CHAPTER

17

Carboxylic Acids and Their Derivatives

NUCLEOPHILIC ADDITION–ELIMINATION AT THE ACYL CARBON

Although there are many different derivatives of carboxylic acids, variations that can account for millions of distinct organic molecules, the vast majority can arise via a common and mechanistically consistent bond-formation process. This event is known as nucleophilic acyl substitution, and it involves the creation of a new bond by a nucleophilic addition and elimination at a carbonyl group. This process is utilized industrially in the synthesis of complex polymers, such as nylon and polyesters (see Special Topic C in *WileyPLUS*). It also occurs in metabolism, in the synthesis of proteins, fats, and steroid precursors, as well as in the breakdown of food for energy and for other biosynthetic raw materials (see Special Topic E in *WileyPLUS*). Its versatility is truly amazing.

IN THIS CHAPTER WE WILL CONSIDER:

- the structure and reactivity of various carboxylic acid derivatives
- many different examples of nucleophilic acyl substitutions, all of which proceed by a similar mechanism though they lead to different products
- methods for the preparation of carboxylic acid derivatives from other functional groups, such as nitriles

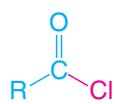
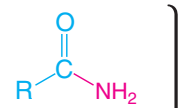
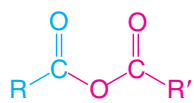
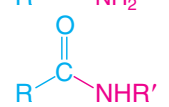
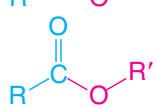
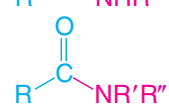
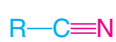
[WHY DO THESE TOPICS MATTER?] At the end of the chapter, we will show you how a key problem in chemical synthesis requiring a nucleophilic acyl substitution—the laboratory preparation of the penicillins—served as inspiration for the development of a powerful class of reagents that has enabled the facile synthesis of amide bonds in many contexts.

17.1 INTRODUCTION

The carboxyl group, 

(abbreviated —CO_2H or —COOH), is one of the most widely occurring functional groups in chemistry and biochemistry. Not only are carboxylic acids themselves important, but the carboxyl group is the parent group of a large family of related compounds called **acyl compounds** or **carboxylic acid derivatives**, shown in Table 17.1.

TABLE 17.1 CARBOXYLIC ACID DERIVATIVES

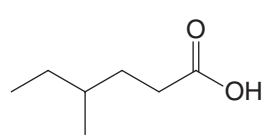
Structure	Name	Structure	Name
	Acyl (or acid) chloride		Amide
	Acid anhydride		
	Ester		
	Nitrile		

17.2 NOMENCLATURE AND PHYSICAL PROPERTIES

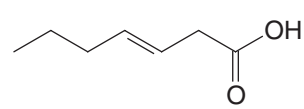
17.2A Carboxylic Acids

- Systematic or substitutive names for carboxylic acids are obtained by dropping the final *-e* of the name of the alkane corresponding to the longest chain in the acid and by adding *-oic acid*. The carboxyl carbon atom is assigned number 1.

The following examples show how this is done:



4-Methylhexanoic acid



(*E*)-3-Heptenoic acid
[or (*E*)-hept-3-enoic acid]

Valerian is a source of valeric acid.

Many carboxylic acids have common names that are derived from Latin or Greek words that indicate one of their natural sources. Methanoic acid is called formic acid (*formica*, Latin: ant). Ethanoic acid is called acetic acid (*acetum*, Latin: vinegar). Butanoic acid is one compound responsible for the odor of rancid butter, so its common name is butyric acid (*butyrum*, Latin: butter). Pentanoic acid, as a result of its occurrence in valerian, a perennial herb, is named valeric acid. Hexanoic acid is one compound associated with the odor of goats, hence its common name, caproic acid (*caper*, Latin: goat). Octadecanoic acid takes its common name, stearic acid, from the Greek word *stear*, for tallow.

Most of these common names have been used for a long time and some are likely to remain in common usage, so it is helpful to be familiar with them. In this text we shall refer to methanoic acid and ethanoic acid as formic acid and acetic acid, respectively. However, in almost all other instances we shall use IUPAC systematic or substitutive names.

Carboxylic acids are polar substances. Their molecules can form strong hydrogen bonds with each other and with water. As a result, carboxylic acids generally have high boiling points, and low-molecular-weight carboxylic acids show appreciable solubility in water. As the length of the carbon chain increases, water solubility declines.

