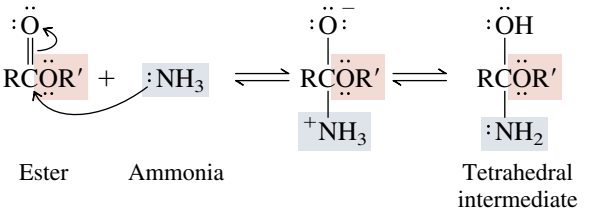
The amine must be primary (RNH_2) or secondary (R_2NH). Tertiary amines (R_3N) cannot form amides, because they have no proton on nitrogen that can be replaced by an acyl group.

PROBLEM 20.15 Give the structure of the expected product of the following reaction:

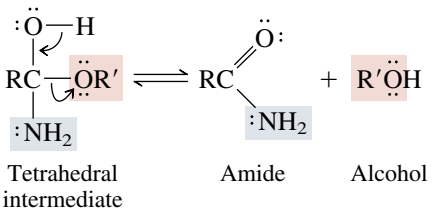


The reaction of ammonia and amines with esters follows the same general mechanistic course as other nucleophilic acyl substitution reactions. A tetrahedral intermediate is formed in the first stage of the process and dissociates in the second stage.

Formation of tetrahedral intermediate



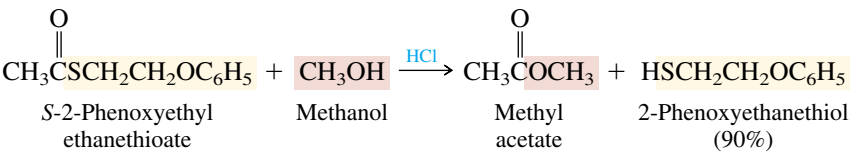
Dissociation of tetrahedral intermediate



Although both stages are written as equilibria, the overall reaction lies far to the right because the amide carbonyl is stabilized to a much greater extent than the ester carbonyl.

20.12 THIOESTERS

Thioesters, compounds of the type $RCSR'$, undergo the same kinds of reactions as esters and by similar mechanisms. Nucleophilic acyl substitution of a thioester gives a *thiol* along with the product of acyl transfer. For example:



PROBLEM 20.16 Write the structure of the tetrahedral intermediate formed in the reaction just described.

The carbon–sulfur bond of a thioester is rather long—typically on the order of 180 pm—and delocalization of the sulfur lone-pair electrons into the π orbital of the carbonyl group is not as effective as in esters. Nucleophilic acyl substitution reactions of thioesters occur faster than those of simple esters. A number of important biological processes involve thioesters; several of these are described in Chapter 26.

20.13 PREPARATION OF AMIDES

Amides are readily prepared by acylation of ammonia and amines with acyl chlorides, anhydrides, or esters.

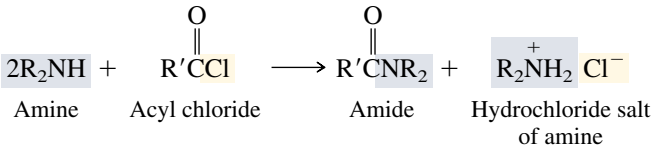
Acylation of *ammonia* (NH_3) yields an amide ($R'CNH_2$).

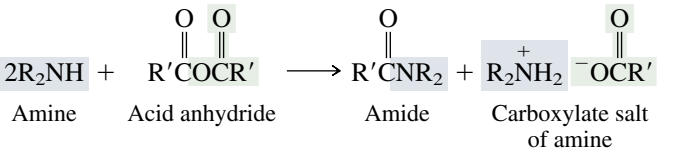
Primary amines (RNH_2) yield *N*-substituted amides ($R'CNHR$).

Secondary amines (R_2NH) yield *N,N*-disubstituted amides ($R'CNR_2$, with =O).

Examples illustrating these reactions may be found in Tables 20.2, 20.3, and 20.6.

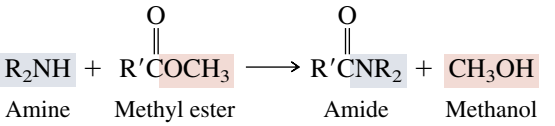
Two molar equivalents of amine are required in the reaction with acyl chlorides and acid anhydrides; one molecule of amine acts as a nucleophile, the second as a Brønsted base.





It is possible to use only one molar equivalent of amine in these reactions if some other base, such as sodium hydroxide, is present in the reaction mixture to react with the hydrogen chloride or carboxylic acid that is formed. This is a useful procedure in those cases in which the amine is a valuable one or is available only in small quantities.

Esters and amines react in a 1:1 molar ratio to give amides. No acidic product is formed from the ester, and so no additional base is required.



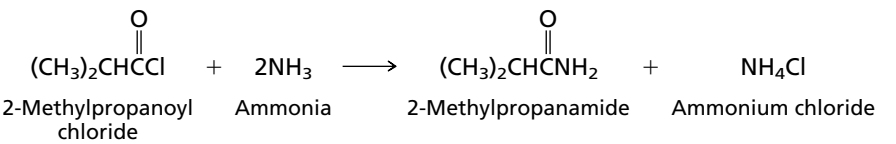
PROBLEM 20.17 Write an equation showing the preparation of the following amides from the indicated carboxylic acid derivative:

(a) $(CH_3)_2CHCNH_2$ (with =O) from an acyl chloride

(b) CH_3CNHCH_3 (with =O) from an acid anhydride

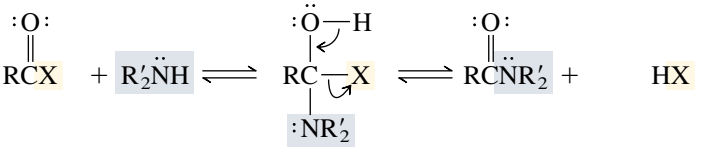
(c) $HCN(CH_3)_2$ (with =O) from a methyl ester

SAMPLE SOLUTION (a) Amides of the type $RCNH_2$ (with =O) are derived by acylation of ammonia.



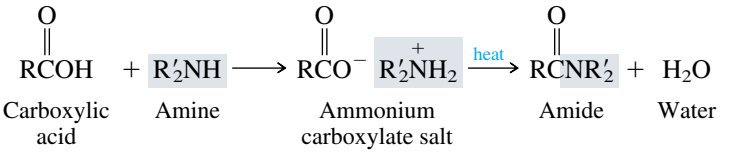
Two molecules of ammonia are needed because its acylation produces, in addition to the desired amide, a molecule of hydrogen chloride. Hydrogen chloride (an acid) reacts with ammonium to give ammonium chloride.

All these reactions proceed by nucleophilic addition of the amine to the carbonyl group. Dissociation of the tetrahedral intermediate proceeds in the direction that leads to an amide.

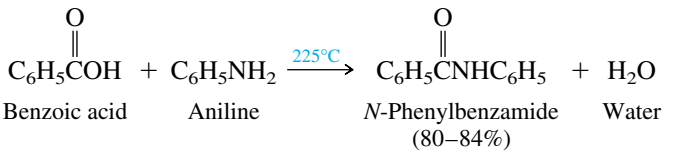


The carbonyl group of an amide is stabilized to a greater extent than that of an acyl chloride, anhydride, or ester; amides are formed rapidly and in high yield from each of these carboxylic acid derivatives.

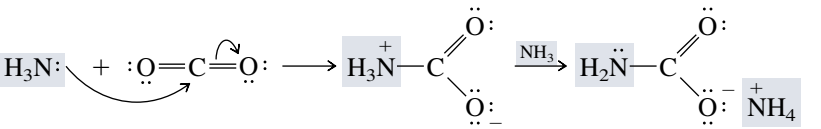
Amides are sometimes prepared directly from carboxylic acids and amines by a two-step process. The first step is an acid–base reaction in which the acid and the amine combine to form an ammonium carboxylate salt. On heating, the ammonium carboxylate salt loses water to form an amide.



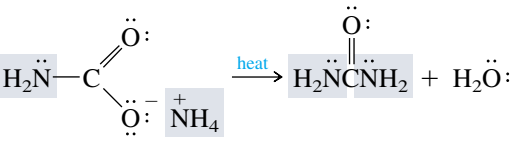
In practice, both steps may be combined in a single operation by simply heating a carboxylic acid and an amine together:



A similar reaction in which ammonia and carbon dioxide are heated under pressure is the basis of the industrial synthesis of *urea.* Here, the reactants first combine, yielding a salt called *ammonium carbamate:*



On being heated, ammonium carbamate undergoes dehydration to form urea:



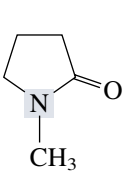
Ammonium carbamate Urea Water

Over 10^{10} lb of urea—most of it used as fertilizer—is produced annually in the United States by this method.

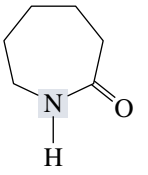
These thermal methods for preparing amides are limited in their generality. Most often amides are prepared in the laboratory from acyl chlorides, acid anhydrides, or esters, and these are the methods that you should apply to solving synthetic problems.

20.14 LACTAMS

Lactams are cyclic amides and are analogous to lactones, which are cyclic esters. Most lactams are known by their common names, as the examples shown illustrate.

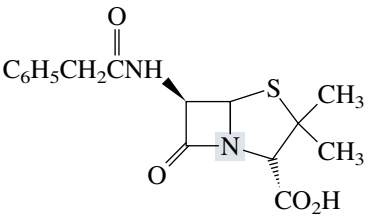


N-Methylpyrrolidone
(a polar aprotic solvent)

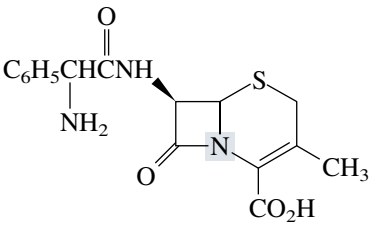


ϵ-Caprolactam
(industrial chemical used to prepare a type of nylon)

Just as amides are more stable than esters, lactams are more stable than lactones. Thus, although β-lactones are difficultly accessible (Section 19.15), β-lactams are among the best known products of the pharmaceutical industry. The penicillins and cephalosporins, which are so useful in treating bacterial infections, are β-lactams and are customarily referred to as *β-lactam antibiotics.*



Penicillin G

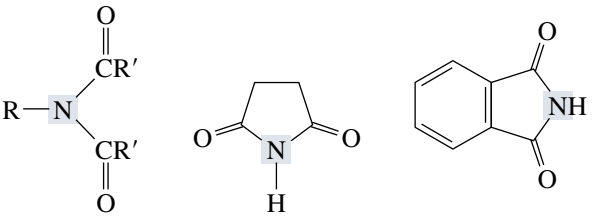


Cephalexin

These antibiotics inhibit a bacterial enzyme that is essential for cell wall formation. A nucleophilic site on the enzyme reacts with the carbonyl group in the four-membered ring, and the ring opens to acylate the enzyme. Once its nucleophilic site is acylated, the enzyme is no longer active and the bacteria die. The β-lactam rings of the penicillins and cephalosporins combine just the right level of stability in aqueous media with reactivity toward nucleophilic substitution to be effective acylating agents toward this critical bacterial enzyme.

