The bark of the white willow tree (*Salix alba*) is a source of salicylic acid, from which aspirin (acetylsalicylic acid) is made.

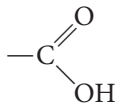
© Geoff Kidd/Earth Scenes/Animals Animals

10

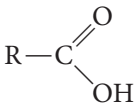
salicylic acid

Carboxylic Acids and Their Derivatives

The taste of vinegar, the sting of an ant, the rancid smell of butter, and the relief derived from aspirin or ibuprofen—all of these are due to compounds that belong to the most important family of organic acids, the **carboxylic acids**. The resilience of polyester and nylon fabrics, the remarkable properties of Velcro, the softness of silk, the no-calorie sugar substitutes, the strength of bacterial cell walls, and the strength of our own cell membranes—all of these are due to properties of derivatives of carboxylic acids. The functional group common to all carboxylic acids is the **carboxyl group**. The name is a contraction of the parts: the *carb*onyl and hydr*oxyl* groups. The general formula for a carboxylic acid can be written in expanded or abbreviated forms.

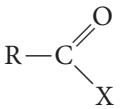


carboxyl group



or RCOOH or RCO_2H

three ways to represent a carboxylic acid



acid derivatives

In this chapter, we will describe the structures, properties, preparation, and reactions of carboxylic acids and will also discuss some common **carboxylic acid derivatives**, in which the hydroxyl group of an acid is replaced by other functional groups.

OWL

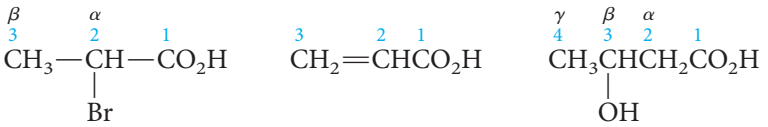
Online homework for this chapter can be assigned in OWL, an online homework assessment tool.

Carboxylic acids are organic acids that contain the **carboxyl group**. In **carboxylic acid derivatives**, the —OH group is replaced by other groups.

10.1 Nomenclature of Acids

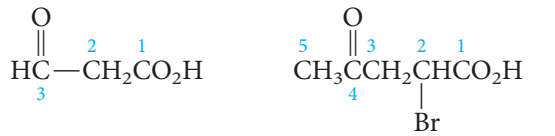
Because of their abundance in nature, carboxylic acids were among the earliest classes of compounds studied by organic chemists. It is not surprising, then, that many of them have common names. These names usually come from some Latin or Greek word that indicates the original source of the acid. Table 10.1 lists the first ten unbranched carboxylic acids, with their common and IUPAC names. To obtain the IUPAC name of a carboxylic acid, we replace the final *e* in the name of the corresponding alkane with the suffix *-oic* and add the word *acid*. Substituted acids are named in two ways. In the IUPAC system, the chain is numbered beginning with the carboxyl carbon atom, and substituents are located in the usual way. If the common name of the acid is used, substituents are located with Greek letters, beginning with the α-carbon atom. IUPAC and common naming systems should not be mixed.

Stinging ants, source of formic acid, HCOOH.



2-bromopropanoic acid (α-bromopropionic acid) | propenoic acid (acrylic acid) | 3-hydroxybutanoic acid (β-hydroxybutyric acid)

The carboxyl group has priority over alcohol, aldehyde, or ketone functionality in naming. In the latter cases, the prefix *oxo-* is used to locate the carbonyl group of the aldehyde or ketone, as in these examples:



3-oxopropanoic acid | 2-bromo-4-oxopentanoic acid

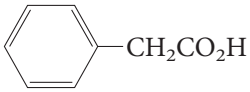
Table 10.1 ■ Aliphatic Carboxylic Acids

Carbon atoms	Formula	Source	Common name	IUPAC name
1	HCOOH	ants (Latin, *formica*)	formic acid	methanoic acid
2	CH_3COOH	vinegar (Latin, *acetum*)	acetic acid	ethanoic acid
3	CH_3CH_2COOH	milk (Greek, *protos pion*, first fat)	propionic acid	propanoic acid
4	$CH_3(CH_2)_2COOH$	butter (Latin, *butyrum*)	butyric acid	butanoic acid
5	$CH_3(CH_2)_3COOH$	valerian root (Latin, *valere*, to be strong)	valeric acid	pentanoic acid
6	$CH_3(CH_2)_4COOH$	goats (Latin, *caper*)	caproic acid	hexanoic acid
7	$CH_3(CH_2)_5COOH$	vine blossom (Greek, *oenanthe*)	enanthic acid	heptanoic acid
8	$CH_3(CH_2)_6COOH$	goats (Latin, *caper*)	caprylic acid	octanoic acid
9	$CH_3(CH_2)_7COOH$	pelargonium (an herb with stork-shaped seed capsules; Greek, *pelargos*, stork)	pelargonic acid	nonanoic acid
10	$CH_3(CH_2)_8COOH$	goats (Latin, *caper*)	capric acid	decanoic acid

PROBLEM 10.1 Write the structure for

a. 3-hydroxyhexanoic acid
b. 2-iodo-2-methyloctanoic acid
c. 2-butynoic acid
d. 5-ethyl-6-oxoheptanoic acid

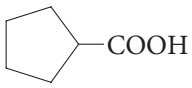
PROBLEM 10.2 Give an IUPAC name for

a. 
b. $Br_2CHCH_2CO_2H$
c. $CH_3CH{=}CHCO_2H$
d. $(CH_3)_3CCH_2CH_2CO_2H$

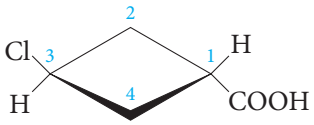
© Alan L. Detrick/Photo Researchers

The root of Garden Heliotrope is a source of valeric acid, $CH_3(CH_2)_3COOH$.

When the carboxyl group is attached to a ring, the ending *-carboxylic acid* is added to the name of the parent cycloalkane.

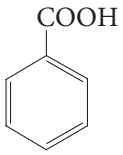


cyclopentanecarboxylic acid

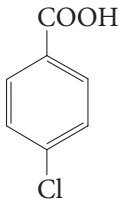


trans-3-chlorocyclobutanecarboxylic acid

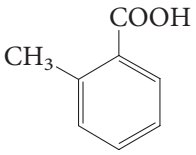
Aromatic acids are named by attaching the suffix *-oic acid* or *-ic acid* to an appropriate prefix derived from the aromatic hydrocarbon.



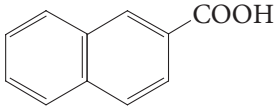
benzoic acid
(benzenecarboxylic acid)



p-chlorobenzoic acid
(4-chlorobenzenecarboxylic acid)



o-toluic acid
(2-methylbenzenecarboxylic acid)



2-naphthoic acid
(2-naphthalenecarboxylic acid)

Mircea Bezergheanu/Shutterstock

Goats, source of caproic, caprylic, and capric acids: $CH_3(CH_2)_nCOOH$, $n = 4, 6, 8$.

PROBLEM 10.3 Write the structure for

a. *cis*-3-isopropylcyclohexanecarboxylic acid
b. *o*-nitrobenzoic acid

PROBLEM 10.4 Give the correct name for

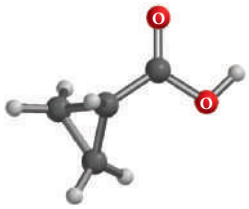
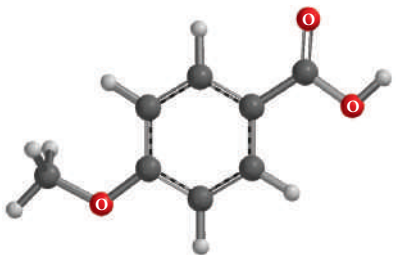
a. 
b. 

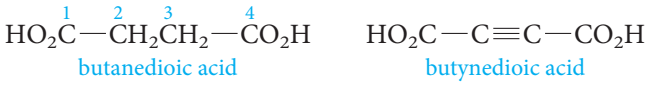
Table 10.2 ■ Aliphatic Dicarboxylic Acids

Formula	Common name	Source	IUPAC name
HOOC—COOH	oxalic acid	plants of the *oxalic* family (for example, sorrel)	ethanedioic acid
HOOC—CH_2—COOH	malonic acid	apple (Gk. *malon*)	propanedioic acid
HOOC—$(CH_2)_2$—COOH	succinic acid	amber (L. *succinum*)	butanedioic acid
HOOC—$(CH_2)_3$—COOH	glutaric acid	gluten	pentanedioic acid
HOOC—$(CH_2)_4$—COOH	adipic acid	fat (L. *adeps*)	hexanedioic acid
HOOC—$(CH_2)_5$—COOH	pimelic acid	fat (Gk. *pimele*)	heptanedioic acid

Juliette Wade/Garden Picture Library/Photolibrary

Rhubarb, a source of oxalic acid, HOOCCOOH.

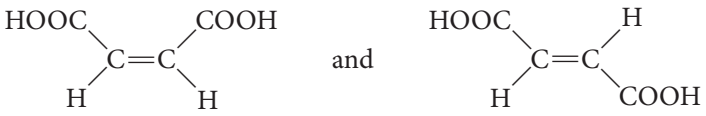
Aliphatic dicarboxylic acids are given the suffix *-dioic acid* in the IUPAC system. For example,



butanedioic acid butynedioic acid

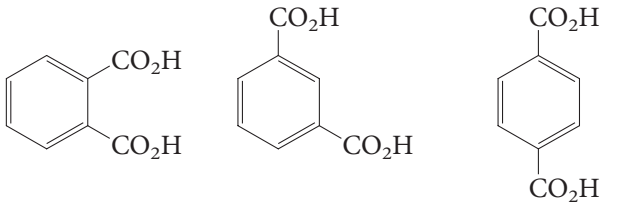
Many dicarboxylic acids occur in nature and go by their common names, which are based on their source. Table 10.2 lists some common aliphatic diacids.* The most important commercial compound in this group is adipic acid, used to manufacture nylon.

The two butenedioic acids played a historic role in the discovery of *cis–trans* isomerism and are usually known by their common names maleic** and fumaric*** acid.



maleic acid (*cis*-2-butenedioic acid) and fumaric acid (*trans*-2-butenedioic acid)

The three benzenedicarboxylic acids are generally known by their common names.



phthalic acid isophthalic acid terephthalic acid

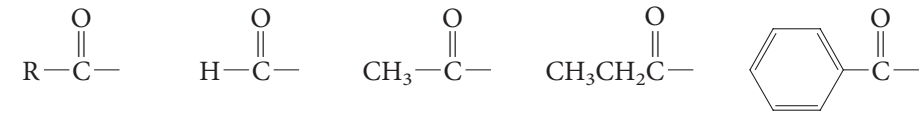
*The first letter of each word in the sentence "Oh my, such good apple pie" gives, in order, the first letters of the common names of these acids and can help you to remember them.

**From the Latin *malum* (apple). Malic acid (2-hydroxybutanedioic acid), found in apples, can be dehydrated on heating to give maleic acid.

***Found in fumitory, an herb of the genus *Fumaria*.

All three are important commercial chemicals, used to make polymers and other useful materials.

Finally, it is useful to have a name for an **acyl group**. Particular acyl groups are named from the corresponding acid by changing the *-ic* ending to *-yl*.



an acyl group | formyl (methanoyl) | acetyl (ethanoyl) | propanoyl | benzoyl

PROBLEM 10.5 Write the formula for

a. 4-formylbenzoic acid
b. benzoyl bromide
c. octanoyl bromide
d. acetylcyclopentane

10.2 Physical Properties of Acids

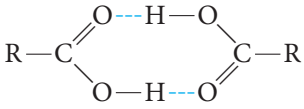
The first members of the carboxylic acid series are colorless liquids with sharp or unpleasant odors. Acetic acid, which constitutes about 4% to 5% of vinegar, provides the characteristic odor and flavor. Butyric acid gives rancid butter its disagreeable odor, and the goat acids (caproic, caprylic, and capric in Table 10.1) smell like goats. 3-Methyl-2-hexenoic acid, produced by bacteria, is responsible for the offensive odor of human armpits. Table 10.3 lists some physical properties of selected carboxylic acids.

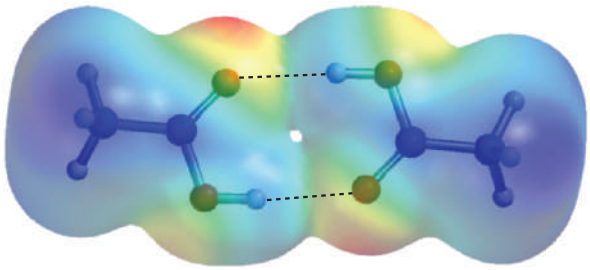
Carboxylic acids are polar. Like alcohols, they form hydrogen bonds with themselves or with other molecules (Sec. 7.4). Therefore, they have high boiling points for their molecular weights—higher even than those of comparable alcohols. For example, acetic acid and propyl alcohol, which have the same formula weights (60 g/mol), boil at 118°C and 97°C, respectively. Carboxylic acids form dimers, with

Table 10.3 ■ Physical Properties of Some Carboxylic Acids

Name	bp, °C	mp, °C	Solubility, g/100 g H_2O at 25°C
formic acid	101	8	miscible (∞)
acetic acid	118	17	
propanoic acid	141	−22	
butanoic acid	164	−8	
hexanoic acid	205	−1.5	1.0
octanoic acid	240	17	0.06
decanoic acid	270	31	0.01
benzoic acid	249	122	0.4 (but 6.8 at 95°C)

the individual units neatly held together by *two* hydrogen bonds between the electron-rich oxygens and the electron-poor hydrogens (see Sec. 7.4).

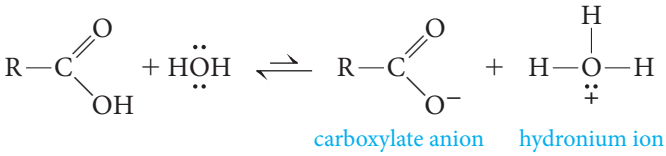




Hydrogen bonding also explains the water solubility of the lower molecular weight carboxylic acids.

10.3 Acidity and Acidity Constants

Carboxylic acids (RCO_2H) dissociate in water, yielding a carboxylate anion (RCO_2^-) and a hydronium ion.



carboxylate anion hydronium ion **(10.1)**

Their acidity constants K_a in water are given by the expression

$$K_a = \frac{[RCO_2^-][H_3O^+]}{[RCO_2H]} \qquad \textbf{(10.2)}$$

(Before proceeding further, it would be a good idea for you to review Secs. 7.5 and 7.6.)

Table 10.4 lists the acidity constants for some carboxylic and other acids. In comparing data in this table, remember that the larger the value of K_a or the smaller the value of pK_a, the stronger the acid.

EXAMPLE 10.1

Which is the stronger acid, formic or acetic, and by how much?

Solution Formic acid is stronger; it has the larger K_a. The ratio of acidities is

$$\frac{2.1 \times 10^{-4}}{1.8 \times 10^{-5}} = 1.17 \times 10^{1} = 11.7$$

This means that formic acid is 11.7 times stronger than acetic acid.

PROBLEM 10.6 Using the data given in Table 10.4, determine which is the stronger acid, acetic or dichloroacetic, and by how much.

Before we can explain the acidity differences in Table 10.4, we must examine the structural features that make carboxylic acids acidic.