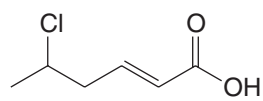
17.2B Carboxylate Salts

Salts of carboxylic acids are named as *-ates*; in both common and systematic names, *-ate* replaces *-ic acid*. The name of the cation precedes that of the carboxylate anion. Thus, CH_3CO_2Na is sodium acetate or sodium ethanoate.

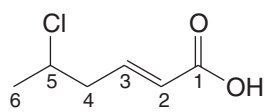
Sodium and potassium salts of most carboxylic acids are readily soluble in water. This is true even of the long-chain carboxylic acids. Sodium or potassium salts of long-chain carboxylic acids are the major ingredients of soap (see Section 23.2C).

SOLVED PROBLEM 17.1

Give an IUPAC systematic name for the following compound.



STRATEGY AND ANSWER: First we number the chain beginning with the carbon of the carboxylic acid group.

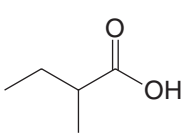


This chain contains six carbons with one double bond, so the base name is **hexenoic acid**. Then we give the position of the double bond and its stereochemistry, and the position and name of the substituent. The name, therefore, is (*E*)-5-chloro-2-hexenoic acid.

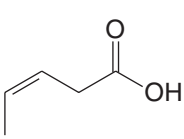
PRACTICE PROBLEM 17.1

Give an IUPAC systematic name for each of the following:

(a)



(b)



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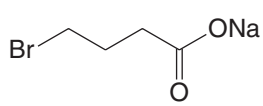
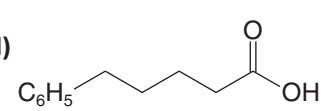
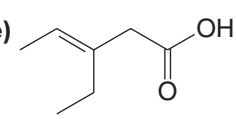


(d)



(e)



PRACTICE PROBLEM 17.2

Experiments show that the molecular weight of acetic acid in the vapor state (just above its boiling point) is approximately 120. Explain the discrepancy between this experimental value and the true value of approximately 60.

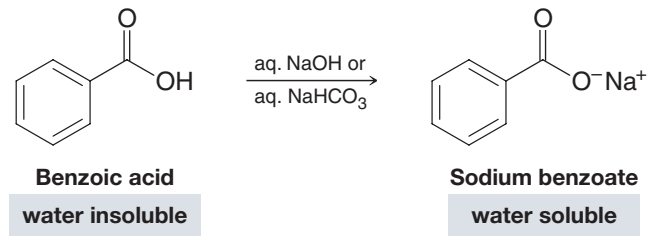
17.2C Acidity of Carboxylic Acids

Most unsubstituted carboxylic acids have K_a values in the range of 10^{-4}–10^{-5} ($pK_a = 4$–5). The pK_a of water is about 16, and the apparent pK_a of H_2CO_3 is about 7. These relative acidities mean that carboxylic acids react readily with aqueous solutions of sodium hydroxide and sodium bicarbonate to form soluble sodium salts. We can use solubility tests, therefore, to distinguish water-insoluble carboxylic acids from water-insoluble phenols (Chapter 21) and alcohols.

Helpful Hint

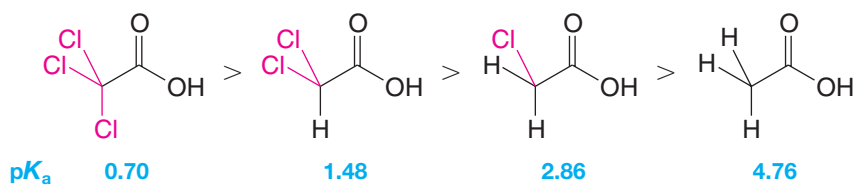
Solubility tests such as these are rapid and useful ways to classify unknown compounds.

- Water-insoluble carboxylic acids dissolve in either aqueous sodium hydroxide or aqueous sodium bicarbonate.



- Water-insoluble phenols (Section 21.5) dissolve in aqueous sodium hydroxide but (except for some nitrophenols) do not dissolve in aqueous sodium bicarbonate.
- Water-insoluble alcohols do not dissolve in either aqueous sodium hydroxide or sodium bicarbonate.