20.15 IMIDES

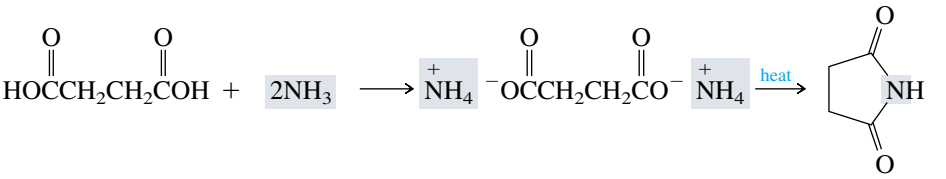
Compounds that have two acyl groups bonded to a single nitrogen are known as **imides.** The most common imides are cyclic ones:



Imide Succinimide Phthalimide

Cyclic imides can be prepared by heating the ammonium salts of dicarboxylic acids:

Replacement of the proton on nitrogen in succinimide by bromine gives *N*-bromosuccinimide, a reagent used for allylic and benzylic brominations (Sections 10.4 and 11.12).

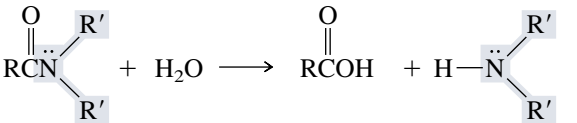


Succinic acid Ammonia Ammonium succinate Succinimide (82–83%)

PROBLEM 20.18 Phthalimide has been prepared in 95% yield by heating the compound formed on reaction of phthalic anhydride (Section 20.4) with excess ammonia. This compound has the molecular formula $C_8H_{10}N_2O_3$. What is its structure?

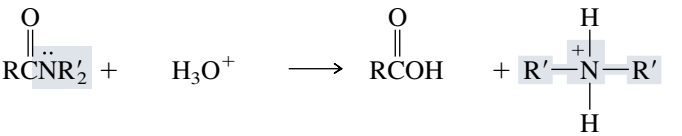
20.16 HYDROLYSIS OF AMIDES

The only nucleophilic acyl substitution reaction that amides undergo is hydrolysis. Amides are fairly stable in water, but the amide bond is cleaved on heating in the presence of strong acids or bases. Nominally, this cleavage produces an amine and a carboxylic acid.



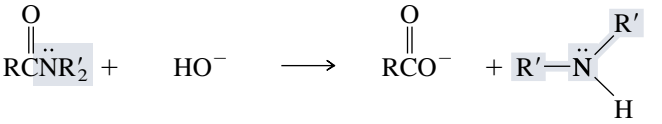
Amide Water Carboxylic acid Amine

In acid, however, the amine is protonated, giving an ammonium ion, $R'_2\overset{+}{N}H_2$:



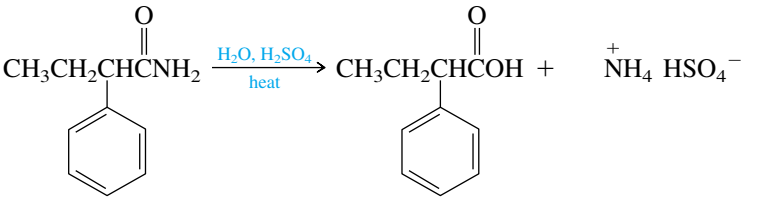
Amide Hydronium ion Carboxylic acid Ammonium ion

In base the carboxylic acid is deprotonated, giving a carboxylate ion:

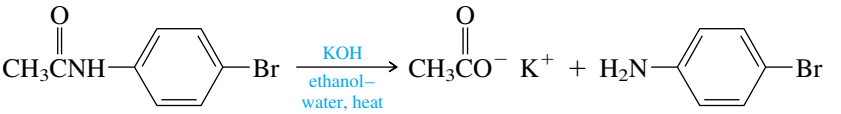


Amide | Hydroxide ion | Carboxylate ion | Amine

The acid–base reactions that occur after the amide bond is broken make the overall hydrolysis irreversible in both cases. The amine product is protonated in acid; the carboxylic acid is deprotonated in base.



2-Phenylbutanamide | 2-Phenylbutanoic acid (88–90%) | Ammonium hydrogen sulfate

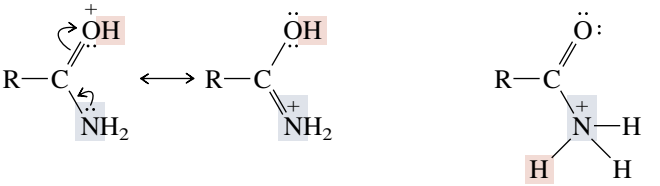


N-(4-Bromophenyl)acetamide (*p*-bromoacetanilide) | Potassium acetate | *p*-Bromoaniline (95%)

Mechanistically, amide hydrolysis is similar to the hydrolysis of other carboxylic acid derivatives. The mechanism of the hydrolysis in acid is presented in Figure 20.6. It proceeds in two stages; a tetrahedral intermediate is formed in the first stage and dissociates in the second.

The amide is activated toward nucleophilic attack by protonation of its carbonyl oxygen. The cation produced in this step is stabilized by resonance involving the nitrogen lone pair and is more stable than the intermediate in which the amide nitrogen is protonated.

Protonation of carbonyl oxygen ***Protonation of amide nitrogen***

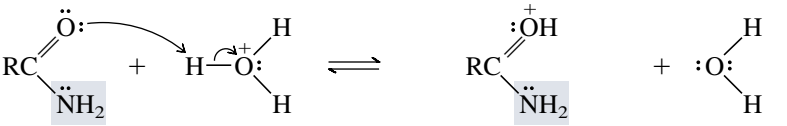


Most stable resonance forms of an *O*-protonated amide | An acylammonium ion; the positive charge is localized on nitrogen

Once formed, the *O*-protonated intermediate is attacked by a water molecule in step 2. The intermediate formed in this step loses a proton in step 3 to give the neutral form of the tetrahedral intermediate. The tetrahedral intermediate has its amino group ($—NH_2$) attached to sp^3-hybridized carbon, and this amino group is the site at which protonation

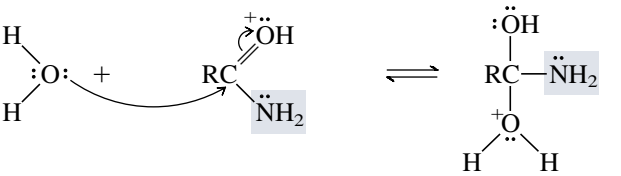
FIGURE 20.6 The mechanism of amide hydrolysis in acid solution. Steps 1 through 3 show the formation of the tetrahedral intermediate. Dissociation of the tetrahedral intermediate is shown in steps 4 through 6.

Step 1: Protonation of the carbonyl oxygen of the amide



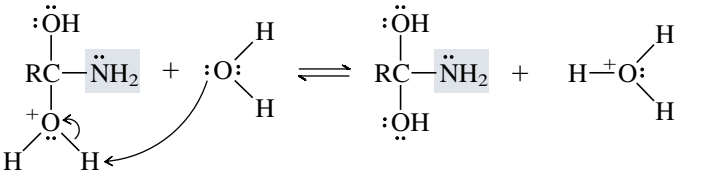
Amide Hydronium ion Protonated form of amide Water

Step 2: Nucleophilic addition of water to the protonated form of the amide



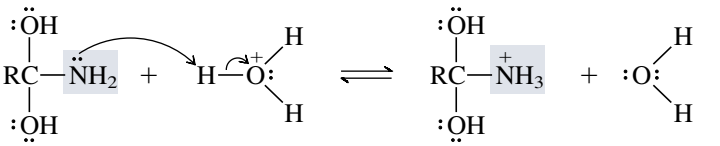
Water Protonated form of amide Oxonium ion

Step 3: Deprotonation of the oxonium ion to give the neutral form of the tetrahedral intermediate



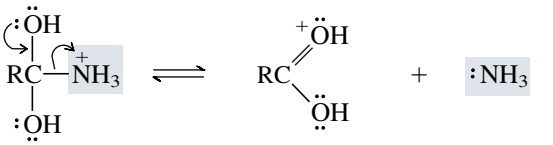
Oxonium ion Water Tetrahedral intermediate Hydronium ion

Step 4: Protonation of the tetrahedral intermediate at its amino nitrogen



Tetrahedral intermediate Hydronium ion Ammonium ion Water

Step 5: Dissociation of the *N*-protonated form of the tetrahedral intermediate to give ammonia and the protonated form of the carboxylic acid



Ammonium ion Protonated form of carboxylic acid Ammonia

—Cont.

Step 6: Proton transfer processes yielding ammonium ion and the carboxylic acid

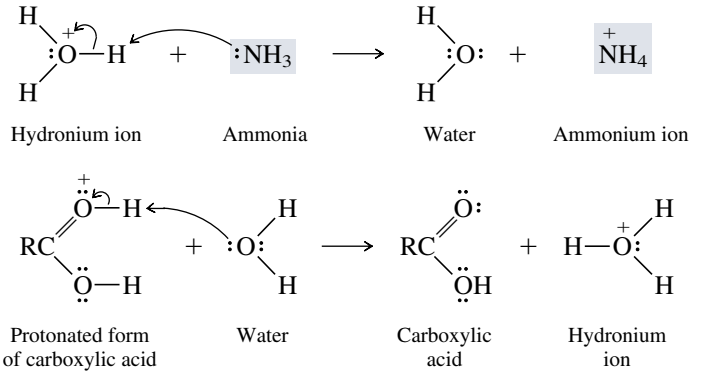


FIGURE 20.6 (*Continued*)

occurs in step 4. Cleavage of the carbon–nitrogen bond in step 5 yields the protonated form of the carboxylic acid, along with a molecule of ammonia. In acid solution ammonia is immediately protonated to give ammonium ion, as shown in step 6. This protonation step has such a large equilibrium constant that it makes the overall reaction irreversible.

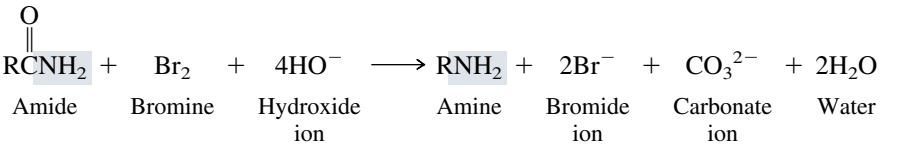
PROBLEM 20.19 On the basis of the general mechanism for amide hydrolysis in acidic solution shown in Figure 20.6, write an analogous sequence of steps for the hydrolysis of acetanilide, $CH_3CNHC_6H_5$.

In base the tetrahedral intermediate is formed in a manner analogous to that proposed for ester saponification. Steps 1 and 2 in Figure 20.7 show the formation of the tetrahedral intermediate in the basic hydrolysis of amides. In step 3 the basic amino group of the tetrahedral intermediate abstracts a proton from water, and in step 4 the derived ammonium ion undergoes basic dissociation. Conversion of the carboxylic acid to its corresponding carboxylate anion in step 5 completes the process and renders the overall reaction irreversible.