Table 10.4 ■ The Ionization Constants of Some Acids

Name	Formula	K_a	pK_a
formic acid	HCOOH	2.1×10^{-4}	3.68
acetic acid	CH_3COOH	1.8×10^{-5}	4.74
propanoic acid	CH_3CH_2COOH	1.4×10^{-5}	4.85
butanoic acid	$CH_3CH_2CH_2COOH$	1.6×10^{-5}	4.80
chloroacetic acid	$ClCH_2COOH$	1.5×10^{-3}	2.82
dichloroacetic acid	$Cl_2CHCOOH$	5.0×10^{-2}	1.30
trichloroacetic acid	Cl_3CCOOH	2.0×10^{-1}	0.70
2-chlorobutanoic acid	$CH_3CH_2CHClCOOH$	1.4×10^{-3}	2.85
3-chlorobutanoic acid	$CH_3CHClCH_2COOH$	8.9×10^{-5}	4.05
benzoic acid	C_6H_5COOH	6.6×10^{-5}	4.18
o-chlorobenzoic acid	*o*-Cl—C_6H_4COOH	12.5×10^{-4}	2.90
m-chlorobenzoic acid	*m*-Cl—C_6H_4COOH	1.6×10^{-4}	3.80
p-chlorobenzoic acid	*p*-Cl—C_6H_4COOH	1.0×10^{-4}	4.00
p-nitrobenzoic acid	*p*-NO_2—C_6H_4COOH	4.0×10^{-4}	3.40
phenol	C_6H_5OH	1.0×10^{-10}	10.00
ethanol	CH_3CH_2OH	1.0×10^{-16}	16.00
water	HOH	1.8×10^{-16}	15.74

10.4 What Makes Carboxylic Acids Acidic?

You might wonder why carboxylic acids are so much more acidic than alcohols, since each class ionizes by losing H^+ from a hydroxyl group. There are two reasons, which can best be illustrated with a specific example.

From Table 10.4, we see that acetic acid is approximately 10^{11}, or 100,000 million, times stronger an acid than ethanol.

$$CH_3CH_2\ddot{O}H \rightleftharpoons CH_3CH_2\ddot{O}:^- + H^+ \qquad K_a = 10^{-16} \qquad \textbf{(10.3)}$$

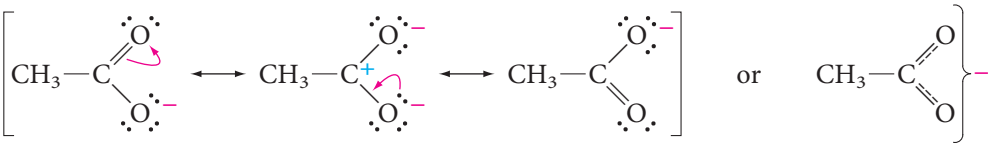
ethoxide ion

$$CH_3\overset{\delta+}{C}(=O)\ddot{O}H \rightleftharpoons CH_3C(=O)\ddot{O}:^- + H^+ \qquad K_a = 10^{-5} \qquad \textbf{(10.4)}$$

acetate ion

The only difference between the structures of acetic acid and ethanol is the replacement of a CH_2 group (in ethanol) by a carbonyl group (in acetic acid). But we saw (Sec. 9.5) that a carbonyl carbon atom carries a substantial *positive* charge ($\delta+$). This charge makes it much easier to place a *negative* charge on the adjacent oxygen atom, which is exactly what happens when we ionize a proton from the hydroxyl group.

In ethoxide ion, *the negative charge is localized on a single oxygen atom.* In acetate ion, on the other hand, *the negative charge can be delocalized through resonance.*



resonance in a carboxylate ion (acetate ion)

The negative charge is spread *equally* over the two oxygens so that each oxygen in the carboxylate ion carries only half the negative charge (Figure 10.1). The acetate ion is stabilized by resonance compared to the ethoxide ion, and this stabilization helps to drive the equilibrium more to the right in eq. 10.4 than in eq. 10.3. Consequently, more H^+ is formed from acetic acid than from ethanol.

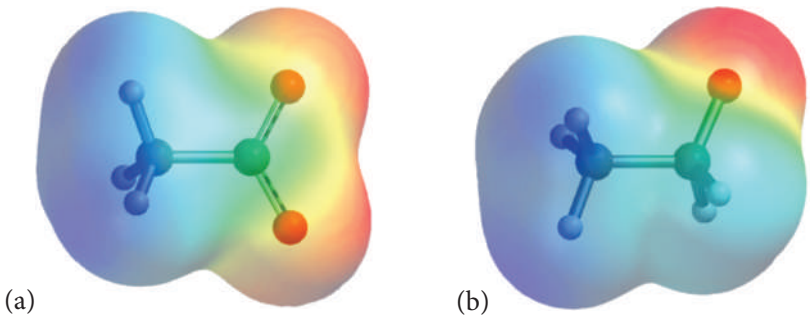


Figure 10.1
Electrostatic potential map of (a) acetate ion and (b) ethoxide ion. Note the negative (red) character for both oxygens in (a).

For both these reasons, the positive charge on the carbonyl carbon and delocalization of the carboxylate ion, carboxylic acids are much more acidic than alcohols.

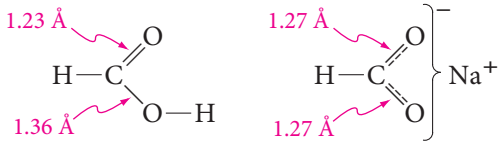
EXAMPLE 10.2

Phenoxide ions are also stabilized by resonance (Sec. 7.6). Why are phenols weaker acids than carboxylic acids?

Solution First, the carbon atom to which the hydroxyl group is attached in a phenol is not as positive as a carbonyl carbon. Second, charge delocalization is not as great in phenoxide ions as in carboxylate ions because the contributors to the resonance hybrid are not equivalent. Some of them put the negative charge on carbon instead of on oxygen and disrupt aromaticity.

PROBLEM 10.7 Write two resonance structures for the benzoate ion ($C_6H_5CO_2^-$) that show how the negative charge is delocalized over the two oxygens. Can the negative charge in the benzoate ion be delocalized into the aromatic ring?

Physical data support the importance of resonance in carboxylate ions. In formic acid molecules, the two carbon–oxygen bonds have different lengths. But in sodium formate, both carbon–oxygen bonds of the formate ion are identical, and their length is between those of normal double and single carbon–oxygen bonds.



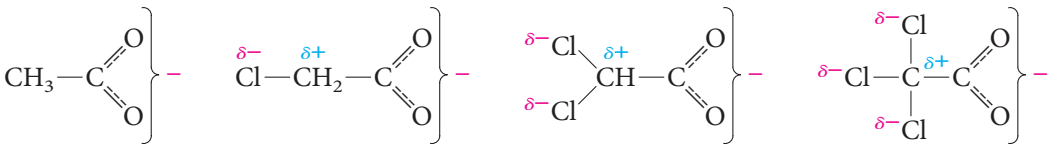
formic acid sodium formate

10.5 Effect of Structure on Acidity; the Inductive Effect Revisited

The data in Table 10.4 show that even among carboxylic acids (where the ionizing functional group is kept constant), acidities can vary depending on what other groups are attached to the molecule. Compare, for example, the K_a of acetic acid with those of mono-, di-, and trichloroacetic acids, and note that the acidity varies by a factor of 10,000.

The most important factor operating here is the inductive effect of the groups close to the carboxyl group. This effect relays charge through bonds, by displacing bonding electrons toward electronegative atoms, or away from electropositive atoms. Recall that *electron-withdrawing groups enhance acidity, and electron-releasing groups reduce acidity* (see Sec. 7.6).

Let us examine the carboxylate ions formed when acetic acid and its chloro derivatives ionize:



acetate chloroacetate dichloroacetate trichloroacetate

Because chlorine is more electronegative than carbon, the C—Cl bond is polarized with the chlorine partially negative and the carbon partially positive. Thus, electrons are pulled away from the carboxylate end of the ion toward the chlorine. The effect tends to spread the negative charge over more atoms than in acetate ion itself and thus stabilizes the ion. The more chlorines, the greater the effect and the greater the strength of the acid.

EXAMPLE 10.3

Explain the acidity order in Table 10.4 for butanoic acid and its 2- and 3-chloro derivatives.

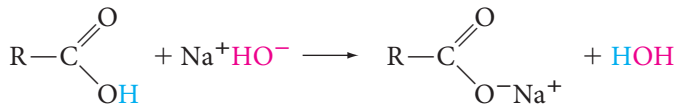
Solution The 2-chloro substituent increases the acidity of butanoic acid substantially, due to its inductive effect. In fact, the effect is about the same as for chloroacetic and acetic acids. The 3-chloro substituent exerts a similar *but much smaller* effect, because the C—Cl bond is now farther away from the carboxylate group. *Inductive effects fall off rapidly with distance.*

PROBLEM 10.8 Account for the relative acidities of benzoic acid and its *ortho, meta,* and *para* chloro derivatives (Table 10.4).

We saw in Example 10.1 that formic acid is a substantially stronger acid than acetic acid. This suggests that the methyl group is more electron-releasing (hence anion-destabilizing and acidity-reducing) than hydrogen. This observation is consistent with what we have already learned about carbocation stabilities—that alkyl groups are more effective than hydrogen atoms at releasing electrons to, and therefore stabilizing, a positive carbon atom (see Sec. 3.10). A similar effect was seen for the relative acidity of ethanol and *t*-butanol in water (see Sec. 7.6).

10.6 Conversion of Acids to Salts

Carboxylic acids, when treated with a strong base, form carboxylate salts. For example,

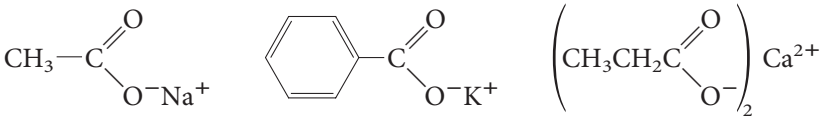


(10.5)

carboxylic acid, pK_a 3–5 | strong base | a sodium carboxylate (weak base) | water, pK_a 16

The salt can be isolated by evaporating the water. As we will see in Chapter 15, carboxylate salts of certain acids are useful as soaps and detergents.

Carboxylate salts are named as shown in the following examples:

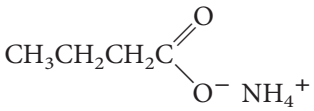


sodium acetate (sodium ethanoate) | potassium benzoate | calcium propanoate

The cation is named first, followed by the name of the carboxylate ion, which is obtained by changing the *-ic* ending of the acid to *-ate*.

EXAMPLE 10.4

Name the following carboxylate salt:



Solution The salt is ammonium butanoate (IUPAC) or ammonium butyrate (common).

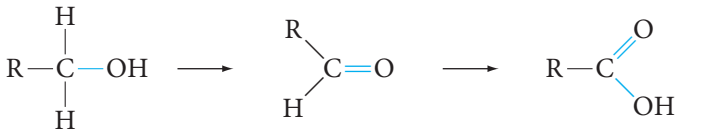
PROBLEM 10.9 Write an equation, analogous to eq. 10.5, for the preparation of potassium 3-bromooctanoate from the corresponding acid.

10.7 Preparation of Acids

Organic acids can be prepared in many ways, four of which are described here: (1) oxidation of primary alcohols or aldehydes, (2) oxidation of alkyl side chains on aromatic rings, (3) reaction of Grignard reagents with carbon dioxide, and (4) hydrolysis of alkyl cyanides (nitriles).

10.7.a Oxidation of Primary Alcohols and Aldehydes

The oxidation of primary alcohols (Sec. 7.12) and aldehydes (Sec. 9.13) to carboxylic acids has already been mentioned. It is easy to see that these are oxidation reactions because going from an alcohol to an aldehyde to an acid requires replacement of C—H bonds by C—O bonds.

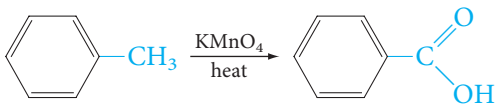


alcohol (one C—O bond) | aldehyde (two C—O bonds) | acid (three C—O bonds) **(10.6)**

The most commonly used oxidizing agents for these purposes are potassium permanganate ($KMnO_4$), chromic acid anhydride (CrO_3), nitric acid (HNO_3), and, with aldehydes only, silver oxide (Ag_2O). For specific examples, see eqs. 7.37, 9.37, 9.38, and 9.41.

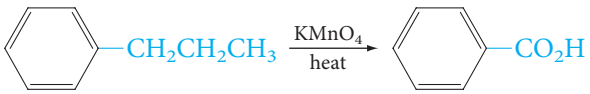
10.7.b Oxidation of Aromatic Side Chains

Aromatic acids can be prepared by oxidizing an alkyl side chain on an aromatic ring.



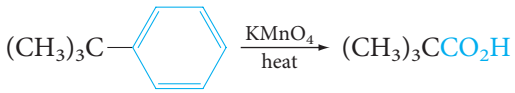
toluene | benzoic acid **(10.7)**

This reaction illustrates the striking stability of aromatic rings; it is the alkane-like methyl group, not the aromatic ring, that is oxidized. The reaction involves attack of the oxidant at a C—H bond adjacent to the benzene ring. Longer side chains are also oxidized to a carboxyl group.



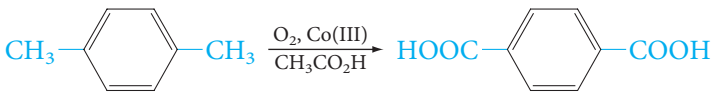
(10.8)

If no C—H bond is in the benzylic position, however, the aromatic ring is oxidized, although only under severe reaction conditions.



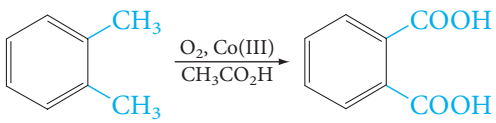
(10.9)

With oxidants other than potassium permanganate, this reaction is commercially important. For example, terephthalic acid (Sec. 10.1), one of the two raw materials needed to manufacture Dacron, is produced in this way, using a cobalt catalyst and air for the oxidation.



p-xylene | terephthalic acid **(10.10)**

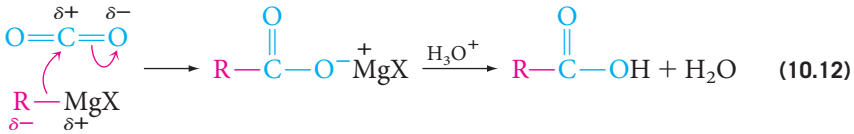
Phthalic acid, used for making plasticizers, resins, and dyestuffs, is manufactured by similar oxidations, starting with *o*-xylene.



o-xylene | phthalic acid **(10.11)**

10.7.c Reaction of Grignard Reagents with Carbon Dioxide

As we saw previously, Grignard reagents add to the carbonyl groups of aldehydes or ketones to give alcohols. In a similar way, they add irreversibly to the carbonyl group of carbon dioxide to give acids, after protonation of the intermediate carboxylate salt with a mineral acid like aqueous HCl.



(10.12)

This reaction gives good yields and is an excellent laboratory method for preparing both aliphatic and aromatic acids. Note that the acid obtained has one more carbon atom than the alkyl or aryl halide from which the Grignard reagent is prepared, so the reaction provides a way to increase the length of a carbon chain.

EXAMPLE 10.5

Show how $(CH_3)_3CBr$ can be converted to $(CH_3)_3CCO_2H$.

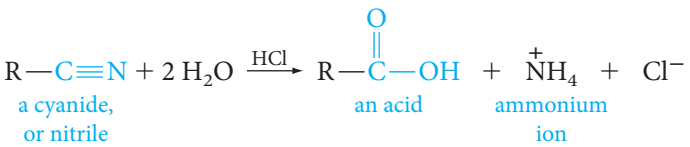
Solution $(CH_3)_3CBr \xrightarrow[\text{ether}]{Mg} (CH_3)_3CMgBr \xrightarrow[2.\ H_3O^+]{1.\ CO_2} (CH_3)_3CCO_2H$

PROBLEM 10.10 Show how 4-methylcyclohexyl chloride can be converted to 4-methylcyclohexanecarboxylic acid.

PROBLEM 10.11 Devise a synthesis of butanoic acid ($CH_3CH_2CH_2CO_2H$) from 1-propanol ($CH_3CH_2CH_2OH$).

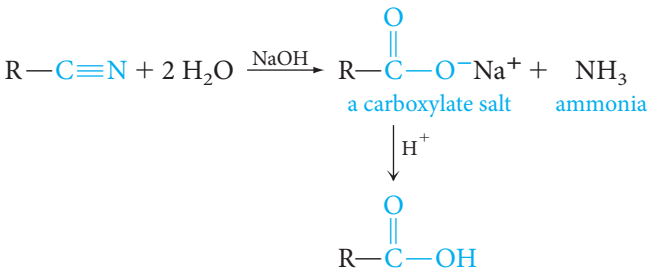
10.7.d Hydrolysis of Cyanides (Nitriles)

The carbon–nitrogen triple bond of organic cyanides can be hydrolyzed to a carboxyl group. The reaction requires either acid or base. In acid, the nitrogen atom of the cyanide is converted to an ammonium ion.



(10.13)

In base, the nitrogen is converted to ammonia and the organic product is the carboxylate salt, which must be neutralized in a separate step to give the acid.



(10.14)

A WORD ABOUT... Green Chemistry and Ibuprofen: A Case Study

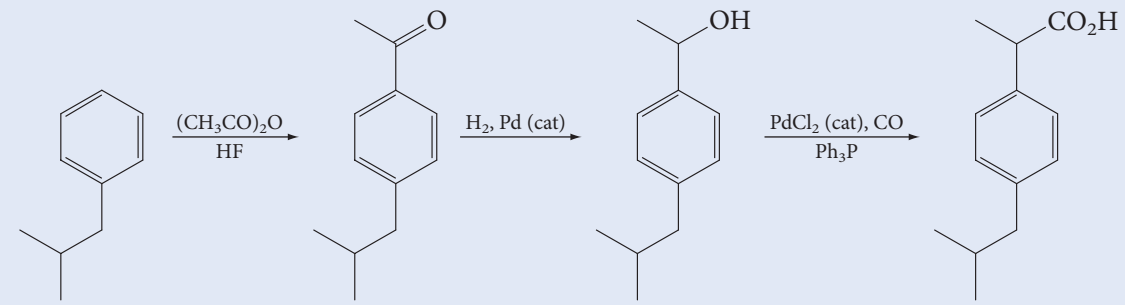
From our increasing need to respect nature and protect our environment has come a new field of chemistry—"green chemistry"—the design and development of chemistry that is environmentally friendly, chemistry that avoids pollution. This presents many challenges to organic synthesis. One notion of an ideal synthesis is one that provides a useful compound in one step with formation of no disposable by-products by a process that consumes little energy. Such a synthesis would certainly be environmentally friendly! This goal is seldom met, but general principles can be applied to try to approach this ideal.

First let us consider some reactions we have learned. Addition reactions (catalytic hydrogenation and Diels–Alder reactions, for example) do not create any by-products. The same can be said for isomerization reactions. Such reactions are said to be "atom economical"—all of the atoms in the reactants appear in the product.* On the other hand, elimination reactions and substitution reactions necessarily produce by-products. This does not mean that they are bad, but if a synthesis can be devised that focuses on addition and isomerization reactions, less attention will have to be devoted to disposing of, or developing uses for, by-products.

Some other general strategies for the development of green chemistry are to use catalysts to accomplish reactions (rather than stoichiometric reagents), to minimize the use of heavy metals as stoichiometric oxidants (for example, chromium), to focus on the use of molecular oxygen and hydrogen peroxide as oxidants, and to minimize the use of solvents in reactions.

Let us examine a synthesis that does a good job of meeting the goals of green chemistry. Ibuprofen is a very important anti-inflammatory drug. It is the active ingredient of many over-the-counter drugs used to relieve pain from headaches and arthritis. Approximately 25 million pounds of this simple carboxylic acid were produced by synthesis in 2000! A large number of ibuprofen syntheses have been developed, and several of these have been commercialized. The following synthesis begins with the reaction of isobutylbenzene with acetic anhydride using HF as the solvent. This is a variation of the Friedel–Crafts acylation in which the anhydride serves as the source of an acylium ion (see Sec. 4.9.d). Through clever engineering processes, the reaction solvent (HF) serves as both the acid catalyst and solvent (recyclable) for the reaction, and water is the only major reaction by-product. The second step is an addition reaction, catalytic hydrogenation of a ketone to an alcohol (see eq. 9.57). The final step is a reaction we have not discussed that involves palladium-catalyzed "insertion" of carbon monoxide into a benzylic C—O bond to give the carboxylic acid (ibuprofen). This reaction is clearly atom economical. Finally, the chemical yields of all of these reactions are very high, and very little chemical waste is produced.** Although this synthesis is an excellent example of green chemistry in action, there is room for improvement. For example, this produces a racemic mixture of ibuprofen, whereas only the (*S*)-enantiomer is biologically active (see "A Word About . . . Enantiomers and Biological Activity" in Chapter 5).

It is clear that green chemistry will play an important role in the twenty-first century. This has been recognized by the Presidential Green Chemistry Challenge, initiated by President Clinton in 1995 to reward the development of environmentally benign chemistry. Although biological processes seldom meet the notion of an ideal synthesis, to strive for this ideal can only lead to new and better chemistry.



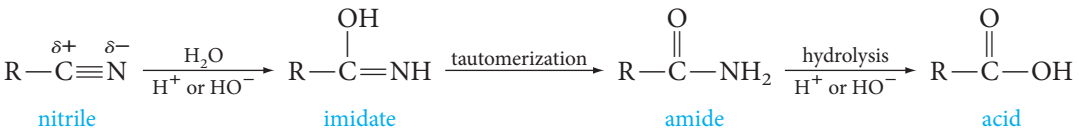
isobutylbenzene ibuprofen

See Problem 10.63.

*For more on "atom economy," see B. M. Trost, *Angew. Chem. Int. Ed. Engl.* **1995**, *34,* 259. For more on green chemistry, see W. Leiner, *Science* **1999**, *284,* 1780, and visit the following Web site: http://www.epa.gov/greenchemistry.

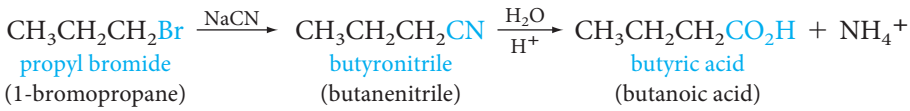
**For an overview of other syntheses of ibuprofen, consult B. G. Reuben and H. A. Wittcoff, *Pharmaceutical Chemicals in Perspective,* John Wiley and Sons, New York, 1989.

The mechanism of nitrile hydrolysis involves acid or base promoted addition of water across the triple bond. This gives an intermediate imidate that tautomerizes to an amide. The amide is then hydrolyzed to the carboxylic acid. The addition of water to the nitrile resembles the hydration of an alkyne (eq. 3.52). The oxygen of water behaves as a nucleophile and bonds to the electrophilic carbon of the nitrile. Amide hydrolysis will be discussed in Section 10.20.



(10.15)

Alkyl cyanides are generally made from the corresponding alkyl halide (usually primary) and sodium cyanide by an S_N2 displacement, as shown in this synthesis of an acid:



(10.16)

PROBLEM 10.12 Why is it *not* possible to convert bromobenzene to benzoic acid by the nitrile method? Instead, how could this conversion be accomplished?

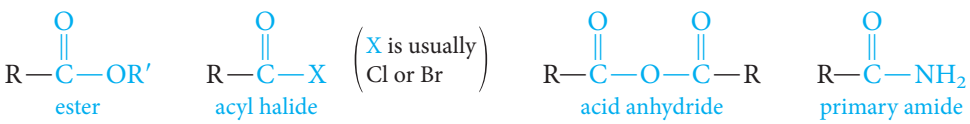
Organic cyanides are commonly named after the corresponding acid, by changing the *-ic* or *-oic* suffix to *-onitrile* (hence, butyronitrile in eq. 10.16). In the IUPAC system, the suffix *-nitrile* is added to the name of the hydrocarbon with the same number of carbon atoms (hence butanenitrile in eq. 10.16).

Note that with the hydrolysis of nitriles, as with the Grignard method, the acid obtained has one more carbon atom than the alkyl halide from which the cyanide is prepared. Consequently, both methods provide ways of increasing the length of a carbon chain.

PROBLEM 10.13 Write equations for synthesizing phenylacetic acid ($C_6H_5CH_2CO_2H$) from benzyl bromide ($C_6H_5CH_2Br$) by two routes.

10.8 Carboxylic Acid Derivatives

Carboxylic acid derivatives are compounds in which the hydroxyl part of the carboxyl group is replaced by various other groups. All acid derivatives can be hydrolyzed to the corresponding carboxylic acid. In the remainder of this chapter, we will consider the preparation and reactions of the more important of these acid derivatives. Their general formulas are as follows:

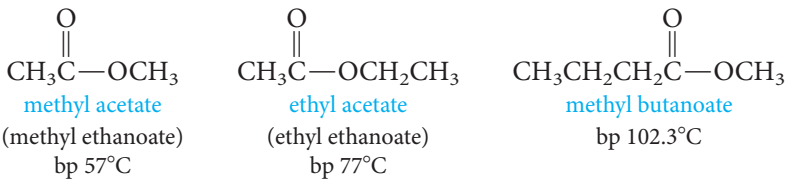


Esters and amides occur widely in nature. Anhydrides, however, are uncommon in nature, and acyl halides are strictly creatures of the laboratory.

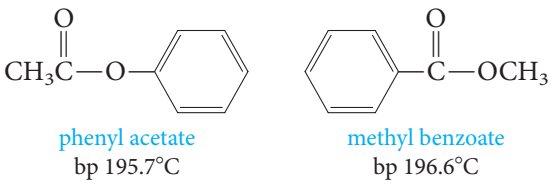
10.9 Esters

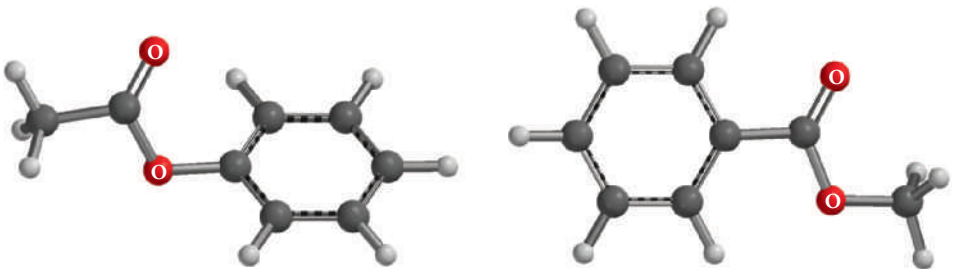
Esters are derived from acids by replacing the —OH group by an —OR group. They are named in a manner analogous to carboxylic acid salts. The R part of the —OR group is named first, followed by the name of the acid, with the *-ic* ending changed to *-ate*.

An **ester** is a carboxylic acid derivative in which the O—H group is replaced by an —OR group.



Notice the different names of the following pair of isomeric esters, where the R and R′ groups are interchanged.





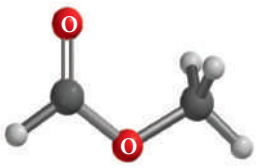
Esters are named as two words that are *not* run together.

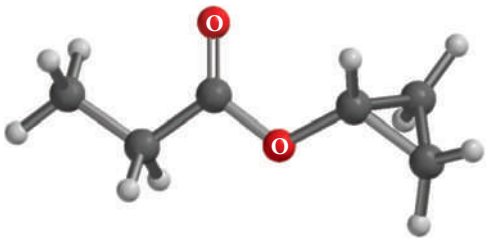
EXAMPLE 10.6

Name $CH_3CH_2CO_2CH(CH_3)_2$.

Solution The related acid is $CH_3CH_2CO_2H$, so the last part of the name is *propanoate* (change the *-ic* of propanoic to *-ate*). The alkyl group that replaces the hydrogen is *isopropyl*, or 2-*propyl*, so the correct name is *isopropyl propanoate*, or 2-*propyl propanoate*.

PROBLEM 10.14 Write the IUPAC name for

a. 

b. 

PROBLEM 10.15 Write the structure of

a. 3-pentyl butanoate

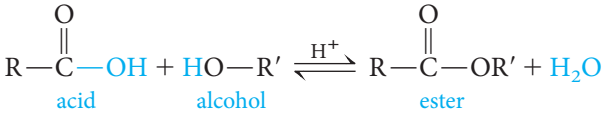
b. methyl 2-methylhexanoate

Female elephants release the ester (*Z*)-7-dodecen-1-yl acetate to attract mates.

Many esters are rather pleasant-smelling substances and are responsible for the flavor and fragrance of many fruits and flowers. Among the more common are pentyl acetate (bananas), octyl acetate (oranges), ethyl butanoate (pineapples), and pentyl butanoate (apricots). Natural flavors can be exceedingly complex. For example, no fewer than 53 esters have been identified among the volatile constituents of Bartlett pears! Mixtures of esters are used as perfumes and artificial flavors. Low-molecular-weight esters are also used by insects and animals to transmit signals. Female elephants release (*Z*)-7-dodecen-1-yl acetate to signal their readiness to mate. Many moths release the same ester to attract mates.

10.10 Preparation of Esters; Fischer Esterification

When a carboxylic acid and an alcohol are heated in the presence of an acid catalyst (usually HCl or H_2SO_4), an equilibrium is established with the ester and water.



(10.17)

Fischer esterification is the acid-catalyzed condensation of a carboxylic acid and an alcohol.

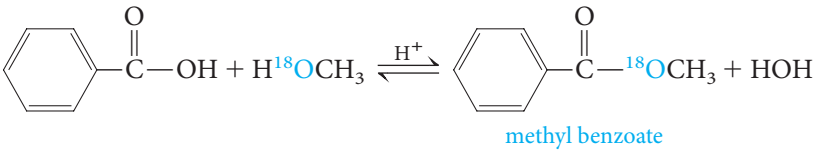
The process is called **Fischer esterification** after Emil Fischer (page 163), who developed the method. Although the reaction is an equilibrium, it can be shifted to the right in several ways. If either the alcohol or the acid is inexpensive, a large excess can be used. Alternatively, the ester and/or water may be removed as formed (by distillation, for example), thus driving the reaction forward.