PROBLEM 20.20 On the basis of the general mechanism for basic hydrolysis shown in Figure 20.7, write an analogous sequence for the hydrolysis of *N,N*-dimethylformamide, $HCN(CH_3)_2$.

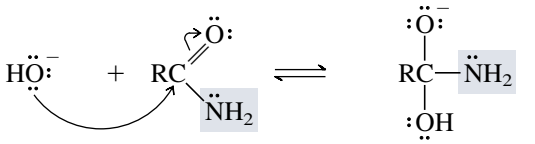
20.17 THE HOFMANN REARRANGEMENT

On treatment with bromine in basic solution, amides of the type $RCNH_2$ undergo an interesting reaction that leads to amines. This reaction was discovered by the nineteenth century German chemist August W. Hofmann and is called the **Hofmann rearrangement.**

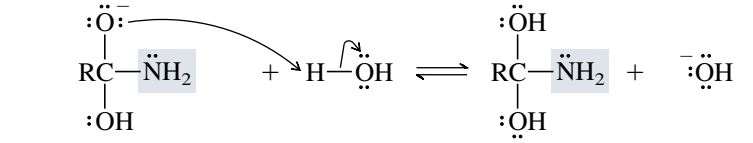


The group R attached to the carboxamide function may be alkyl or aryl.

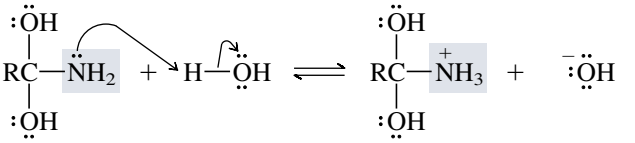
Step 1: Nucleophilic addition of hydroxide ion to the carbonyl group



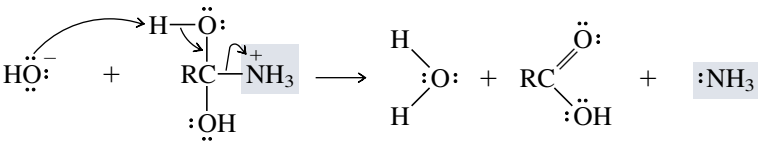
Step 2: Proton transfer to anionic form of tetrahedral intermediate



Step 3: Protonation of amino nitrogen of tetrahedral intermediate



Step 4: Dissociation of *N*-protonated form of tetrahedral intermediate



Step 5: Irreversible formation of carboxylate anion

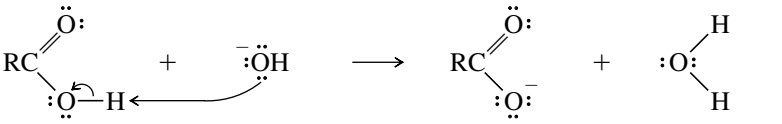


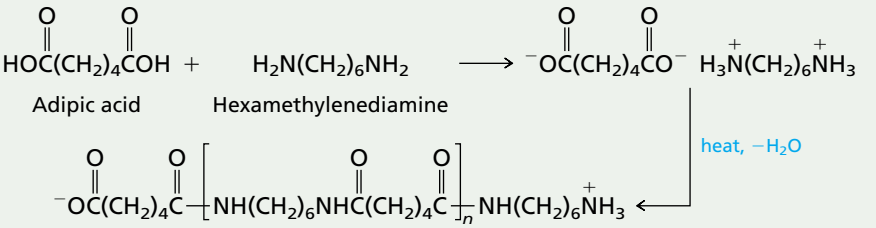
FIGURE 20.7 The mechanism of amide hydrolysis in basic solution.

CONDENSATION POLYMERS. POLYAMIDES AND POLYESTERS

All fibers are polymers of one kind or another. Cotton, for example, is cellulose, and cellulose is a naturally occurring polymer of glucose. Silk and wool are naturally occurring polymers of amino acids. An early goal of inventors and entrepreneurs was to produce fibers from other naturally occurring polymers. Their earliest efforts consisted of chemically modifying the short cellulose fibers obtained from wood so that they could be processed into longer fibers more like cotton and silk. These efforts were successful, and the resulting fibers of modified cellulose, known generically as *rayon,* have been produced by a variety of techniques since the late nineteenth century.

A second approach involved direct chemical synthesis of polymers by connecting appropriately chosen small molecules together into a long chain. In 1938, E. I. Du Pont de Nemours and Company announced the development of *nylon,* the first synthetic polymer fiber.

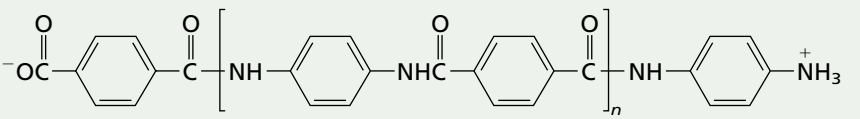
The leader of Du Pont's effort was Wallace H. Carothers,* who reasoned that he could reproduce the properties of silk by constructing a polymer chain held together, as is silk, by amide bonds. The necessary amide bonds were formed by heating a dicarboxylic acid with a diamine. Hexanedioic acid *(adipic acid)* and 1,6-hexanediamine *(hexamethylenediamine)* react to give a salt that, when heated, gives a **polyamide** called *nylon 66.* The amide bonds form by a condensation reaction, and nylon 66 is an example of a **condensation polymer.**



Nylon 66

The first "6" in nylon 66 stands for the number of carbons in the diamine, the second for the number of carbons in the dicarboxylic acid. Nylon 66 was an immediate success and fostered the development of a large number of related polyamides, many of which have also found their niche in the marketplace.

A slightly different class of polyamides is the *aramids (aromatic polyamides).* Like the nylons, the aramids are prepared from a dicarboxylic acid and a diamine, but the functional groups are anchored to benzene rings. An example of an aramid is *Kevlar,* which is a polyamide derived from 1,4-benzenedicarboxylic acid *(terephthalic acid)* and 1,4-benzenediamine *(p-phenylenediamine):*



Kevlar (a polyamide of the aramid class)

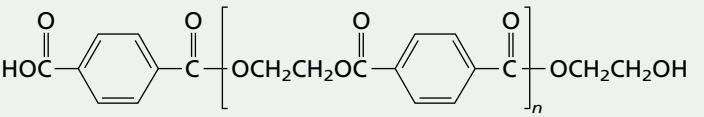
Kevlar fibers are very strong, which makes Kevlar a popular choice in applications where the ratio of strength to weight is important. For example, a cable made from Kevlar weighs only one fifth as much as a steel one but is just as strong. Kevlar is also used to make lightweight bulletproof vests.

Nomex is another aramid fiber. Kevlar and Nomex differ only in that the substitution pattern in the aromatic rings is para in Kevlar but meta in Nomex. Nomex is best known for its fire-resistant properties and is used in protective clothing for firefighters, astronauts, and race-car drivers.

*For an account of Carothers' role in the creation of nylon, see the September 1988 issue of the *Journal of Chemical Education* (pp. 803–808).

—Cont.

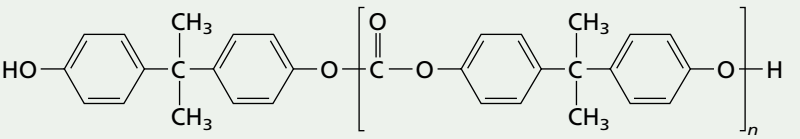
Polyesters are a second class of condensation polymers, and the principles behind their synthesis parallel those of polyamides. Ester formation between the functional groups of a dicarboxylic acid and a diol serve to connect small molecules together into a long polyester. The most familiar example of a polyester is *Dacron,* which is prepared from 1,4-benzenedicarboxylic acid and 1,2-ethanediol (*ethylene glycol*):



Dacron (a polyester)

The production of polyester fibers leads that of all other types. Annual United States production of polyester fibers is 1.6 million tons versus 1.4 million tons for cotton and 1.0 million tons for nylon. Wool and silk trail far behind at 0.04 and 0.01 million tons, respectively.

Not all synthetic polymers are used as fibers. *Mylar,* for example, is chemically the same as Dacron, but is prepared in the form of a thin film instead of a fiber. *Lexan* is a polyester which, because of its impact resistance, is used as a shatterproof substitute for glass. It is a **polycarbonate** having the structure shown:

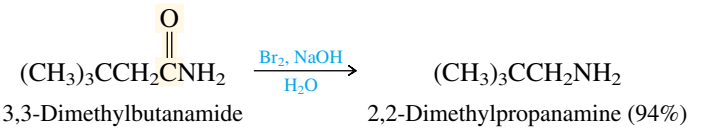


Lexan (a polycarbonate)

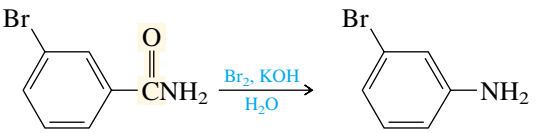
In terms of the number of scientists and engineers involved, research and development in polymer chemistry is the principal activity of the chemical industry. The initial goal of making synthetic materials that are the equal of natural fibers has been more than met; it has been far exceeded. What is also important is that all of this did not begin with a chance discovery. It began with a management decision to do basic research in a specific area, and to support it in the absence of any guarantee that success would be quickly achieved.[†]

[†]The April 1988 issue of the *Journal of Chemical Education* contains a number of articles on polymers, including a historical review entitled "Polymers Are Everywhere" (pp. 327–334) and a glossary of terms (pp. 314–319).

The relationship of the amine product to the amide reactant is rather remarkable. The overall reaction appears as if the carbonyl group had been plucked out of the amide, leaving behind a primary amine having one less carbon atom than the amide.



3,3-Dimethylbutanamide — 2,2-Dimethylpropanamine (94%)



m-Bromobenzamide — *m*-Bromoaniline (87%)

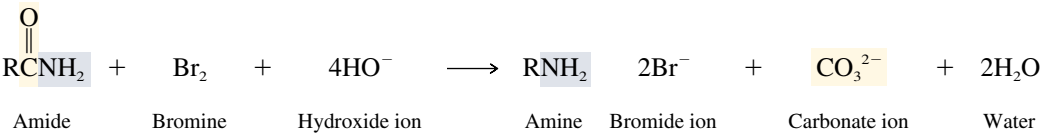
PROBLEM 20.21 Outline an efficient synthesis of 1-propanamine ($CH_3CH_2CH_2NH_2$) from butanoic acid.

The mechanism of the Hofmann rearrangement (Figure 20.8) involves three stages:

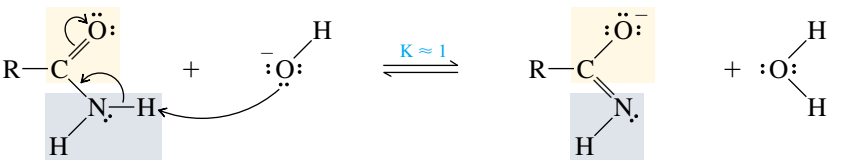
1. Formation of an *N*-bromo amide intermediate (steps 1 and 2)
2. Rearrangement of the *N*-bromo amide to an isocyanate (steps 3 and 4)
3. Hydrolysis of the isocyanate (steps 5 and 6)

FIGURE 20.8 The mechanism of the Hofmann rearrangement.

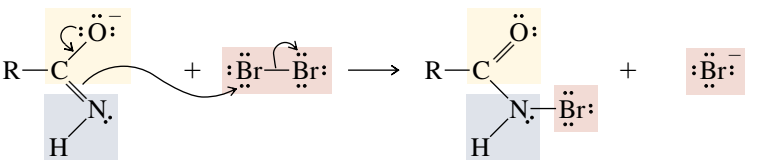
Overall Reaction



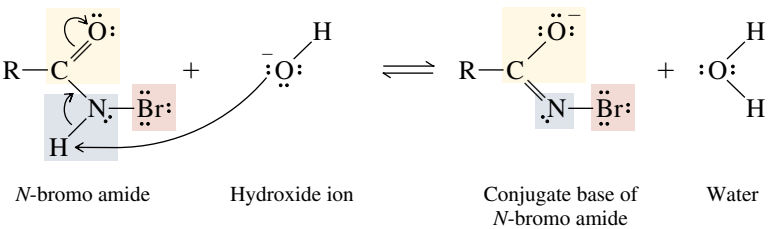
Step 1: Deprotonation of the amide. Amides of the type $RCNH_2$ are about as acidic as water, so appreciable quantities of the conjugate base are present at equilibrium in aqueous base. The conjugate base of an amide is stabilized by electron delocalization in much the same way that an enolate anion is.



Step 2: Reaction of the conjugate base of the amide with bromine. The product of this step is an *N*-bromo amide.

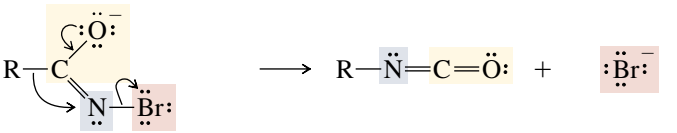


Step 3: Deprotonation of the *N*-bromo amide. The electron-withdrawing effect of the bromine substituent reinforces that of the carbonyl group and makes the *N*-bromo amide even more acidic than the starting amide.



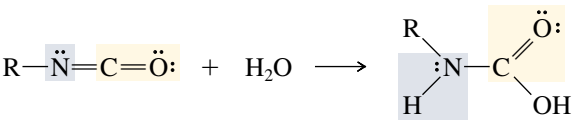
—Cont.

Step 4: Rearrangement of the conjugate base of the *N*-bromo amide. The group R migrates from carbon to nitrogen, and bromide is lost as a leaving group from nitrogen. The product of this rearrangement is an *N*-alkyl isocyanate.



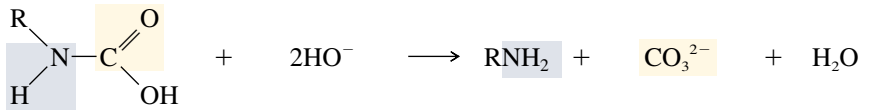
Conjugate base of *N*-bromo amide | *N*-Alkyl isocyanate | Bromide ion

Step 5: Hydrolysis of the isocyanate begins by base-catalyzed addition of water to form an *N*-alkylcarbamic acid.



N-Alkyl isocyanate | *N*-Alkylcarbamic acid

Step 6: The *N*-alkylcarbamic acid is unstable and dissociates to an amine and carbon dioxide. Carbon dioxide is converted to carbonate ion in base. (Several steps are actually involved; in the interests of brevity, they are summarized as shown.)



N-Alkylcarbamic acid | Hydroxide ion | Amine | Carbonate ion | Water

FIGURE 20.8 (*Continued*)

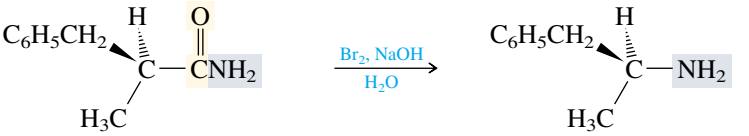
Formation of the *N*-bromo amide intermediate is relatively straightforward. The base converts the amide to its corresponding anion (step 1), which acts as a nucleophile toward bromine (step 2).

Conversion of the *N*-bromo amide to its conjugate base in step 3 is also easy to understand. It is an acid–base reaction exactly analogous to that of step 1. The anion produced in step 3 is a key intermediate; it rearranges in step 4 by migration of the alkyl (or aryl) group from carbon to nitrogen, with loss of bromide from nitrogen. The product of this rearrangement is an isocyanate. The isocyanate formed in the rearrangement step then undergoes basic hydrolysis in steps 5 and 6 to give the observed amine.

Among the experimental observations that contributed to elaboration of the mechanism shown in Figure 20.8 are the following:

1. Only amides of the type $RC(=O)NH_2$ undergo the Hofmann rearrangement. The amide nitrogen must have *two* protons attached to it, of which one is replaced by bromine to give the *N*-bromo amide, whereas abstraction of the second by base is necessary to trigger the rearrangement. Amides of the type $RC(=O)NHR'$ form *N*-bromo amides under the reaction conditions, but these *N*-bromo amides do not rearrange.

2. Rearrangement proceeds with *retention of configuration* at the migrating group.



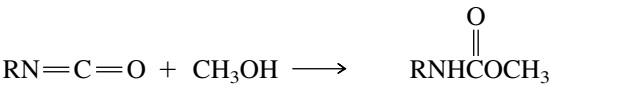
(*S*)-(+)-2-Methyl-3-phenylpropanamide (*S*)-(+)-1-Phenyl-2-propanamine

The new carbon–nitrogen bond is formed at the same face of the migrating carbon as the bond that is broken. The rearrangement step depicted in Figure 20.8 satisfies this requirement. Presumably, carbon–nitrogen bond formation is concerted with carbon–carbon bond cleavage.

3. Isocyanates are intermediates. When the reaction of an amide with bromine is carried out in methanol containing sodium methoxide instead of in aqueous base, the product that is isolated is a **carbamate.**

Hexadecanamide Methyl *N*-pentadecylcarbamate (84–94%)

Carbamates are esters of **carbamic acid** (H_2NCOH). Carbamates are also known as **urethans.** They are relatively stable and are formed by addition of alcohols to isocyanates.



Isocyanate Methanol Methyl *N*-alkylcarbamate

Carbamic acid itself (H_2NCOH) and *N*-substituted derivatives of carbamic acid are unstable; they decompose spontaneously to carbon dioxide and ammonia or an amine. Thus in aqueous solution, an isocyanate intermediate yields an amine via the corresponding carbamic acid; in methanol, an isocyanate is converted to an isolable methyl carbamate. If desired, the carbamate can be isolated, purified, and converted to an amine in a separate hydrolysis operation.

Although the Hofmann rearrangement is complicated with respect to mechanism, it is easy to carry out and gives amines that are sometimes difficult to prepare by other methods.

20.18 PREPARATION OF NITRILES

Nitriles are organic compounds that contain the —C≡N functional group. We have already discussed the two main procedures by which they are prepared, namely, the nucleophilic substitution of alkyl halides by cyanide and the conversion of aldehydes and ketones to cyanohydrins. Table 20.7 reviews aspects of these reactions. Neither of the reactions in Table 20.7 is suitable for aryl nitriles (ArC≡N); these compounds are readily prepared by a reaction to be discussed in Chapter 22.

TABLE 20.7 Preparation of Nitriles

Reaction (section) and comments	General equation and specific example
Nucleophilic substitution by cyanide ion (Sections 8.1, 8.13) Cyanide ion is a good nucleophile and reacts with alkyl halides to give alkyl nitriles. The reaction is of the S_N2 type and is limited to primary and secondary alkyl halides. Tertiary alkyl halides undergo elimination; aryl and vinyl halides do not react.	$:N\equiv\bar{C}: + R-X \longrightarrow RC\equiv N + X^-$ Cyanide ion; Alkyl halide; Nitrile; Halide ion $CH_3(CH_2)_8CH_2Cl \xrightarrow[\text{ethanol–water}]{KCN} CH_3(CH_2)_8CH_2CN$ 1-Chlorodecane; Undecanenitrile (95%)
Cyanohydrin formation (Section 17.7) Hydrogen cyanide adds to the carbonyl group of aldehydes and ketones.	$RCR' + HCN \longrightarrow RCR'(OH)(C\equiv N)$ Aldehyde or ketone; Hydrogen cyanide; Cyanohydrin $CH_3CH_2CCH_2CH_3 \xrightarrow[H^+]{KCN} CH_3CH_2C(OH)(CN)CH_2CH_3$ 3-Pentanone; 3-Pentanone cyanohydrin (75%)

Both alkyl and aryl nitriles are accessible by dehydration of amides.

$$RCNH_2 \longrightarrow RC\equiv N + H_2O$$

Amide (R may be alkyl or aryl); Nitrile (R may be alkyl or aryl); Water

Among the reagents used to effect the dehydration of amides is the compound P_4O_{10}, known by the common name *phosphorus pentoxide* because it was once thought to have the molecular formula P_2O_5. Phosphorus pentoxide is the anhydride of phosphoric acid and is used in a number of reactions requiring dehydrating agents.

$$(CH_3)_2CHCNH_2 \xrightarrow[200°C]{P_4O_{10}} (CH_3)_2CHC\equiv N$$

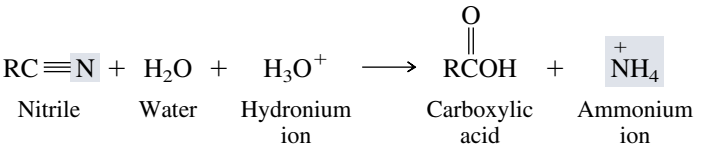
2-Methylpropanamide; 2-Methylpropanenitrile (69–86%)

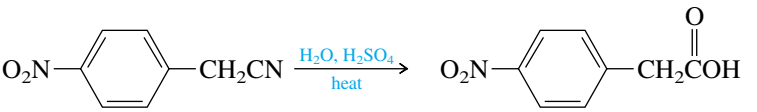
PROBLEM 20.22 Show how ethyl alcohol could be used to prepare (a) CH_3CN and (b) CH_3CH_2CN. Along with ethyl alcohol you may use any necessary inorganic reagents.

An important nitrile is *acrylonitrile,* $CH_2{=}CHCN$. It is prepared industrially from propene, ammonia, and oxygen in the presence of a special catalyst. Polymers of acrylonitrile have many applications, the most prominent being their use in the preparation of acrylic fibers.

20.19 HYDROLYSIS OF NITRILES

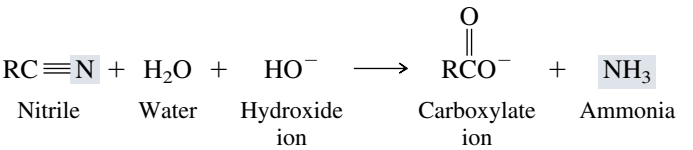
Nitriles are classified as carboxylic acid derivatives because they are converted to carboxylic acids on hydrolysis. The conditions required are similar to those for the hydrolysis of amides, namely, heating in aqueous acid or base for several hours. Like the hydrolysis of amides, nitrile hydrolysis is irreversible in the presence of acids or bases. Acid hydrolysis yields ammonium ion and a carboxylic acid.