PROBLEM 10.16 Following eq. 10.17, write an equation for the preparation of ethyl pentanoate from the correct acid and alcohol.

10.11 The Mechanism of Acid-Catalyzed Esterification; Nucleophilic Acyl Substitution

We can ask the following simple mechanistic question about Fischer esterification: Is the water molecule formed from the hydroxyl group of the acid and the hydrogen of the alcohol (as shown in color in eq. 10.17) or from the hydrogen of the acid and the hydroxyl group of the alcohol? This question may seem rather trivial, but the answer provides a key to understanding much of the chemistry of acids, esters, and their derivatives.

This question was resolved using isotopic labeling. For example, Fischer esterification of benzoic acid with methanol that had been enriched with the ^{18}O isotope of oxygen gave labeled methyl benzoate.*

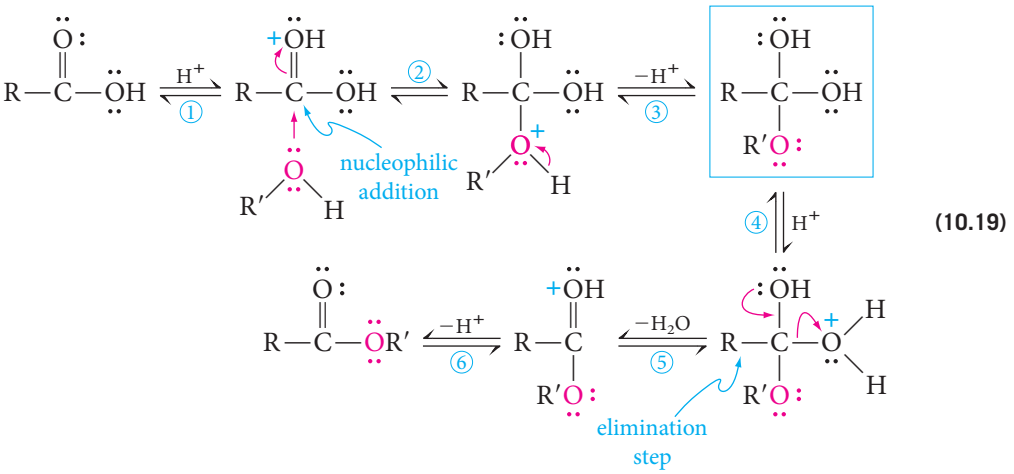


(10.18)

*^{18}O is oxygen with two additional neutrons in its nucleus. It is two mass units heavier than ^{16}O. ^{18}O can be distinguished from ^{16}O by mass spectrometry (see Chapter 12).

None of the ^{18}O appeared in the water. Thus it is clear that *the water was formed using the hydroxyl group of the acid and the hydrogen of the alcohol.* In other words, in Fischer esterification, the —OR group of the alcohol replaces the —OH group of the acid.

How can we explain this experimental fact? A mechanism consistent with this result is as follows (the oxygen atom of the alcohol is shown in color so that its path can be traced):



(10.19)

Let us go through this mechanism, which looks more complicated than it really is, one step at a time.

Step 1. The carbonyl group of the acid is reversibly protonated. This step explains how the acid catalyst works. Protonation increases the positive charge on the carboxyl carbon and enhances its reactivity toward nucleophiles (recall the similar effect of acid catalysts with aldehydes and ketones, eq. 9.9). Note that the carbonyl oxygen gets protonated because it is the more basic oxygen.

Step 2. *This is the crucial step.* The alcohol, as a nucleophile, attacks the carbonyl carbon of the protonated acid. This is the step in which the new C—O bond (the ester bond) is formed.

Steps 3 and 4. These steps are equilibria in which oxygens lose or gain a proton. Such acid–base equilibria are reversible and rapid and go on constantly in any acidic solution of an oxygen-containing compound. In step 4, it does not matter which —OH group is protonated since these groups are equivalent.

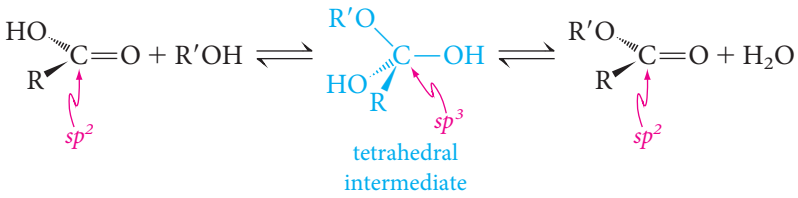
Step 5. This is the step in which water, one product of the overall reaction, is formed. For this step to occur, an —OH group must be protonated to improve its leaving-group capacity. (This step is similar to the reverse of step 2.)

Step 6. This deprotonation step gives the ester and regenerates the acid catalyst. (This step is similar to the reverse of step 1.)

Some other features of the mechanism in eq. 10.19 are worth examining. The reaction begins with a carboxylic acid, in which the carboxyl carbon is trigonal and sp^2-hybridized. The end product is an ester; the ester carbon is also trigonal and sp^2-hybridized. However, the reaction proceeds through a neutral **tetrahedral intermediate** (shown in a box in eq. 10.19 and in color in eq. 10.20), in which the carbon atom has

A **tetrahedral intermediate** has an sp^3-hybridized carbon atom.

four groups attached to it and is thus sp^3-hybridized. If we omit all of the proton-transfer steps in eq. 10.19, we can focus on this feature of the reaction:



(10.20)

Nucleophilic acyl substitution is substitution of another group for the —OH group of a carboxylic acid.

The net result of this process is substitution of the —OR′ group of the alcohol for the —OH group of the acid. Hence the reaction is referred to as **nucleophilic acyl substitution**. But the reaction is not a direct substitution. Instead, it occurs in two steps: (1) nucleophilic addition, followed by (2) elimination. We will see in the next and subsequent sections of this chapter that this is a general mechanism for nucleophilic substitutions at the carbonyl carbon atoms of carboxylic acid derivatives.

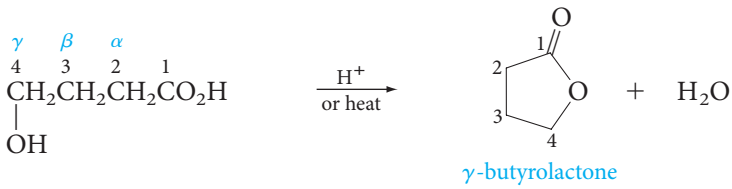
PROBLEM 10.17 Following eq. 10.19, write out the steps in the mechanism for the acid-catalyzed preparation of ethyl acetate from ethanol and acetic acid. In the United States, this method is used commercially to produce more than 100 million pounds of ethyl acetate annually, mainly for use as a solvent in the paint industry, but also as a solvent for nail polish and various glues.

10.12 Lactones

Hydroxy acids contain a hydroxyl group and a carboxyl group.

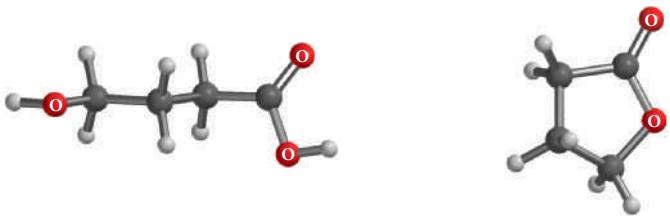
Lactones are **cyclic esters**.

Hydroxy acids contain both functional groups required for ester formation. If these groups can come in contact through bending of the chain, they may react with one another to form **cyclic esters** called **lactones**. For example,



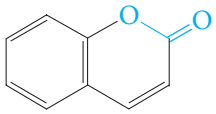
γ-butyrolactone

(10.21)

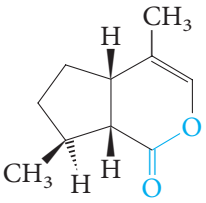


Most common lactones have five- or six-membered rings, although lactones with smaller or larger rings are known. Two examples of six-membered lactones from nature are coumarin, which is responsible for the pleasant odor of newly mown hay, and nepetalactone, the compound in catnip that excites cats. Erythromycin, widely used as an antibiotic, is an example of a macrocyclic lactone.*

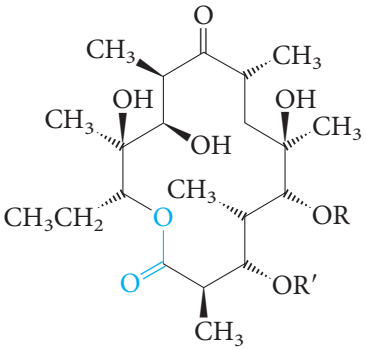
*The R and R′ groups in erythromycin are carbohydrate units (see Chapter 16).



coumarin



nepetalactone



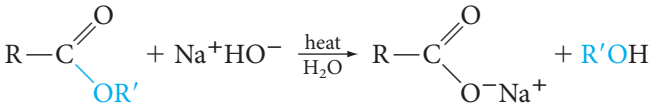
erythromycin

PROBLEM 10.18 Write the steps in the mechanism for the acid-catalyzed reaction in eq. 10.21.

10.13 Saponification of Esters

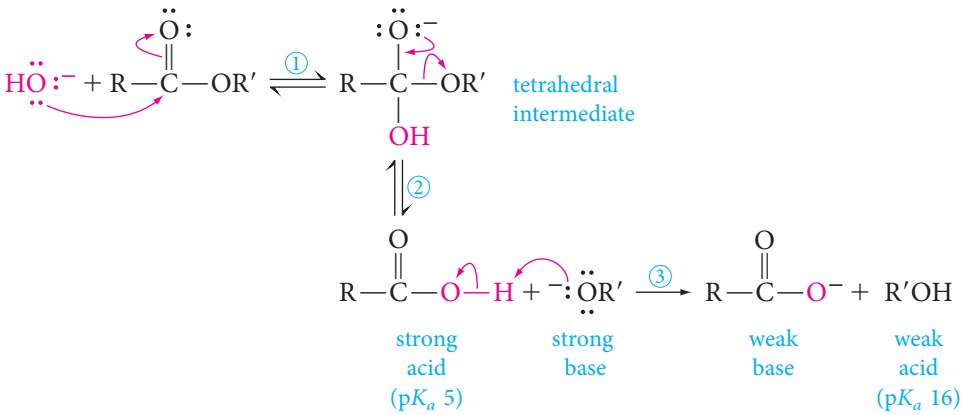
Esters are commonly hydrolyzed with base. The reaction is called **saponification** (from the Latin *sapon,* soap) because this type of reaction is used to make soaps from fats (Chapter 15). The general reaction is as follows:

Saponification is the hydrolysis of an ester with a base.



(10.22)

The mechanism is another example of a nucleophilic acyl substitution. It involves nucleophilic attack by hydroxide ion, a strong nucleophile, on the carbonyl carbon of the ester.

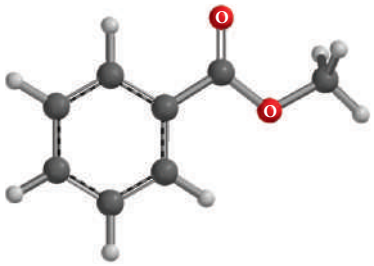


(10.23)

The key step is nucleophilic addition to the carbonyl group (step 1). The reaction proceeds via a tetrahedral intermediate, but the reactant and the product are trigonal. *Saponification is not reversible;* in the final step (3), the strongly basic alkoxide ion removes a proton from the acid to form a carboxylate ion and an alcohol molecule—a step that proceeds completely in the forward direction.

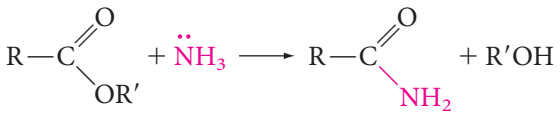
Saponification is especially useful for breaking down an unknown ester, perhaps isolated from a natural source, into its component acid and alcohol for structural determination.

PROBLEM 10.19 Following eq. 10.22, write an equation for the saponification of methyl benzoate.



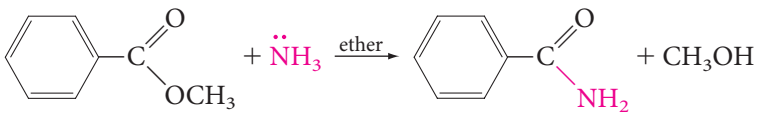
10.14 Ammonolysis of Esters

Ammonia converts esters to amides.



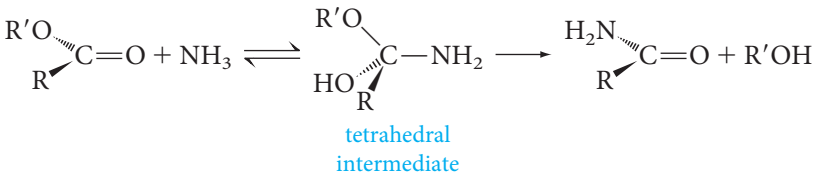
(10.24)

For example,



(10.25)

The reaction mechanism is very much like that of saponification. The unshared electron pair on the ammonia nitrogen initiates nucleophilic attack on the ester carbonyl group.

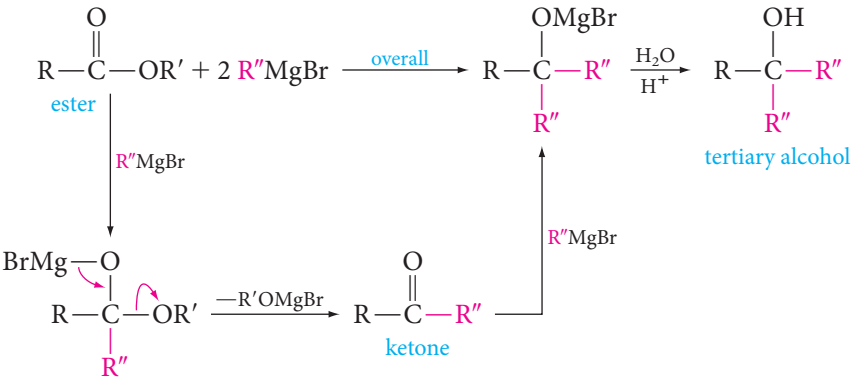


(10.26)

PROBLEM 10.20 The first step in eq. 10.26 really involves two reactions, *addition* of ammonia to the carbonyl carbon to form an ammonium alkoxide followed by a *proton transfer* from the nitrogen to the alkoxide oxygen. Illustrate this process with equations using the arrow-pushing formalism. The second step in eq. 10.26 also involves two steps, *elimination* of an alkoxide ($R'O^-$) followed by deprotonation of the hydroxyl group. Write a detailed mechanism for these steps.

10.15 Reaction of Esters with Grignard Reagents

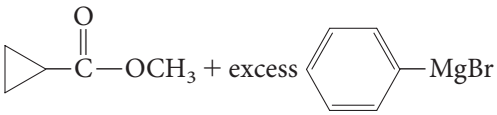
Esters react with two equivalents of a Grignard reagent to give tertiary alcohols. The reaction proceeds by *irreversible* nucleophilic attack of the Grignard reagent on the ester carbonyl group. The initial product, a ketone, reacts further in the usual way to give the tertiary alcohol.



(10.27)

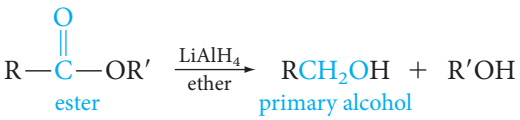
This method is useful for making tertiary alcohols in which at least two of three alkyl groups attached to the hydroxyl-bearing carbon atom are identical.

PROBLEM 10.21 Using eq. 10.27 as a guide, write the structure of the tertiary alcohol that is obtained from



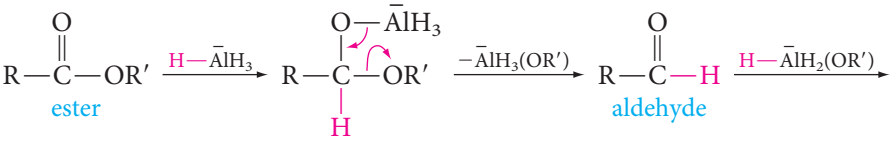
10.16 Reduction of Esters

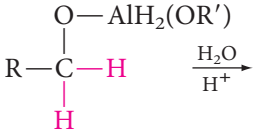
Esters can be reduced to primary alcohols by lithium aluminum hydride ($LiAlH_4$).



(10.28)

The mechanism is similar to the hydride reduction of aldehydes and ketones (eq. 9.33).





(10.29)

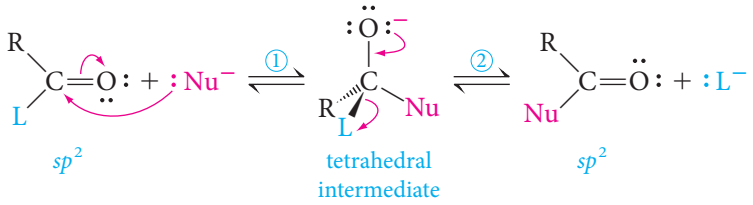
The intermediate aldehyde is not usually isolable and reacts rapidly with additional hydride to produce the alcohol.

Thus, with $LiAlH_4$, it is possible to reduce the carbonyl group of an ester without reducing a C═C bond in the same molecule. For example,

$$\underset{\text{ethyl 2-butenoate}}{CH_3CH{=}CHC(=O)OCH_2CH_3} \xrightarrow[2.\ H_2O,\ H^+]{1.\ LiAlH_4} \underset{\text{2-buten-1-ol}}{CH_3CH{=}CHCH_2OH} + CH_3CH_2OH \qquad \textbf{(10.30)}$$

10.17 The Need for Activated Acyl Compounds

As we have seen, most reactions of carboxylic acids, esters, and related compounds involve, as the first step, nucleophilic attack on the carbonyl carbon atom. Examples are Fischer esterification, saponification and ammonolysis of esters, and the first stage of the reaction of esters with Grignard reagents or lithium aluminum hydride. All of these reactions can be summarized by a single mechanistic equation:



(10.31)

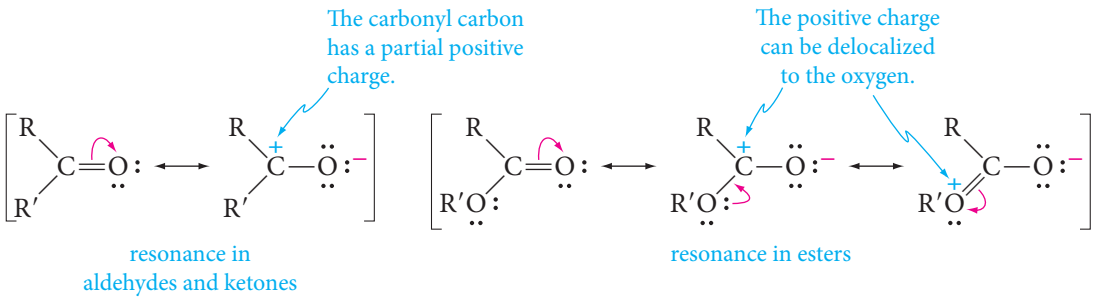
The carbonyl carbon, initially trigonal, is attacked by a nucleophile $Nu:^-$ to form a tetrahedral intermediate (step 1). Loss of a leaving group $:L^-$ (step 2) then regenerates the carbonyl group with its trigonal carbon atom. The net result is the replacement of L by Nu.

An **acyl transfer** is the transfer of an acyl group from a leaving group to a nucleophile.

Biochemists look at eq. 10.31 in a slightly different way. They refer to the overall reaction as an **acyl transfer**. The acyl group is transferred from L in the starting material to Nu in the product.

Regardless of how we consider the reaction, one important feature that can affect the rate of both steps is the nature of the leaving group. *The rates of both steps in a nucleophilic acyl substitution reaction are enhanced by increasing the electron-withdrawing properties of the leaving group.* Step 1 is favored because the more electronegative L is, the more positive the carbonyl carbon becomes, and therefore the more susceptible the carbonyl carbon is to nucleophilic attack. Step 2 is also facilitated because the more electronegative L is, the better leaving group it becomes.

In general, esters are *less* reactive toward nucleophiles than are aldehydes or ketones because the positive charge on the carbonyl carbon in esters can be delocalized to the oxygen atom. Consequently, the ester is more stable and less prone to attack.

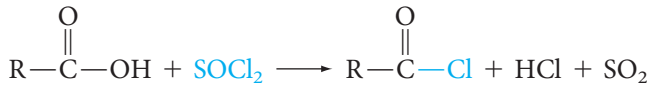


Now let us examine some of the ways in which the carboxyl group can be modified to *increase* its reactivity toward nucleophiles.

10.18 Acyl Halides

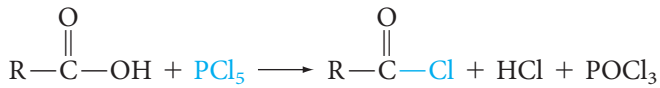
An **acyl halide** is a carboxylic acid derivative in which the —OH group is replaced by a halogen atom.

Acyl halides are among the most reactive of carboxylic acid derivatives. *Acyl chlorides* are more common and less expensive than bromides or iodides. They can be prepared from acids by reaction with thionyl chloride.



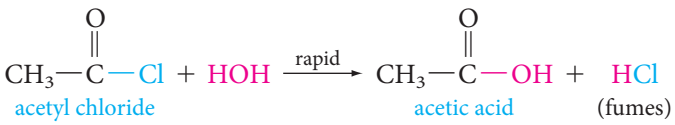
$$R{-}C(=O){-}OH + SOCl_2 \longrightarrow R{-}C(=O){-}Cl + HCl + SO_2 \qquad \textbf{(10.32)}$$

The mechanism is similar to that for the formation of chlorides from alcohols and thionyl chloride. The hydroxyl group is converted to a good leaving group by thionyl chloride, followed by a nucleophilic acyl substitution in which chloride is the nucleophile (compare with Sec. 7.10). Phosphorus pentachloride and other reagents can also be used to prepare acyl chlorides from carboxylic acids.



$$R{-}C(=O){-}OH + PCl_5 \longrightarrow R{-}C(=O){-}Cl + HCl + POCl_3 \qquad \textbf{(10.33)}$$

Acyl halides react rapidly with most nucleophiles. For example, they are rapidly hydrolyzed by water.



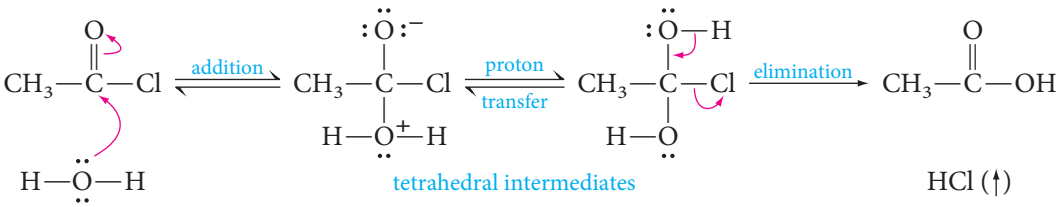
$$CH_3{-}C(=O){-}Cl + HOH \xrightarrow{\text{rapid}} CH_3{-}C(=O){-}OH + HCl \qquad \textbf{(10.34)}$$

For this reason, acyl halides have irritating odors. Benzoyl chloride (eq. 10.35), for example, is a lachrymator (tear gas).

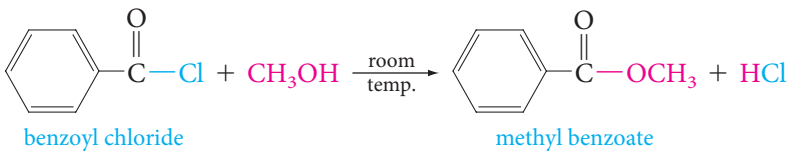
EXAMPLE 10.7

Write a mechanism for the reaction shown in eq. 10.34.

Solution Nucleophilic addition of water to the carbonyl group, followed by proton transfer and elimination of HCl from the tetrahedral intermediate, gives the observed products.



Acyl halides react rapidly with alcohols to form esters.



$$C_6H_5{-}C(=O){-}Cl + CH_3OH \xrightarrow{\text{room temp.}} C_6H_5{-}C(=O){-}OCH_3 + HCl \qquad \textbf{(10.35)}$$

Indeed, the most common way to prepare an ester *in the laboratory* is to convert an acid to its acid chloride, then react the latter with an alcohol. Even though two steps are necessary (compared with one step for Fischer esterification), the method may be

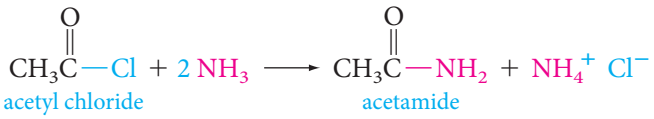
preferable, especially if either the acid or the alcohol is expensive. (Recall that Fischer esterification is an equilibrium reaction and must often be carried out with a large excess of one of the reactants.)

PROBLEM 10.22 Rewrite eq. 10.32 to show the preparation of benzoyl chloride (see eq. 10.35).

PROBLEM 10.23 Explain why acyl halides may be irritating to the nose.

PROBLEM 10.24 Write a mechanism for the reaction shown in eq. 10.35.

Acyl halides react rapidly with ammonia to form amides.



(10.36)

The reaction is much more rapid than the ammonolysis of esters. Two equivalents of ammonia are required, however—one to form the amide and one to neutralize the hydrogen chloride.

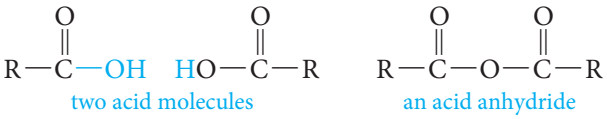
Acyl halides are used to synthesize aromatic ketones, through Friedel–Crafts acylation of aromatic rings (review Sec. 4.9.d).

PROBLEM 10.25 Devise a synthesis of 4-methylphenyl propyl ketone from toluene and butanoic acid as starting materials.

10.19 Acid Anhydrides

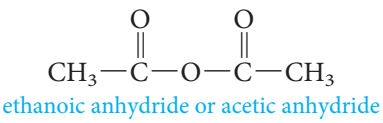
Acid anhydrides are carboxylic acid derivatives formed by condensing two carboxylic acid molecules.

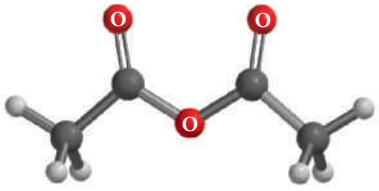
Acid anhydrides are derived from acids by removing water from two carboxyl groups and connecting the fragments.



The most important commercial aliphatic anhydride is acetic anhydride (R=CH_3). About 1 million tons are manufactured annually, mainly to react with alcohols to form acetates. The two most common uses are in making cellulose acetate (rayon) and aspirin (acetylsalicylic acid).

The name of an anhydride is obtained by naming the acid from which it is derived and replacing the word *acid* with *anhydride.*

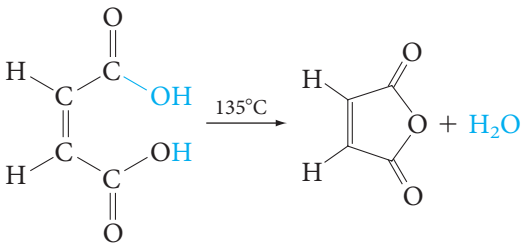




PROBLEM 10.26 Write the structural formula for

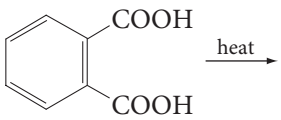
a. butanoic anhydride b. benzoic anhydride

Anhydrides are prepared by dehydration of acids. Dicarboxylic acids with appropriately spaced carboxyl groups lose water on heating to form cyclic anhydrides with five- and six-membered rings. For example,



(10.37)

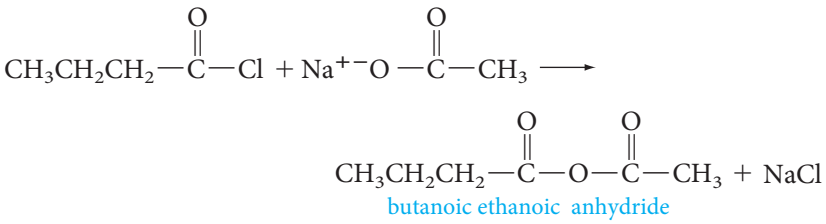
PROBLEM 10.27 Predict and name the product of the following reaction:



PROBLEM 10.28 Do you expect fumaric acid (page 290) to form a cyclic anhydride on heating? Explain.

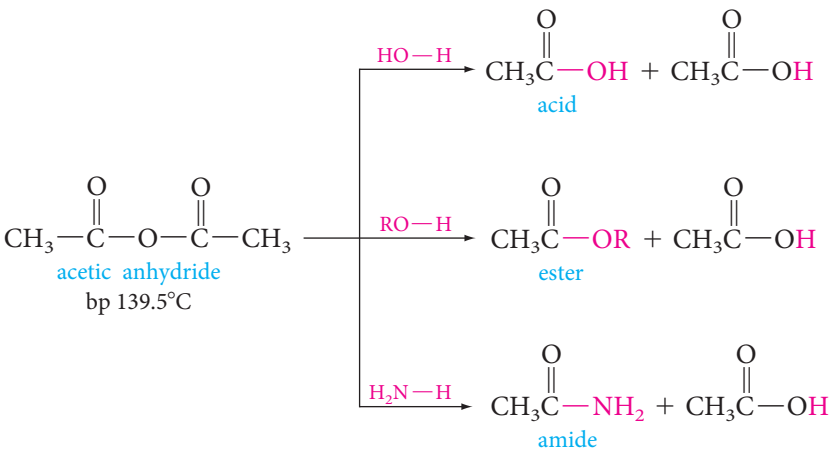
Anhydrides can also be prepared from acid chlorides and carboxylate salts in a reaction that occurs by a nucleophilic acyl substitution mechanism. This is a good method for preparing anhydrides derived from two different carboxylic acids, called **mixed anhydrides**.

Mixed anhydrides are prepared from two different carboxylic acids.