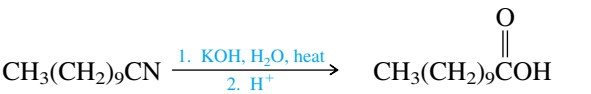




p-Nitrobenzyl cyanide *p*-Nitrophenylacetic acid (92–95%)

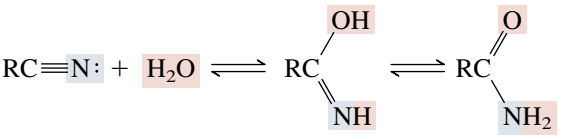
In aqueous base, hydroxide ion abstracts a proton from the carboxylic acid. In order to isolate the acid a subsequent acidification step is required.





Undecanenitrile Undecanoic acid (80%)

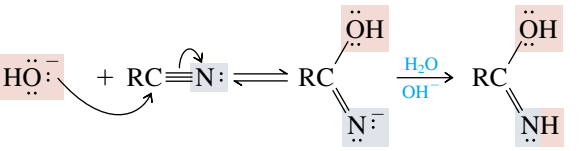
Nitriles are susceptible to nucleophilic addition. In their hydrolysis, water adds across the carbon–nitrogen triple bond. In a series of proton-transfer steps, an amide is produced:



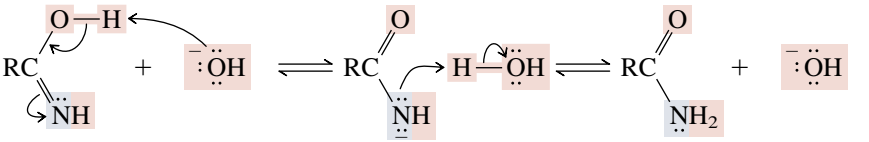
Nitrile Water Imino acid Amide

We already discussed both the acidic and basic hydrolysis of amides (see Section 20.16). All that remains to complete the mechanistic picture of nitrile hydrolysis is to examine the conversion of the nitrile to the corresponding amide.

Nucleophilic addition to the nitrile may be either acid- or base-catalyzed. In aqueous base, hydroxide adds to the carbon–nitrogen triple bond:



The imino acid is transformed to the amide by the sequence

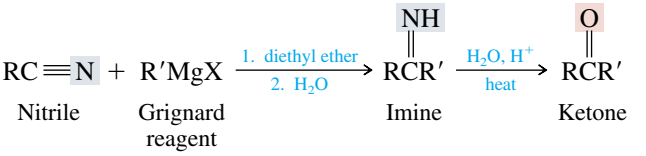


PROBLEM 20.23 Suggest a reasonable mechanism for the conversion of a nitrile (RCN) to the corresponding amide in aqueous acid.

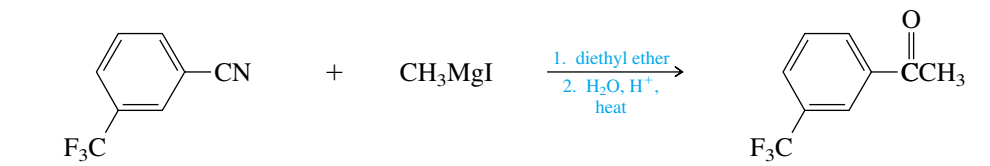
Nucleophiles other than water can also add to the carbon–nitrogen triple bond of nitriles. In the following section we will see a synthetic application of such a nucleophilic addition.

20.20 ADDITION OF GRIGNARD REAGENTS TO NITRILES

The carbon–nitrogen triple bond of nitriles is much less reactive toward nucleophilic addition than is the carbon–oxygen double bond of aldehydes and ketones. Strongly basic nucleophiles such as Grignard reagents, however, do react with nitriles in a reaction that is of synthetic value:



The imine formed by nucleophilic addition of the Grignard reagent to the nitrile is normally not isolated but is hydrolyzed directly to a ketone. The overall sequence is used as a means of preparing ketones.

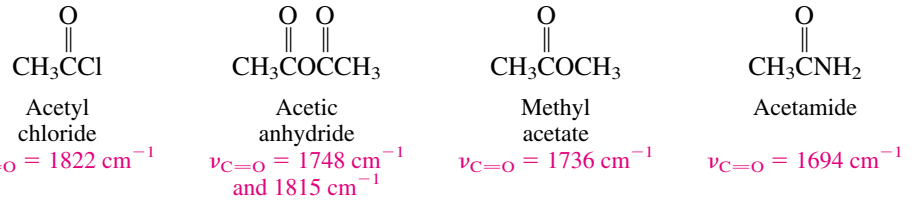


PROBLEM 20.24 Write an equation showing how you could prepare ethyl phenyl ketone from propanenitrile and a Grignard reagent. What is the structure of the imine intermediate?

Organolithium reagents react in the same way and are often used instead of Grignard reagents.

20.21 SPECTROSCOPIC ANALYSIS OF CARBOXYLIC ACID DERIVATIVES

Infrared: Infrared spectroscopy is quite useful in identifying carboxylic acid derivatives. The carbonyl stretching vibration is very strong, and its position is sensitive to the nature of the carbonyl group. In general, electron donation from the substituent decreases the double-bond character of the bond between carbon and oxygen and decreases the stretching frequency. Two distinct absorptions are observed for the symmetric and antisymmetrical stretching vibrations of the anhydride function.



Nitriles are readily identified by absorption due to —C≡N stretching in the 2210–2260 cm^{-1} region.

^{1}H NMR: Chemical-shift differences in their ^{1}H NMR spectra aid the structure determination of esters. Consider the two isomeric esters: ethyl acetate and methyl propanoate. As Figure 20.9 shows, the number of signals and their multiplicities are the same for both esters. Both have a methyl singlet and a triplet–quartet pattern for their ethyl group.

The C=O stretching vibrations of these compounds may be viewed on *Learning By Modeling.*

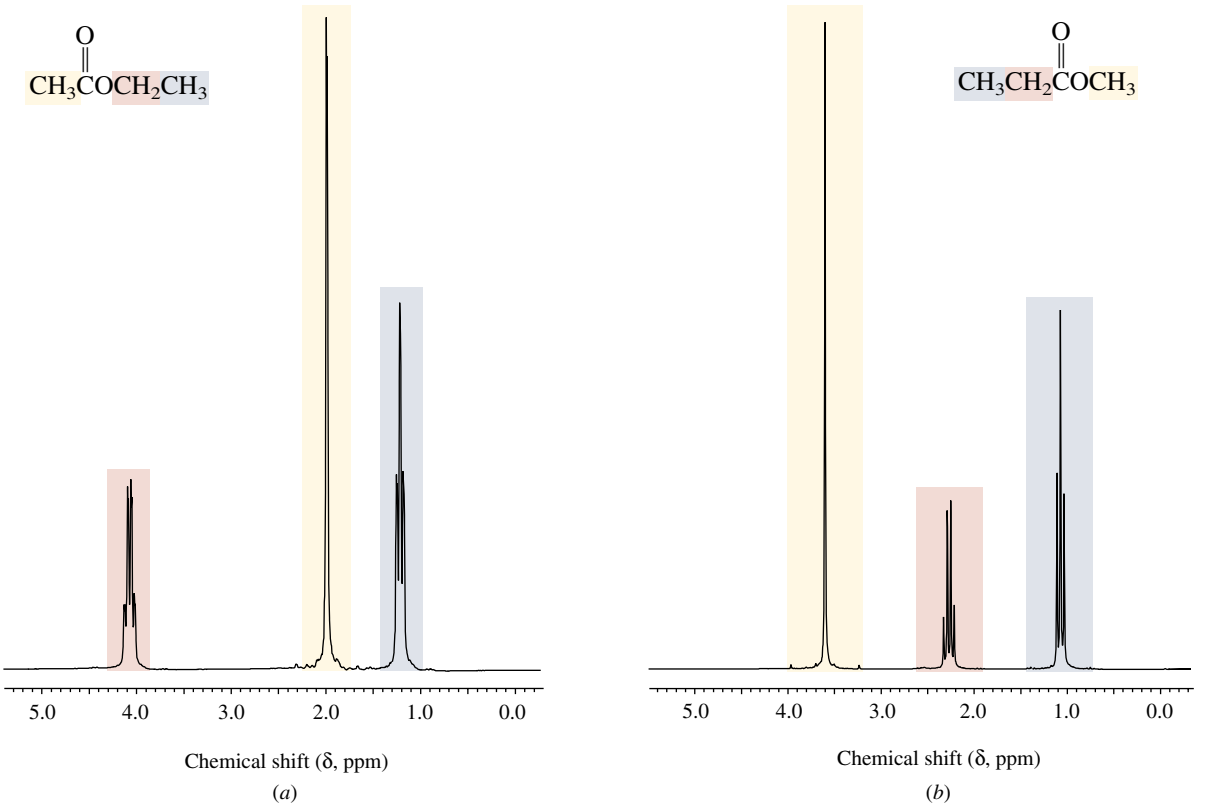
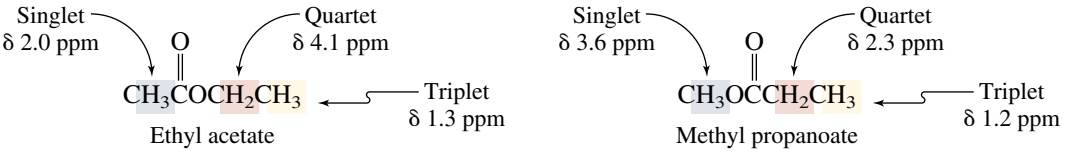


FIGURE 20.9 The 200-MHz ^{1}H NMR spectra of (*a*) ethyl acetate and (*b*) methyl propanoate.



Notice, however, that there is a significant difference in the chemical shifts of the corresponding signals in the two spectra. The methyl singlet is more shielded (δ 2.0 ppm) when it is bonded to the carbonyl group of ethyl acetate than when it is bonded to the oxygen of methyl propanoate (δ 3.6 ppm). The methylene quartet is more shielded (δ 2.3 ppm) when it is bonded to the carbonyl group of methyl propanoate than when it is bonded to the oxygen of ethyl acetate (δ 4.1 ppm). Analysis of the number of peaks and their splitting patterns will not provide an unambiguous answer to structure assignment in esters; chemical-shift data must also be considered.

The chemical shift of the N—H proton of amides appears in the range δ 5–8 ppm. It is often a very broad peak; sometimes it is so broad that it does not rise much over the baseline and can be lost in the background noise.

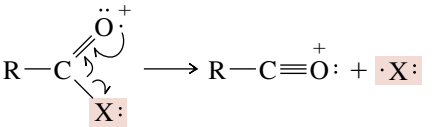
^{13}C NMR: The ^{13}C NMR spectra of carboxylic acid derivatives, like the spectra of carboxylic acids themselves, are characterized by a low-field resonance for the carbonyl carbon in the range δ 160–180 ppm. The carbonyl carbons of carboxylic acid derivatives are more shielded than those of aldehydes and ketones, but less shielded than the sp^2-hybridized carbons of alkenes and arenes.