(10.38)

Anhydrides undergo nucleophilic acyl substitution reactions. They are more reactive than esters, but less reactive than acyl halides, toward nucleophiles. Some typical reactions of acetic anhydride follow:

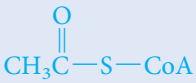


(10.39)

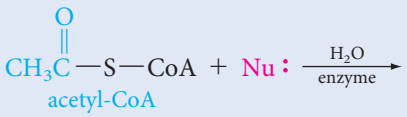
A WORD ABOUT... Thioesters, Nature's Acyl-Activating Groups

Acyl transfer plays an important role in many biochemical processes. However, acyl halides and anhydrides are far too corrosive to be cell constituents—they are hydrolyzed quite rapidly by water and are therefore incompatible with cellular fluid. Most ordinary esters, on the other hand, react too slowly with nucleophiles for acyl transfer to be carried out efficiently at body temperatures. Consequently, other functional groups have evolved to activate acyl groups in the cell. The most important of these is **coenzyme A** (the A stands for acetylation, one of the functions of this enzyme). Coenzyme A is a complex *thiol* (Figure 10.2). It is usually abbreviated by the symbol **CoA—SH**. Though its structure is made up of three parts—adenosine diphosphate (ADP), pantothenic acid (a vitamin), and 2-aminoethanethiol—it is the thiol group that gives coenzyme A its most important functions.

Coenzyme A can be converted to **thioesters**, the active acyl-transfer agents in the cell. Of the thioesters that coenzyme A forms, the acetyl ester, called **acetyl-coenzyme A** and abbreviated as



is the most important. Acetyl-CoA reacts with many nucleophiles to transfer the acetyl group.



The reactions are usually enzyme-mediated and occur rapidly at ordinary cell temperatures.

Why are thioesters superior to ordinary esters as acyl-transfer agents? Part of the answer lies in the acidity difference between alcohols and thiols (Sec. 7.17). Since thiols are much stronger acids than are alcohols, their conjugate bases, $^{-}$SR, are much weaker bases than $^{-}$OR. Thus, the —SR group of thioesters is a much better leaving group, in nucleophilic substitution reactions, than is the —OR group of ordinary esters. Thioesters are not so reactive that they hydrolyze in cellular fluid, but they are appreciably more reactive than simple esters. Nature makes use of this feature.

See Problem 10.64.

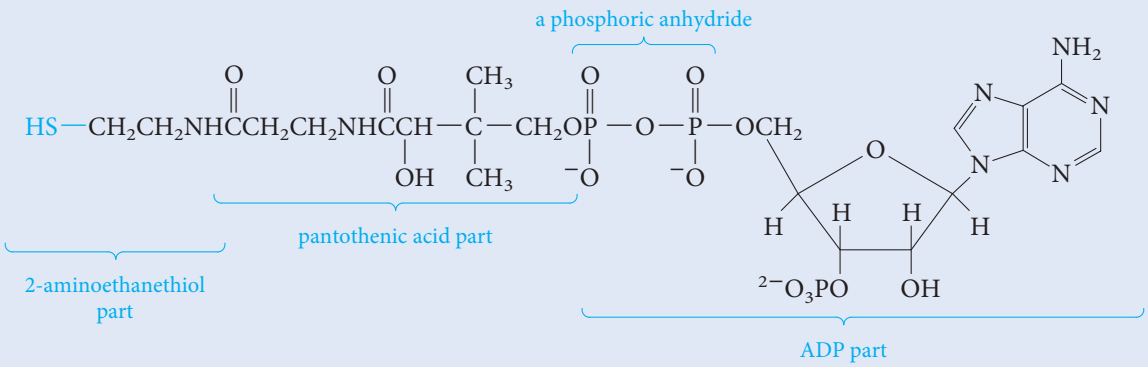


Figure 10.2
Coenzyme A.

Water hydrolyzes an anhydride to the corresponding acid. Alcohols give esters, and ammonia gives amides. In each case, one equivalent of acid is also produced.

PROBLEM 10.29 Write an equation for the reaction of acetic anhydride with 1-pentanol ($CH_3CH_2CH_2CH_2CH_2OH$).

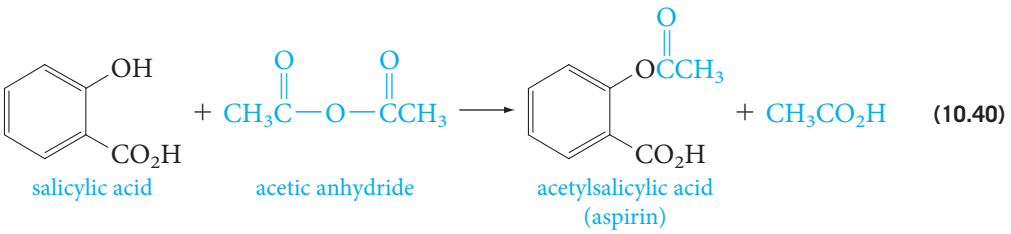
PROBLEM 10.30 Write equations for the reactions of maleic anhydride (see eq. 10.37) with

a. water b. 1-propanol c. ammonia

The reaction of acetic anhydride with salicylic acid (*o*-hydroxybenzoic acid) is used to synthesize aspirin. In this reaction, the phenolic hydroxyl group is **acetylated** (converted to its acetate ester).

An alcohol is said to be **acetylated** when converted to its acetate ester.

Annual aspirin production in the United States is more than 24 million pounds, enough to produce over 30 billion standard 5-grain (325 mg) tablets. Aspirin is widely used, either by itself or mixed with other drugs, as an analgesic and antipyretic. It is not without dangers, however. Repeated use may cause gastrointestinal bleeding, and a large single dose (10 to 20 g) can cause death.

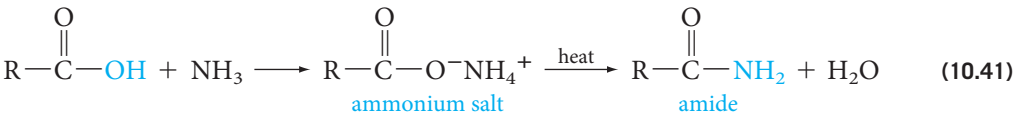


10.20 Amides

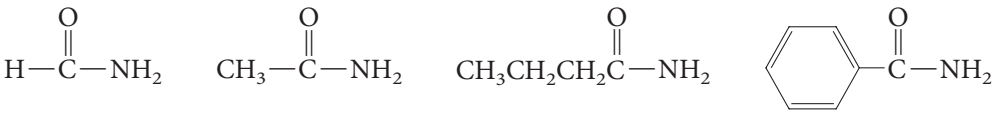
Amides are carboxylic acid derivatives in which the —OH group is replaced by —NH_2, —NHR, or —NR_2.

Amides are the least reactive of the common carboxylic acid derivatives. They occur widely in nature. The most important amides are the proteins, whose chemistry we will discuss in Chapter 17. Here we will concentrate on just a few properties of simple amides.

Primary amides have the general formula $RCONH_2$. They can be prepared by the reaction of ammonia with esters (eq. 10.24), with acyl halides (eq. 10.36), or with acid anhydrides (eq. 10.39). Amides can also be prepared by heating the ammonium salts of acids.



Amides are named by replacing the *-ic* or *-oic* ending of the acid name, either the common or the IUPAC name, with the *-amide* ending.

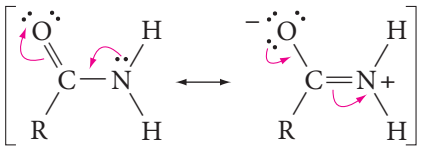


PROBLEM 10.31

a. Name $(CH_3)_2CHCH_2CONH_2$
b. Write the structure of 1-phenylcyclopentanecarboxamide

The above examples are all primary amides. Secondary and tertiary amides, in which one or both of the hydrogens on the nitrogen atom are replaced by organic groups, are described in the next chapter.

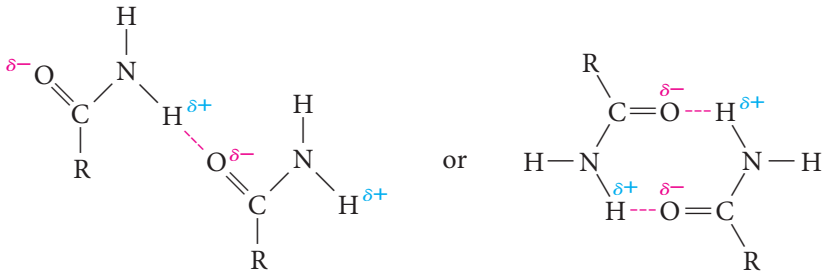
Amides have a planar geometry. Even though the carbon–nitrogen bond is normally written as a single bond, rotation around that bond is restricted because of resonance.



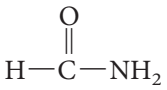
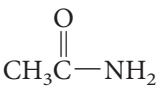
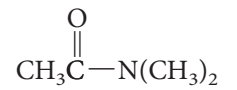
amide resonance

The dipolar contributor is so important that the carbon–nitrogen bond behaves much like a double bond. Consequently, the nitrogen and the carbonyl carbon, and the two atoms attached to each of them, lie in the same plane, and rotation at the C—N bond is restricted. Indeed, the C—N bond in amides is only 1.32 Å long—much shorter than the usual carbon–nitrogen single bond length (which is about 1.47 Å).

As the dipolar resonance contributor suggests, amides are highly polar and form strong hydrogen bonds.

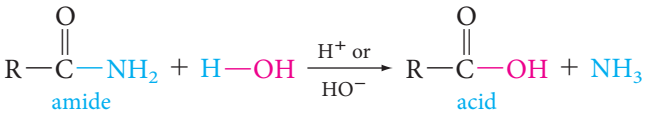


Amides have exceptionally high boiling points for their molecular weights, although alkyl substitution on the nitrogen lowers the boiling and melting points by decreasing the hydrogen-bonding possibilities, as shown in the following two pairs of compounds:

			
formamide	*N*,*N*-dimethylformamide	acetamide	*N*,*N*-dimethylacetamide
bp 210°C	153°C	222°C	165°C
mp 2.5°C	−60.5°C	81°C	−20°C

PROBLEM 10.32 Show that hydrogen bonding is possible for acetamide, but not for *N*,*N*-dimethylacetamide.

Like other acid derivatives, amides react with nucleophiles. For example, they can be hydrolyzed by water.



(10.42)

The reactions are slow, and prolonged heating or acid or base catalysis is usually necessary.

PROBLEM 10.33 Using eq. 10.42 as a model, write an equation for the hydrolysis of acetamide.

Amides can be reduced by lithium aluminum hydride to give amines.

$$\underset{\text{amide}}{R{-}\overset{\overset{O}{\|}}{C}{-}NH_2} \xrightarrow[\text{ether}]{LiAlH_4} \underset{\text{amine}}{RCH_2NH_2} \qquad (10.43)$$

This is an excellent way to make primary amines, whose chemistry is discussed in the next chapter.

PROBLEM 10.34 Using eq. 10.43 as a model, write an equation for the reduction of acetamide with $LiAlH_4$.

Urea is a special amide, a diamide of carbonic acid. A colorless, water-soluble, crystalline solid, urea is the normal end product of protein metabolism. An average adult excretes approximately 30 g of urea in his or her urine daily. Urea is produced commercially from carbon dioxide and ammonia, mainly for use as a fertilizer.

$$\underset{\text{carbonic acid}}{HO{-}\overset{\overset{O}{\|}}{C}{-}OH} \qquad \underset{\substack{\text{urea}\\ \text{mp 133°C}}}{H_2N{-}\overset{\overset{O}{\|}}{C}{-}NH_2}$$

10.21 A Summary of Carboxylic Acid Derivatives

We have studied a rather large number of reactions in this chapter. However, most of them can be summarized in a single chart, shown in Table 10.5, and visually presented in Figure 10.3.

Table 10.5 ■ Reactions of Acid Derivatives with Certain Nucleophiles

	Nucleophile		
Acid derivative	**HOH (hydrolysis)**	**R′OH (alcoholysis)**	**NH_3 (ammonolysis)**
decreasing reactivity ↓			
$R{-}\overset{\overset{O}{\|}}{C}{-}Cl$ acyl halide	$R{-}\overset{\overset{O}{\|}}{C}{-}OH + HCl$	$R{-}\overset{\overset{O}{\|}}{C}{-}OR' + HCl$	$R{-}\overset{\overset{O}{\|}}{C}{-}NH_2 + NH_4^+Cl^-$
$R{-}\overset{\overset{O}{\|}}{C}{-}O{-}\overset{\overset{O}{\|}}{C}{-}R$ acid anhydride	$2\,R{-}\overset{\overset{O}{\|}}{C}{-}OH$	$R{-}\overset{\overset{O}{\|}}{C}{-}OR' + RCO_2H$	$R{-}\overset{\overset{O}{\|}}{C}{-}NH_2 + RCO_2H$
$R{-}\overset{\overset{O}{\|}}{C}{-}O{-}R''$ ester	$R{-}\overset{\overset{O}{\|}}{C}{-}OH + R''OH$	$R{-}\overset{\overset{O}{\|}}{C}{-}OR' + R''OH$ (ester interchange)	$R{-}\overset{\overset{O}{\|}}{C}{-}NH_2 + R''OH$
$R{-}\overset{\overset{O}{\|}}{C}{-}NH_2$ amide	$R{-}\overset{\overset{O}{\|}}{C}{-}OH + NH_3$	———	———
Main organic product	acid	ester	amide

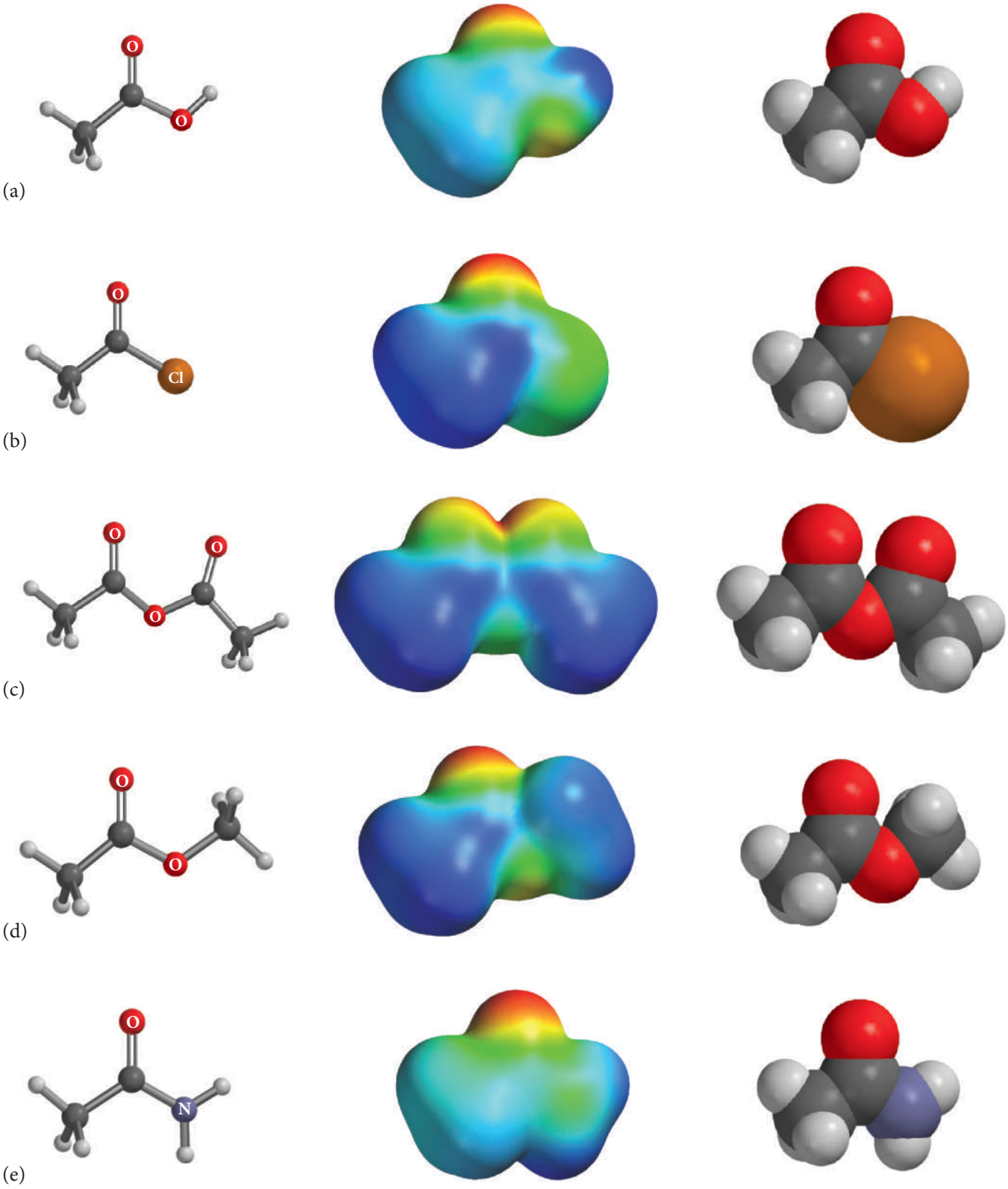


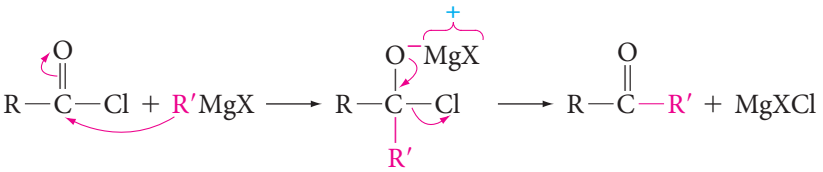
Figure 10.3

Three-dimensional representations and electrostatic potential maps of representative carboxylic acid derivatives. Ball-and-stick structures are provided on the left, electrostatic potential maps in the center, and space-filling models on the right for (a) acetic acid (CH_3CO_2H); (b) acetyl chloride ($CH_3C(=O)Cl$); (c) acetic anhydride ($CH_3C(=O)—O—C(=O)CH_3$); (d) methyl acetate ($CH_3C(=O)OCH_3$); and (e) acetamide ($CH_3C(=O)NH_2$).

The four types of acid derivatives are listed at the left of the chart in order of decreasing reactivity toward nucleophiles. Three common nucleophiles are listed across the top. Note that the main organic product in each column is the same, regardless of which type of carboxylic acid derivative we start with. For example, hydrolysis gives the corresponding organic acid, whether we start with an acyl halide, acid anhydride, ester, or amide. Similarly, alcoholysis gives an ester, and ammonolysis gives an amide. Note also that the *other* reaction product is generally the same from a given carboxylic acid derivative (horizontally across the table), regardless of the nucleophile. For example, starting with an ester, RCO_2R'', we obtain as the second product the alcohol R″OH, regardless of whether the reaction type is hydrolysis, alcoholysis, or ammonolysis.

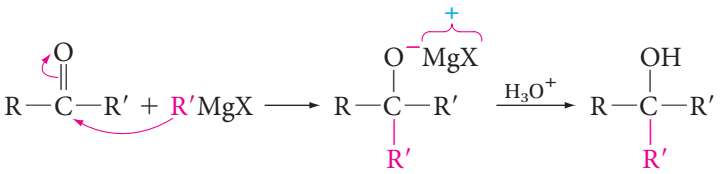
All of the reactions in Table 10.5 take place via attack of the nucleophile on the carbonyl carbon of the carboxylic acid derivative, as described in eq. 10.31. Indeed, most of the reactions from Sections 10.10 through 10.19 occur by that same mechanism. We can sometimes use this idea to predict new reactions.

For example, the reaction of esters with Grignard reagents (eq. 10.27) involves nucleophilic attack of the Grignard reagent on the ester's carbonyl group. Keeping in mind that all carboxylic acid derivatives are susceptible to nucleophilic attack, it is understandable that acyl halides also react with Grignard reagents to give tertiary alcohols. The first steps involve ketone formation as follows:



(10.44)

The ketone can sometimes be isolated, but usually it reacts with a second mole of Grignard reagent to give a tertiary alcohol.



(10.45)

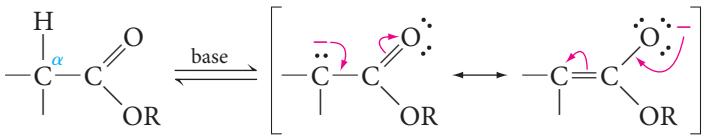
PROBLEM 10.35 Predict the product from the reaction of phenylmagnesium bromide (C_6H_5MgBr) with benzoyl chloride (C_6H_5COCl).

10.22 The α-Hydrogen of Esters; the Claisen Condensation

In this final section, we describe an important reaction of esters that resembles the aldol condensation of aldehydes and ketones (Sec. 9.17). It makes use of the α-hydrogen (see pages 272–275) of an ester.

An **ester enolate** is the anion formed by removing the α-hydrogen of an ester.

Being adjacent to a carbonyl group, the α-hydrogens of an ester are weakly acidic ($pK_a \sim 23$) and can be removed by a *strong base.* The product is an **ester enolate**.

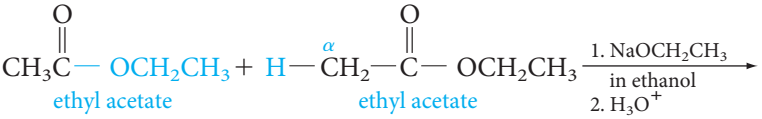


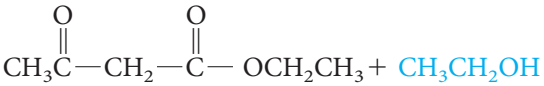
(10.46)

resonance contributors to an ester enolate

Common bases used for this purpose are sodium alkoxides or sodium hydride. The ester enolate, once formed, can act as a carbon nucleophile and add to the carbonyl group of another ester molecule. This reaction is called the Claisen condensation. It is a way of making β-keto esters. We will use ethyl acetate as an example to see how the reaction works.

Treatment of ethyl acetate with sodium ethoxide in ethanol produces the β-keto ester, ethyl acetoacetate:



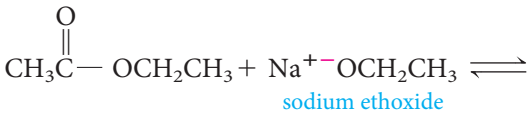


(10.47)

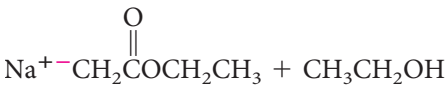
ethyl acetoacetate
(ethyl 3-oxobutanoate)

The Claisen condensation takes place in three steps.

Step 1.



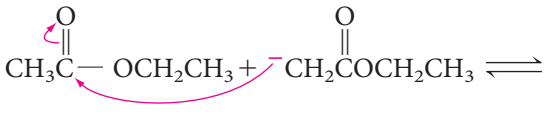
sodium ethoxide

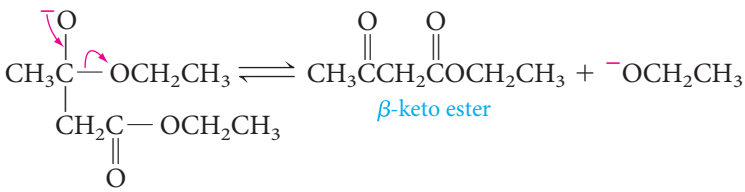


(10.48)

ester enolate

Step 2.

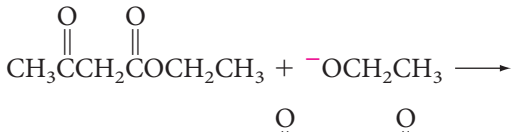




(10.49)

β-keto ester

Step 3.



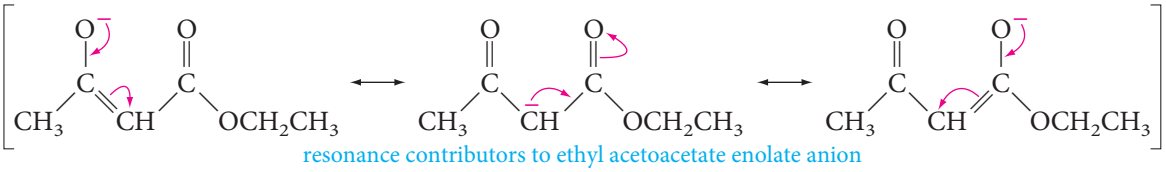
(10.50)

enolate ion of a β-keto ester

In step 1, the base (sodium ethoxide) removes an α-hydrogen from the ester to form an ester enolate. In step 2, this ester enolate, acting as a nucleophile, adds to the

carbonyl group of a second ester molecule, displacing ethoxide ion. This step follows the mechanism in eq. 10.31 and proceeds through a tetrahedral intermediate. These first two steps of the reaction are completely reversible.

Step 3 drives the equilibrium forward. In this step, the β-keto ester is converted to *its* enolate anion. The methylene (CH_2) hydrogens in ethyl acetoacetate are *α to two carbonyl groups* and hence are appreciably more acidic than ordinary α-hydrogens. They have a pK_a of 12 and are easily removed by the base (ethoxide ion) to form a resonance-stabilized β-keto enolate ion, *with the negative charge delocalized to both carbonyl oxygen atoms.*

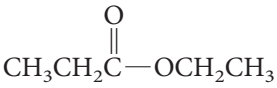


resonance contributors to ethyl acetoacetate enolate anion

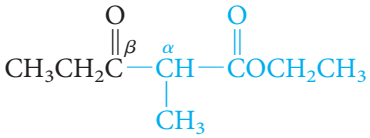
To complete the Claisen condensation, the solution is acidified, to regenerate the β-keto ester from its enolate anion.

EXAMPLE 10.8

Identify the product of the Claisen condensation of ethyl propanoate:



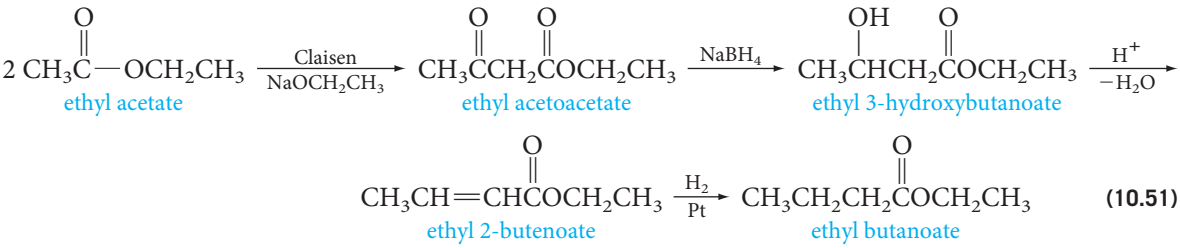
Solution The product is



The α-carbon of one ester molecule displaces the —OR group and becomes joined to the carbonyl carbon of the other ester. The product is always a β-keto ester.

PROBLEM 10.36 Using eqs. 10.48 through 10.50 as a model, write out the steps in the mechanism for the Claisen condensation of ethyl propanoate.

The Claisen condensation, like the aldol condensation (Sec. 9.17), is useful for making new carbon–carbon bonds. The resulting β-keto esters can be converted to a variety of useful products. For example, ethyl acetate can be converted to ethyl butanoate by the following sequence.



ethyl acetate; ethyl acetoacetate; ethyl 3-hydroxybutanoate; ethyl 2-butenoate; ethyl butanoate (10.51)

In this way, the acetate chain is lengthened by two carbon atoms. Nature makes use of a similar process, catalyzed by various enzymes, to construct the long-chain carboxylic acids that are components of fats and oils (Chapter 15).

REACTION SUMMARY

1. Preparation of Acids

a. From Alcohols or Aldehydes (Sec. 10.7)

$$RCH_2OH \xrightarrow{CrO_3,\ H_2SO_4,\ H_2O} RCO_2H \xleftarrow[\text{or } O_2 \text{ or } Ag^+]{CrO_3,\ H_2SO_4,\ H_2O} RCH{=}O$$

b. From Alkylbenzenes (Sec. 10.7)

$$ArCH_3 \xrightarrow[\text{or } O_2,\ Co^{+3}]{KMnO_4} ArCO_2H$$

c. From Grignard Reagents (Sec. 10.7)

$$RMgX + CO_2 \longrightarrow RCO_2MgX \xrightarrow{H_3O^+} RCO_2H$$

d. From Nitriles (Sec. 10.7)

$$RC{\equiv}N + 2\,H_2O \xrightarrow{H^+ \text{ or } HO^-} RCO_2H + NH_3$$

2. Reactions of Acids

a. Acid–Base (Secs. 10.4 and 10.6)

$$RCO_2H \rightleftharpoons RCO_2^- + H^+ \quad \text{(ionization)}$$

$$RCO_2H + NaOH \longrightarrow RCO_2^-Na^+ + H_2O \quad \text{(salt formation)}$$

b. Preparation of Esters (Secs. 10.10 and 10.12)

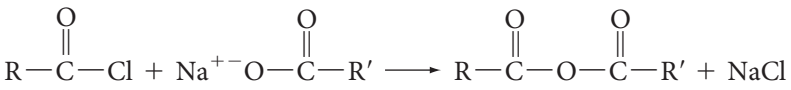
$$RCO_2H + R'OH \xrightarrow{H^+} RCO_2R' + H_2O$$

c. Preparation of Acid Chlorides (Sec. 10.18)

$$RCO_2H + SOCl_2 \longrightarrow RCOCl + HCl + SO_2$$

$$RCO_2H + PCl_5 \longrightarrow RCOCl + HCl + POCl_3$$

d. Preparation of Anhydrides (Sec. 10.19)



e. Preparation of Amides (Sec. 10.20)

$$RCO_2^-NH_4^+ \xrightarrow{\text{heat}} RCONH_2 + H_2O$$

Also see reactions of esters, acid chlorides, and anhydrides in Section 10.21.