The carbon of a C≡N group appears near δ 120 ppm.

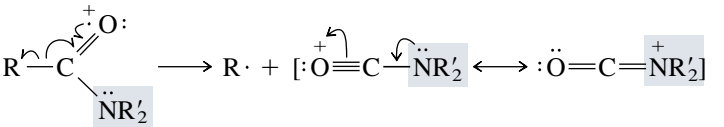
UV-VIS: The following values are typical for the $n \rightarrow \pi,^*$ absorption associated with the C=O group of carboxylic acid derivatives.

	CH_3CCl	CH_3COCCH_3	CH_3COCH_3	CH_3CNH_2
	Acetyl chloride	Acetic anhydride	Methyl acetate	Acetamide
λ_{max}	235nm	225nm	207nm	214nm

Mass Spectrometry: A prominent peak in the mass spectra of most carboxylic acid derivatives corresponds to an acylium ion derived by cleavage of the bond to the carbonyl group:

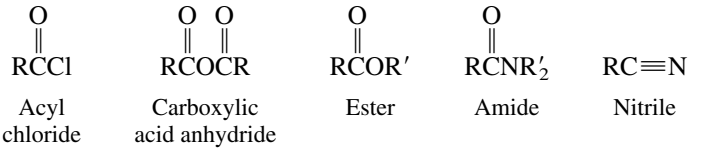


Amides, however, tend to cleave in the opposite direction to produce a nitrogen-stabilized acylium ion:

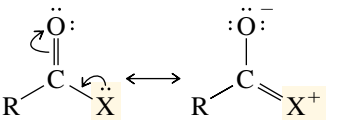


20.22 SUMMARY

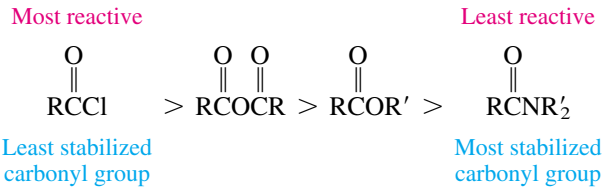
Section 20.1 This chapter concerns the preparation and reactions of *acyl chlorides, acid anhydrides, esters, amides,* and *nitriles.* These compounds are generally classified as carboxylic acid derivatives, and their nomenclature is based on that of carboxylic acids (Section 20.1).



Section 20.2 The structure and reactivity of carboxylic acid derivatives depend on how well the atom bonded to the carbonyl group donates electrons to it.

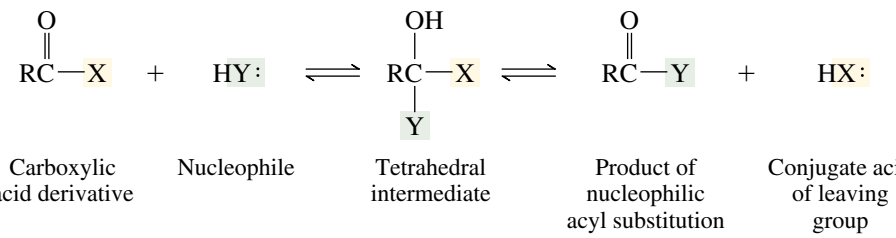


Electron-pair donation stabilizes the carbonyl group and makes it less reactive toward nucleophilic acyl substitution.

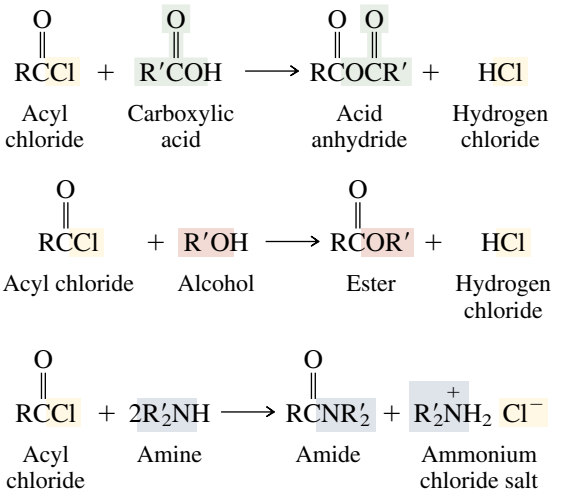


Nitrogen is a better electron-pair donor than oxygen, and amides have a more stabilized carbonyl than esters and anhydrides. Chlorine is the poorest electron-pair donor, and acyl chlorides have the least stabilized carbonyl group and are the most reactive.

Section 20.3 The characteristic reaction of acyl chlorides, acid anhydrides, esters, and amides is **nucleophilic acyl substitution.** Addition of a nucleophilic reagent HY: to the carbonyl group leads to a tetrahedral intermediate that dissociates to give the product of substitution:



Acyl chlorides are converted to anhydrides, esters, and amides by nucleophilic acyl substitution.



Examples of each of these reactions may be found in Table 20.2.

Section 20.4 Acid anhydrides may be prepared from acyl chlorides in the laboratory, but the most commonly encountered ones (acetic anhydride, phthalic anhydride, and maleic anhydride) are industrial chemicals prepared by specialized methods.

Section 20.5 Acid anhydrides are less reactive toward nucleophilic acyl substitution than acyl chlorides, but are useful reagents for preparing esters and amides.

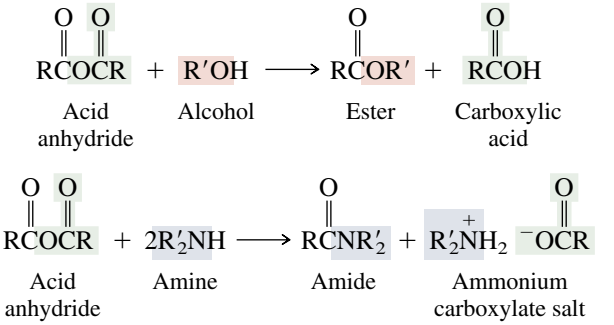


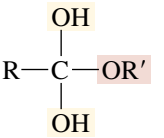
Table 20.3 presents examples of these reactions.

Section 20.6 Esters occur naturally or are prepared from alcohols by Fischer esterification or by acylation with acyl chlorides or acid anhydrides (see Table 20.4).

Section 20.7 Esters are polar and have higher boiling points than alkanes of comparable size and shape. Esters don't form hydrogen bonds to other ester molecules so have lower boiling points than analogous alcohols. They can form hydrogen bonds to water and so are comparable to alcohols with respect to their solubility in water.

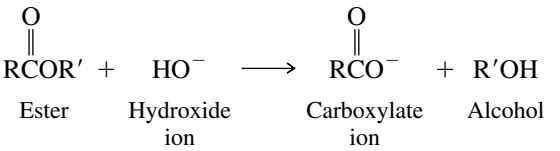
Section 20.8 Esters react with Grignard reagents and are reduced by lithium aluminum hydride (Table 20.5).

Section 20.9 Ester hydrolysis can be catalyzed by acids and its mechanism (Figure 20.4) is the reverse of the mechanism for Fischer esterification. The reaction proceeds via a tetrahedral intermediate.



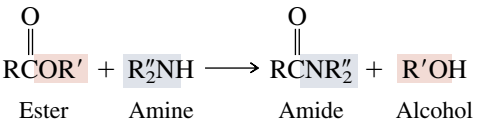
Tetrahedral intermediate
in ester hydrolysis

Section 20.10 Ester hydrolysis in basic solution is called *saponification* and proceeds through the same tetrahedral intermediate (Figure 20.5) as in acid-catalyzed hydrolysis. Unlike acid-catalyzed hydrolysis, saponification is irreversible because the carboxylic acid is deprotonated under the reaction conditions.



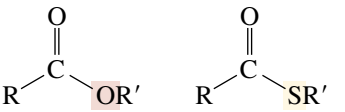
Ester — Hydroxide ion — Carboxylate ion — Alcohol

Section 20.11 Esters react with amines to give amides.



Ester — Amine — Amide — Alcohol

Section 20.12 Thioesters undergo reactions analogous to those of esters, but at faster rates. A sulfur atom stabilizes a carbonyl group less effectively than an oxygen.



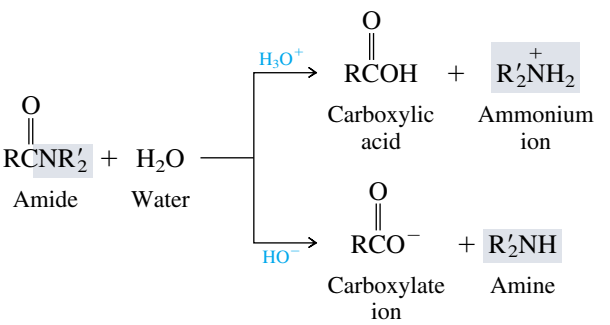
Ester — Thioester

Section 20.13 Amides are normally prepared by the reaction of amines with acyl chlorides, anhydrides, or esters.

Section 20.14 Lactams are cyclic amides.

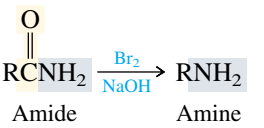
Section 20.15 Imides are compounds that have two acyl groups attached to nitrogen.

Section 20.16 Like ester hydrolysis, amide hydrolysis can be achieved in either aqueous acid or aqueous base. The process is irreversible in both media. In base, the carboxylic acid is converted to the carboxylate anion; in acid, the amine is protonated to an ammonium ion:



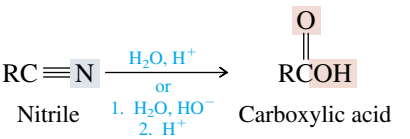
Amide — Water — Carboxylic acid — Ammonium ion — Carboxylate ion — Amine

Section 20.17 The **Hofmann rearrangement** converts amides of the type $RC(=O)NH_2$ to primary amines (RNH_2). The carbon chain is shortened by one carbon with loss of the carbonyl group:

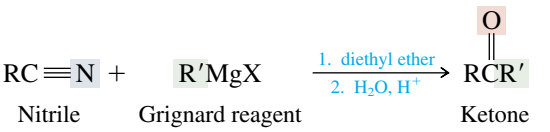


Section 20.18 Nitriles are prepared by nucleophilic substitution (S_N2) of alkyl halides with cyanide ion, by converting aldehydes or ketones to cyanohydrins (Table 20.7) or by dehydration of amides.

Section 20.19 The hydrolysis of nitriles to carboxylic acids is irreversible in both acidic and basic solution.



Section 20.20 Nitriles are useful starting materials for the preparation of ketones by reaction with Grignard reagents.



Section 20.21 Acyl chlorides, anhydrides, esters, and amides all show a strong band for C=O stretching in the infrared. The range extends from about 1820 cm^{-1} (acyl chlorides) to 1690 cm^{-1} (amides). Their ^{13}C NMR spectra are characterized by a peak near δ180 ppm for the carbonyl carbon. ^1H NMR spectroscopy is useful for distinguishing between the groups R and R′ in esters (RCO_2R'). The protons on the carbon bonded to O in R′ appear at lower field (less shielded) than those on the carbon bonded to C=O.

PROBLEMS

20.25 Write a structural formula for each of the following compounds:

(a) *m*-Chlorobenzoyl bromide

(b) Trifluoroacetic anhydride

(c) *cis*-1,2-Cyclopropanedicarboxylic anhydride

(d) Ethyl cycloheptanecarboxylate

(e) 1-Phenylethyl acetate

(f) 2-Phenylethyl acetate

(g) *p*-Ethylbenzamide

(h) *N*-Ethylbenzamide

(i) 2-Methylhexanenitrile

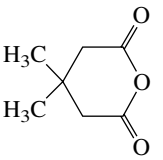
20.26 Give an acceptable IUPAC name for each of the following compounds:

(a) CH_3CHCH_2CBr (O; Cl)

(b) $CH_3COCH_2C_6H_5$

(c) $CH_3OCCH_2C_6H_5$

(d) $ClCH_2CH_2COCCH_2CH_2Cl$ (O; O)

(e) 

(f) $(CH_3)_2CHCH_2CH_2C{\equiv}N$

(g) $(CH_3)_2CHCH_2CH_2CNH_2$

(h) $(CH_3)_2CHCH_2CH_2CNHCH_3$

(i) $(CH_3)_2CHCH_2CH_2CN(CH_3)_2$

20.27 Write a structural formula for the principal organic product or products of each of the following reactions:

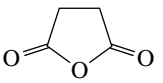
(a) Acetyl chloride and bromobenzene, $AlCl_3$

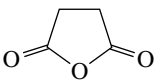
(b) Acetyl chloride and 1-butanethiol

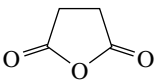
(c) Propanoyl chloride and sodium propanoate

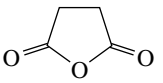
(d) Butanoyl chloride and benzyl alcohol

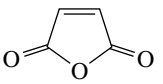
(e) *p*-Chlorobenzoyl chloride and ammonia

(f)  and water

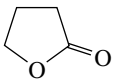
(g)  and aqueous sodium hydroxide

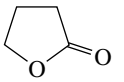
(h)  and aqueous ammonia

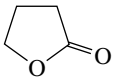
(i)  and benzene, $AlCl_3$

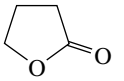
(j)  and 1,3-pentadiene

(k) Acetic anhydride and 3-pentanol

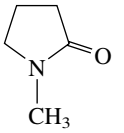
(l)  and aqueous sodium hydroxide

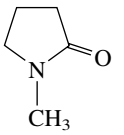
(m)  and aqueous ammonia

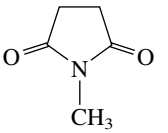
(n)  and lithium aluminum hydride, then H_2O

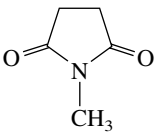
(o)  and excess methylmagnesium bromide, then H_3O^+

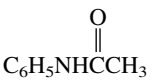
(p) Ethyl phenylacetate and methylamine (CH_3NH_2)

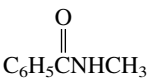
(q)  and aqueous sodium hydroxide

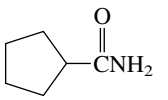
(r)  and aqueous hydrochloric acid, heat

(s)  and aqueous sodium hydroxide

(t)  and aqueous hydrochloric acid, heat

(u)  and aqueous hydrochloric acid, heat

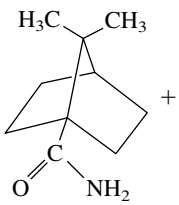
(v)  and aqueous sulfuric acid, heat

(w)  and P_4O_{10}

(x) $(CH_3)_2CHCH_2C{\equiv}N$ and aqueous hydrochloric acid, heat

(y) *p*-Methoxybenzonitrile and aqueous sodium hydroxide, heat

(z) Propanenitrile and methylmagnesium bromide, then H_3O^+

(aa)  + Br_2 $\xrightarrow[CH_3OH]{NaOCH_3}$

(bb) Product of (aa) $\xrightarrow{KOH,\ H_2O}$

20.28 Using ethanol as the ultimate source of all the carbon atoms, along with any necessary inorganic reagents, show how you could prepare each of the following:

(a) Acetyl chloride
(b) Acetic anhydride
(c) Ethyl acetate
(d) Ethyl bromoacetate
(e) 2-Bromoethyl acetate
(f) Ethyl cyanoacetate
(g) Acetamide
(h) Methylamine (CH_3NH_2)
(i) 2-Hydroxypropanoic acid

20.29 Using toluene as the ultimate source of all the carbon atoms, along with any necessary inorganic reagents, show how you could prepare each of the following:

(a) Benzoyl chloride
(b) Benzoic anhydride
(c) Benzyl benzoate
(d) Benzamide
(e) Benzonitrile
(f) Benzyl cyanide
(g) Phenylacetic acid
(h) *p*-Nitrobenzoyl chloride
(i) *m*-Nitrobenzoyl chloride
(j) Aniline

20.30 The saponification of ^{18}O-labeled ethyl propanoate was described in Section 20.10 as one of the significant experiments that demonstrated acyl–oxygen cleavage in ester hydrolysis. The ^{18}O-labeled ethyl propanoate used in this experiment was prepared from ^{18}O-labeled ethyl alcohol, which in turn was obtained from acetaldehyde and ^{18}O-enriched water. Write a series of equations showing the preparation of $CH_3CH_2C(=O)OCH_2CH_3$ (where O = ^{18}O) from these starting materials.

20.31 Suggest a reasonable explanation for each of the following observations:

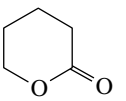
(a) The second-order rate constant k for saponification of ethyl trifluoroacetate is over 1 million times greater than that for ethyl acetate (25°C).

(b) The second-order rate constant for saponification of ethyl 2,2-dimethylpropanoate, $(CH_3)_3CCO_2CH_2CH_3$, is almost 100 times smaller than that for ethyl acetate (30°C).

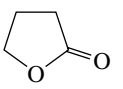
(c) The second-order rate constant k for saponification of methyl acetate is 100 times greater than that for *tert*-butyl acetate (25°C).

(d) The second-order rate constant k for saponification of methyl *m*-nitrobenzoate is 40 times greater than that for methyl benzoate (25°C).

(e) The second-order rate constant k for saponification of 5-pentanolide is over 20 times greater than that for 4-butanolide (25°C).

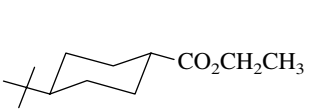


5-Pentanolide

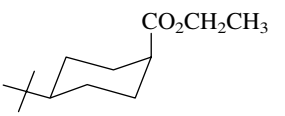


4-Butanolide

(f) The second-order rate constant k for saponification of ethyl *trans*-4-*tert*-butylcyclohexanecarboxylate is 20 times greater than that for its cis diastereomer (25°C).

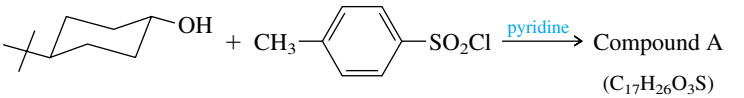


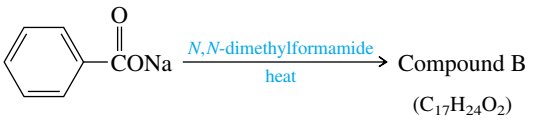
Ethyl *trans*-4-*tert*-butylcyclohexanecarboxylate

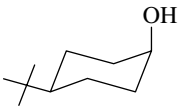


Ethyl *cis*-4-*tert*-butylcyclohexanecarboxylate

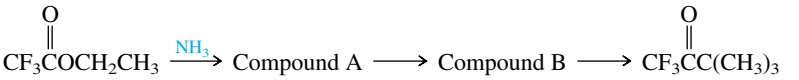
20.32 The preparation of *cis*-4-*tert*-butylcyclohexanol from its trans stereoisomer was carried out by the following sequence of steps. Write structural formulas, including stereochemistry, for compounds A and B.

Step 1: 

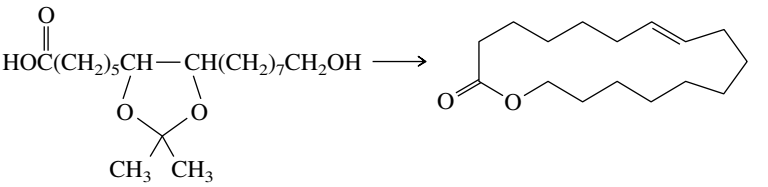
Step 2: Compound A + 

Step 3: Compound B $\xrightarrow[H_2O]{NaOH}$ 

20.33 The ketone shown was prepared in a three-step sequence from ethyl trifluoroacetate. The first step in the sequence involved treating ethyl trifluoroacetate with ammonia to give a compound A. Compound A was in turn converted to the desired ketone by way of a compound B. Fill in the missing reagents in the sequence shown, and give the structures of compounds A and B.



20.34 *Ambrettolide* is obtained from hibiscus and has a musk-like odor. Its preparation from a compound A is outlined in the table that follows. Write structural formulas, ignoring stereochemistry, for compounds B through G in this synthesis. (*Hint:* Zinc, as used in step 4, converts vicinal dibromides to alkenes.)



Compound A Ambrettolide

Step	Reactant	Reagents	Product
1.	Compound A	H_2O, H^+, heat	Compound B ($C_{16}H_{32}O_5$)
2.	Compound B	HBr	Compound C ($C_{16}H_{29}Br_3O_2$)
3.	Compound C	Ethanol, H_2SO_4	Compound D ($C_{18}H_{33}Br_3O_2$)
4.	Compound D	Zinc, ethanol	Compound E ($C_{18}H_{33}BrO_2$)
5.	Compound E	Sodium acetate, acetic acid	Compound F ($C_{20}H_{36}O_4$)
6.	Compound F	KOH, ethanol, then H^+	Compound G ($C_{16}H_{30}O_3$)
7.	Compound G	Heat	Ambrettolide ($C_{16}H_{28}O_2$)

20.35 The preparation of the sex pheromone of the bollworm moth, (*E*)-9,11-dodecadien-1-yl acetate, from compound A has been described. Suggest suitable reagents for each step in this sequence.