3. Reactions of Carboxylic Acid Derivatives

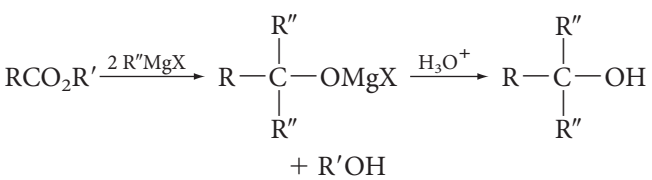
a. Saponification of Esters (Sec. 10.13)

$$RCO_2R' + NaOH \longrightarrow RCO_2^-Na^+ + R'OH$$

b. Ammonolysis of Esters (Sec. 10.14)

$$RCO_2R' + NH_3 \longrightarrow RCONH_2 + R'OH$$

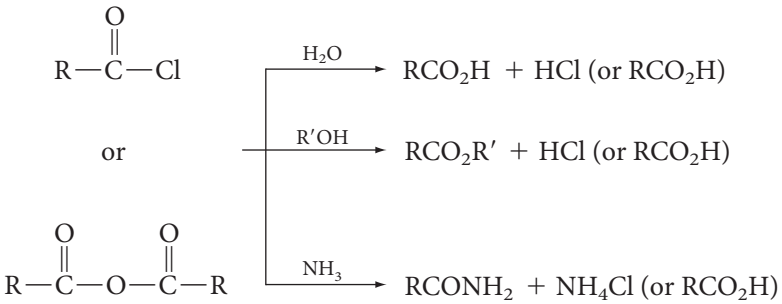
c. Esters with Grignard Reagents (Sec. 10.15)



d. Reduction of Esters (Sec. 10.16)

$$RCO_2R' + LiAlH_4 \longrightarrow RCH_2OH + R'OH$$

e. Nucleophilic Acyl Substitution Reactions of Acid Chlorides and Anhydrides (Secs. 10.18 and 10.19)



f. Hydrolysis of Amides (Sec. 10.20)

$$RCONH_2 + H_2O \xrightarrow{H^+ \text{ or } HO^-} RCO_2H + NH_3$$

g. Reduction of Amides (Sec. 10.20)

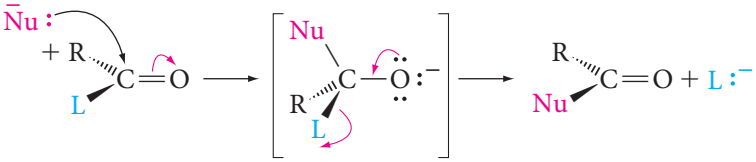
$$RCONH_2 \xrightarrow{LiAlH_4} RCH_2NH_2$$

h. Claisen Condensation (Sec. 10.22)

$$2\ RCH_2CO_2R' \xrightarrow[2.\ H_3O^+]{1.\ R'O^-Na^+} RCH_2\underset{\displaystyle R}{\overset{\displaystyle O}{\overset{\|}{C}}}CHCO_2R' + R'OH$$

MECHANISM SUMMARY

Nucleophilic Acyl Substitution (Secs. 10.11 and 10.17)



ADDITIONAL PROBLEMS

OWL Interactive versions of these problems are assignable in OWL.

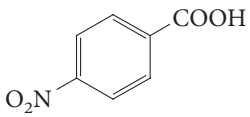
Nomenclature and Structure of Carboxylic Acids

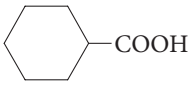
10.37 Write a structural formula for each of the following acids:

a. 4-ethylhexanoic acid
b. 2-bromobutanoic acid
c. 3-chlorohexanoic acid
d. cyclopentanecarboxylic acid
e. 2-isopropylbenzoic acid
f. 3-oxooctanoic acid
g. *p*-toluic acid
h. 2-ethylbutanedioic acid
i. *p*-methoxyphenylacetic acid
j. 1-naphthoic acid
k. 2,3-dimethyl-3-butenoic acid

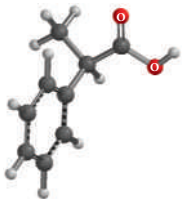
10.38 Name each of the following acids:

a. $(CH_3)_2C(Br)CH_2CH_2COOH$ **b.** $CH_3CH(OCH_3)CH(CH_3)COOH$

c. 

d. 

e. $CH_2{=}CHCOOH$

f. 

g. CH_3CF_2COOH **h.** $HC{\equiv}CCH_2CO_2H$

Synthesis and Properties of Carboxylic Acids

10.39 Which will have the higher boiling point? Explain your reasoning.

a. CH_3CH_2COOH or $CH_3CH_2CH_2CH_2OH$
b. $CH_3CH_2CH_2CH_2COOH$ or $(CH_3)_3CCOOH$

10.40 In each of the following pairs of acids, which would be expected to be the stronger acid, and why?

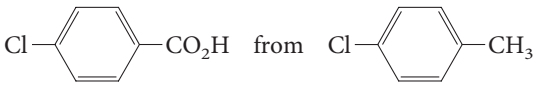
a. $ClCH_2CO_2H$ and $BrCH_2CO_2H$ **b.** *o*-$BrC_6H_4CO_2H$ and *m*-$BrC_6H_4CO_2H$
c. Cl_3CCO_2H and F_3CCO_2H **d.** $C_6H_5CO_2H$ and *p*-$CH_3OC_6H_4CO_2H$
e. $ClCH_2CH_2CO_2H$ and $CH_3CHClCO_2H$

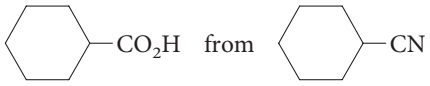
10.41 Write a balanced equation for the reaction of

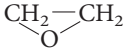
a. $ClCH_2CH_2CO_2H$ with KOH **b.** $CH_3(CH_2)_4CO_2H$ with $Ca(OH)_2$

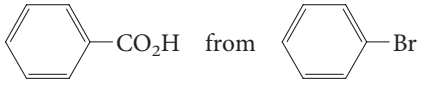
10.42 Give equations for the synthesis of

a. $CH_3CH_2CH_2CO_2H$ from $CH_3CH_2CH_2CH_2OH$
b. $CH_3CH_2CH_2CO_2H$ from $CH_3CH_2CH_2OH$ (two ways)

c. 

d. 

e. $CH_3OCH_2CO_2H$ from  (two steps)

f. 

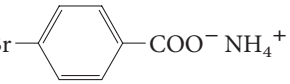
10.43 The Grignard route for the synthesis of $(CH_3)_3CCO_2H$ from $(CH_3)_3CBr$ (Example 10.5) is far superior to the nitrile route. Explain why.

Nomenclature and Structure of Carboxylic Acid Derivatives

10.44 Write a structure for each of the following compounds:

a. isobutyl acetate
b. isopropyl formate
c. sodium 2-chlorobutanoate
d. calcium acetate
e. phenyl benzoate
f. *o*-toluamide
g. 2-methoxybutanoyl chloride
h. benzonitrile
i. propanoic anhydride
j. 2-acetylcyclohexanecarboxylic acid
k. α-methyl-γ-butyrolactone

10.45 Name each of the following compounds:

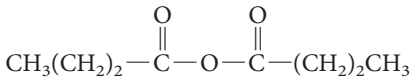
a. 

b. $[CH_3(CH_2)_2CO_2^-]_2Ca^{2+}$

c. $(CH_3)_2CHCH_2CH_2COOC_6H_5$

d. $CF_3CO_2CH_3$

e. $HCONH_2$

f. 

10.46 Draw the structure of the mating pheromone of the female elephant, (*Z*)-7-dodecen-1-yl acetate (see page 302).

10.47 Organic emissions from mobile sources (cars, trucks, planes, and so on) become oxidized in the troposphere and can then assist the formation of particulate secondary organic aerosols. Such small particulate matter can penetrate deep into our lungs and cause acute irritations. It has been reported that carboxylic acids, such as benzoic acid, can form stable complexes with sulfuric acid (H_2SO_4) in a similar manner that carboxylic acids can form dimers (Sec. 10.2). Suggest a structure for a stable complex between benzoic acid and sulfuric acid.

Synthesis and Reactions of Esters

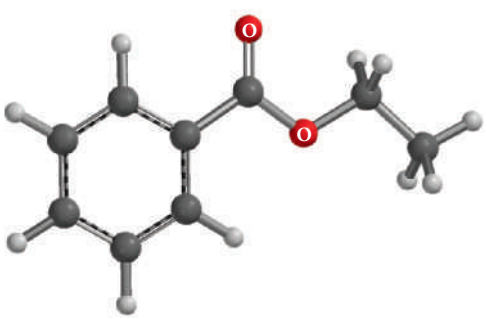
10.48 Write an equation for the Fischer esterification of butanoic acid ($CH_3CH_2CH_2CO_2H$) with ethanol.

10.49 Write out each step in the Fischer esterification of benzoic acid with methanol. (You may wish to use eq. 10.19 as a model.)

10.50 Starting from bromobenzene, provide a short synthesis of methyl benzoate ($C_6H_5CO_2CH_3$).

10.51 Write an equation for the reaction of propyl benzoate with

a. hot aqueous sodium hydroxide
b. ammonia (heat)
c. phenylmagnesium iodide (two equivalents), then H_3O^+
d. lithium aluminum hydride (two equivalents), then H_3O^+

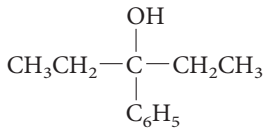


ethyl benzoate

10.52 Write out all of the steps in the mechanism for

a. saponification of $CH_3CH_2CO_2CH_2CH_3$ **b.** ammonolysis of $CH_3CH_2CO_2CH_2CH_3$

10.53 Identify the Grignard reagent and the ester that would be used to prepare

a. 

b. $CH_3CH_2CH_2C(C_6H_5)_2OH$

Reactions of Carboxylic Acid Derivatives

10.54 Explain each difference in reactivity toward nucleophiles.

a. Esters are less reactive than ketones.
b. Benzoyl chloride is less reactive than cyclohexanecarbonyl chloride.

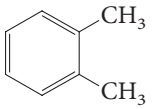
10.55 Write an equation for

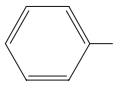
a. hydrolysis of butanoyl chloride
b. ammonolysis of butanoyl bromide
c. 2-methylpropanoyl chloride + ethylbenzene + $AlCl_3$
d. succinic acid + heat (235°C)
e. benzoyl chloride with ethanol
f. esterification of 1-pentanol with acetic anhydride
g. phthalic anhydride + ethanol (1 equiv.) + H^+
h. phthalic anhydride + ethanol (excess) + H^+
i. adipoyl chloride + ammonia (excess)

10.56 Complete the equation for each of the following reactions:

a. $CH_3CH_2CH_2CO_2H + PCl_5 \longrightarrow$

b. $CH_3(CH_2)_6CO_2H + SOCl_2 \longrightarrow$

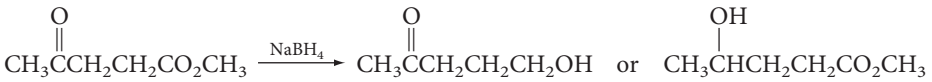
c.  $+ KMnO_4 \longrightarrow$

d.  $+ \text{heat} \longrightarrow$

e. $CH_3(CH_2)_5CONH_2 + LiAlH_4 \longrightarrow$

f.  $+ LiAlH_4 \longrightarrow$

10.57 Considering the relative reactivities of ketones and esters toward nucleophiles, which of the following products seems the more likely?

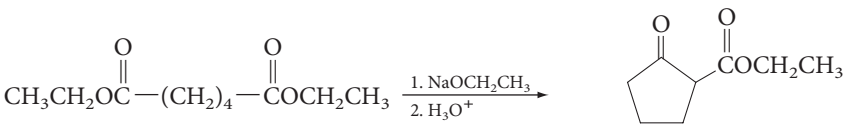


10.58 Mandelic acid, which has the formula $C_6H_5CH(OH)COOH$, can be isolated from bitter almonds (called *mandel* in German). It is sometimes used in medicine to treat urinary infections. Devise a two-step synthesis of mandelic acid from benzaldehyde, using the latter's cyanohydrin (see Sec. 9.10) as an intermediate.

The Claisen Condensation

10.59 Write the structure of the Claisen condensation product of methyl 3-phenylpropanoate ($C_6H_5CH_2CH_2CO_2CH_3$), and show the steps in its formation.

10.60 Diethyl adipate, when heated with sodium ethoxide, gives the product shown, by an *intra*molecular Claisen condensation:



diethyl adipate ethyl 2-oxocyclopentanecarboxylate

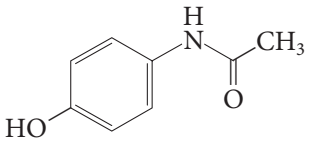
Write out the steps in a plausible mechanism for the reaction.

10.61 Analogous to the mixed aldol condensation (Sec. 9.18), mixed Claisen condensations are possible. Predict the structure of the product obtained when a mixture of ethyl benzoate and ethyl acetate is heated with sodium ethoxide in ethanol.

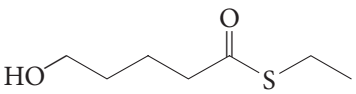
Miscellaneous Problems

10.62 Write the important resonance contributors to the structure of acetamide and tell which atoms lie in a single plane.

10.63 On page 299, "A Word About . . . Green Chemistry and Ibuprofen: A Case Study" showed how efficiently ibuprofen can be prepared on a large scale. Another nonsteroidal, anti-inflammatory drug (NSAID) is acetaminophen. Suggest a short synthesis of acetaminophen from *p*-hydroxyaniline.



10.64 As noted in the "A Word About . . . Thioesters, Nature's Acyl-Activating Groups" on page 312, biological systems rely on thioesters for acyl transfer, but thioesters can be exploited in the laboratory as well. Provide the product for the treatment of

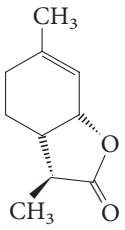


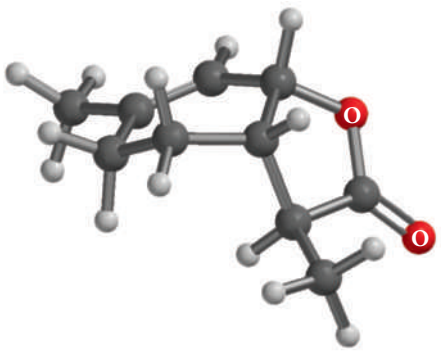
with catalytic NaOH.

10.65 Consider the structure of the catnip ingredient nepetalactone (page 305).

a. Show with dotted lines that the structure is composed of two isoprene units.
b. Circle the stereogenic centers and determine their configurations (*R* or *S*).

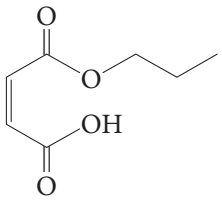
10.66 The lactone shown below, known as *wine lactone*, is a sweet and coconut-like smelling odorant isolated recently from white wines such as Gewürztraminer.



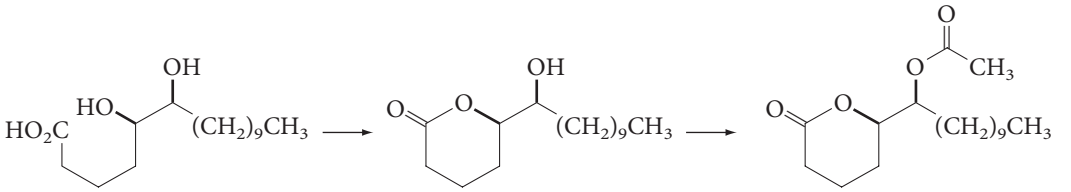


How many stereocenters are present, and what is the configuration (*R* or *S*) at each?

10.67 Provide a short synthesis of the ester-acid below, starting from maleic acid; see Section 10.1 for a structure of maleic acid. (Note, an ideal synthesis would avoid creating a mixture.)



10.68 (5*R*,6*S*)-6-Acetoxy-5-hexadecanolide is a pheromone that attracts certain disease-carrying mosquitoes to sites where they like to lay their eggs. Such compounds might be used to lure these insects away from populated areas to locations where they can be destroyed. The last two steps in a recent synthesis of this compound are shown below. Provide reagents that would accomplish these transformations.



(5*R*, 6*S*)-6-Acetoxy-5-hexadecanolide