(a) $HOCH_2CH{=}CH(CH_2)_7CO_2CH_3 \longrightarrow HC(=O)CH{=}CH(CH_2)_7CO_2CH_3$

Compound A (*E* isomer) — Compound B

(b) Compound B $\longrightarrow CH_2{=}CHCH{=}CH(CH_2)_7CO_2CH_3$

Compound C

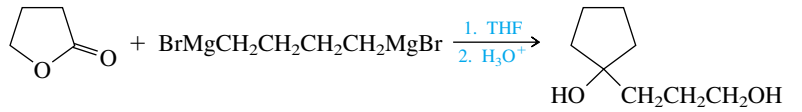
(c) Compound C $\longrightarrow CH_2{=}CHCH{=}CH(CH_2)_7CH_2OH$

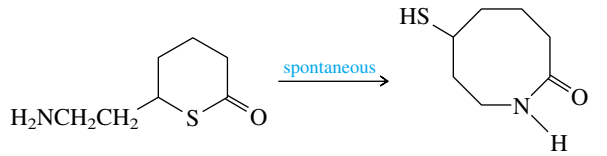
Compound D

(d) Compound D $\longrightarrow CH_2{=}CHCH{=}CH(CH_2)_7CH_2OC(=O)CH_3$

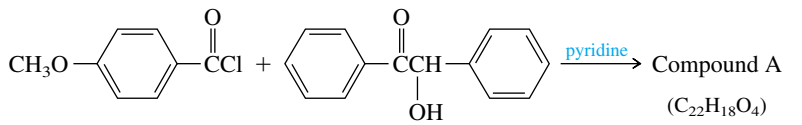
(*E*)-9,11-Dodecadien-1-yl acetate

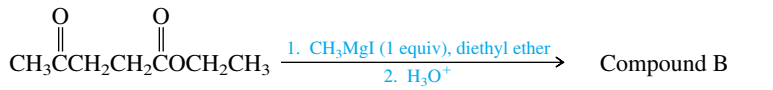
20.36 Outline reasonable mechanisms for each of the following reactions:

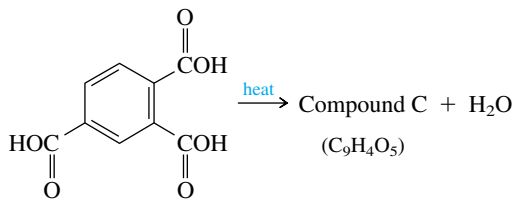
(a) 

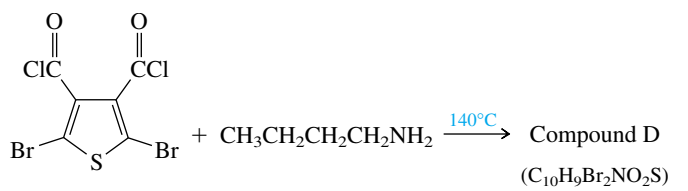
(b) 

20.37 Identify compounds A through D in the following equations:

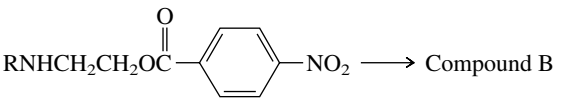
(a) 

(b) 

(c) 

(d) 

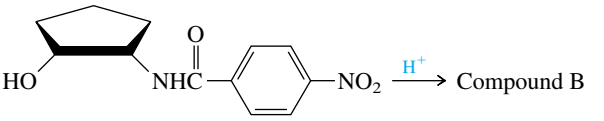
20.38 When compounds of the type represented by A are allowed to stand in pentane, they are converted to a constitutional isomer.



Compound A

Hydrolysis of either A or B yields $RNHCH_2CH_2OH$ and *p*-nitrobenzoic acid. Suggest a reasonable structure for compound B, and demonstrate your understanding of the mechanism of this reaction by writing the structure of the key intermediate in the conversion of compound A to compound B.

20.39 (a) In the presence of dilute hydrochloric acid, compound A is converted to a constitutional isomer, compound B.

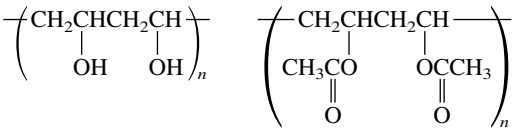


Compound A

Suggest a reasonable structure for compound B.

(b) The trans stereoisomer of compound A is stable under the reaction conditions. Why does it not rearrange?

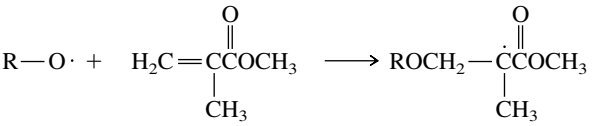
20.40 Poly(vinyl alcohol) is a useful water-soluble polymer. It cannot be prepared directly from vinyl alcohol, because of the rapidity with which vinyl alcohol ($CH_2{=}CHOH$) isomerizes to acetaldehyde. Vinyl acetate, however, does not rearrange and can be polymerized to poly(vinyl acetate). How could you make use of this fact to prepare poly(vinyl alcohol)?



Poly(vinyl alcohol) Poly(vinyl acetate)

20.41 *Lucite* is a polymer of methyl methacrylate.

(a) Assuming the first step in the polymerization of methyl methacrylate is as shown,

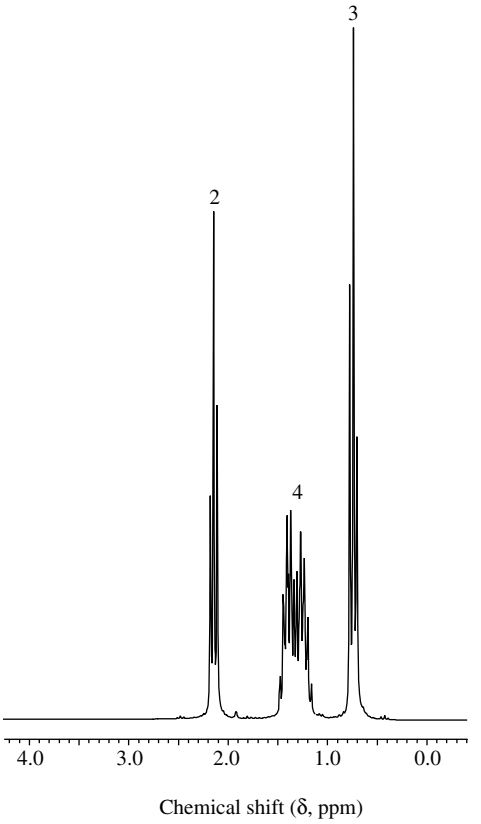


Methyl methacrylate

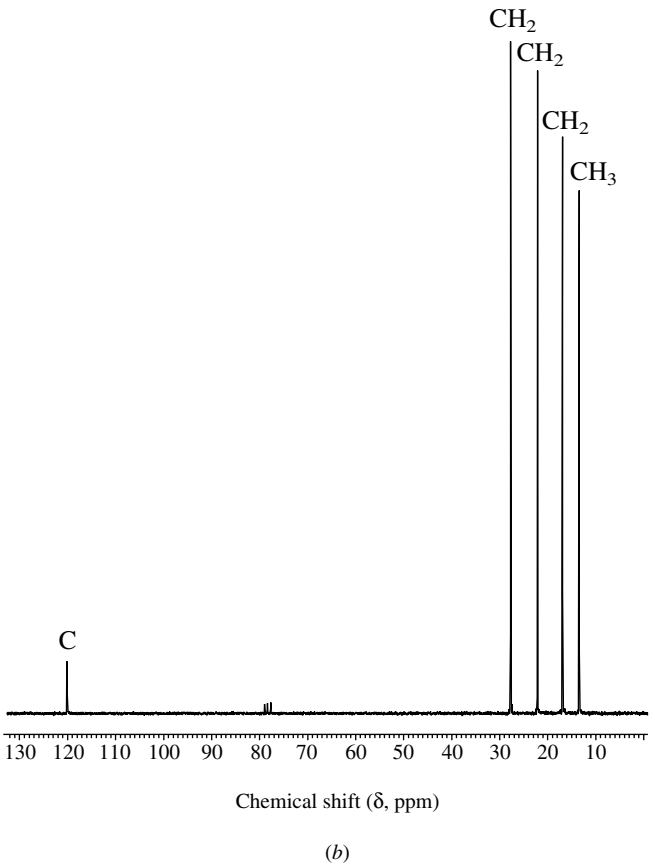
write a structural formula for the free radical produced after the next two propagation steps.

(b) Outline a synthesis of methyl methacrylate from acetone, sodium cyanide, and any necessary organic or inorganic reagents.

20.42 A certain compound has a molecular weight of 83 and contains nitrogen. Its infrared spectrum contains a moderately strong peak at 2270 cm^{-1}. Its ^1H and ^{13}C NMR spectra are shown in Figure 20.10. What is the structure of this compound?



(*a*)



(*b*)

FIGURE 20.10 The 200-MHz (*a*) ^{1}H and (*b*) ^{13}C NMR spectra of the compound in problem 20.42.

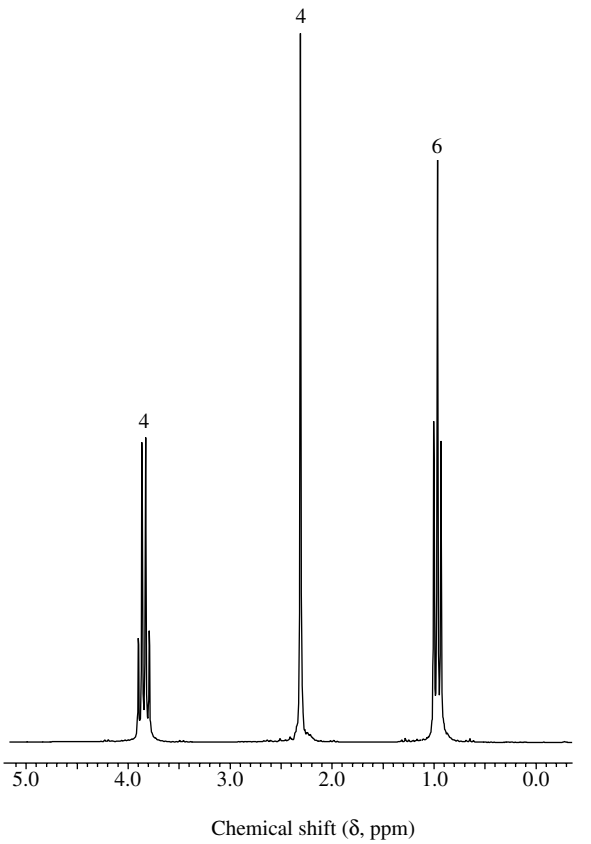


FIGURE 20.11 The 200-MHz ^{1}H NMR spectrum of the compound $C_8H_{14}O_4$ in problem 20.43.

20.43 A compound has a molecular formula of $C_8H_{14}O_4$, and its infrared spectrum contains an intense peak at 1730 cm^{-1}. The ^{1}H NMR spectrum of the compound is shown in Figure 20.11. What is its structure?

20.44 A compound ($C_4H_6O_2$) has a strong band in the infrared at 1760 cm^{-1}. Its ^{13}C NMR spectrum exhibits signals at δ 20.2 (CH_3), 96.8 (CH_2), 141.8 (CH), and 167.6 ppm (C). The ^{1}H NMR spectrum of the compound has a three-proton singlet at δ 2.1 ppm along with three other signals, each of which is a doublet of doublets, at δ 4.7, 4.9, and 7.3 ppm. What is the structure of the compound?

20.45 Excluding enantiomers, there are three isomeric cyclopropanedicarboxylic acids. Two of them, A and B, are constitutional isomers of each other, and each forms a cyclic anhydride on being heated. The third diacid, C, does not form a cyclic anhydride. C is a constitutional isomer of A and a stereoisomer of B. Identify A, B, and C. Construct molecular models of the cyclic anhydrides formed on heating A and B. Why doesn't C form a cyclic anhydride?