Carboxylic acids having electron-withdrawing groups are more acidic than unsubstituted acids. The chloroacetic acids, for example, show the following order of acidities:



As we saw in Section 3.11, this acid-strengthening effect of electron-withdrawing groups arises from a combination of inductive effects and entropy effects. We can visualize inductive charge delocalization when we compare the electrostatic potential maps for carboxylate anions of acetic acid and trichloroacetetic acid in Fig. 17.1. The maps show more negative charge localized near the acetate carboxyl group than the trichloroacetate carboxyl group. Delocalization of the negative charge in trichloroacetate by the electron-withdrawing effect of its three chlorine atoms contributes to its being a stronger acid than acetic acid.

- In general, the more delocalization of charge in the conjugate base, the more stable is the anion, and the stronger the acid.

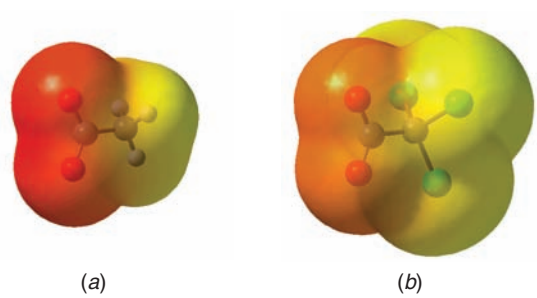
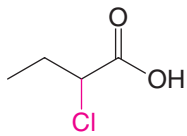
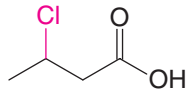


FIGURE 17.1 Electrostatic potential maps for the carboxylate anions of (*a*) acetic acid and (*b*) trichloroacetic acid. There is greater delocalization of negative charge in trichloroacetate than acetate due to the inductive electron-withdrawing effect of the three chlorine atoms in trichloroacetate.

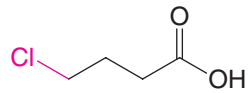
Since inductive effects are not transmitted very effectively through covalent bonds, the acid-strengthening effect decreases as the distance between the electron-withdrawing group and the carboxyl group increases. Of the chlorobutanoic acids that follow, the strongest acid is 2-chlorobutanoic acid:



2-Chlorobutanoic acid
(pK_a = 2.85)



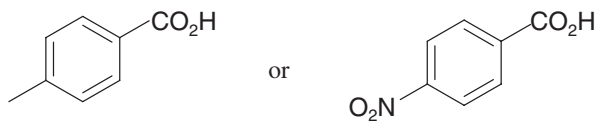
3-Chlorobutanoic acid
(pK_a = 4.05)



4-Chlorobutanoic acid
(pK_a = 4.50)

SOLVED PROBLEM 17.2

Which carboxylic acid would you expect to be stronger, **A** or **B**?



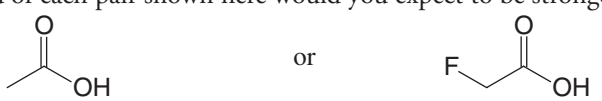
A **B**

STRATEGY AND ANSWER: The electron-withdrawing effect of the nitro group would help stabilize the conjugate base of **B**, whereas the electron-donating effect of the methyl group in **A** would destabilize its conjugate base. Therefore, **B** is expected to be the stronger acid.

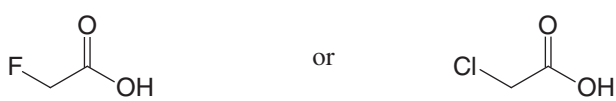
PRACTICE PROBLEM 17.3

Which acid of each pair shown here would you expect to be stronger?

(a)



(b)



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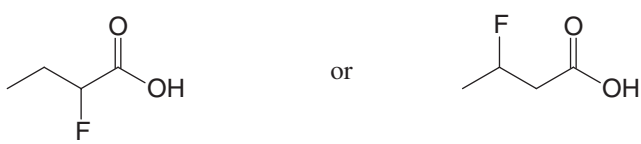
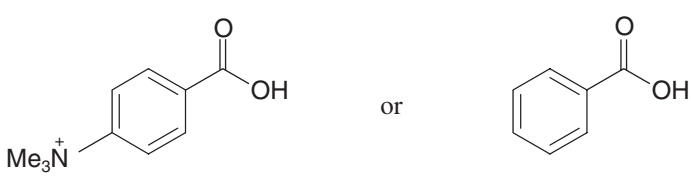


(d)



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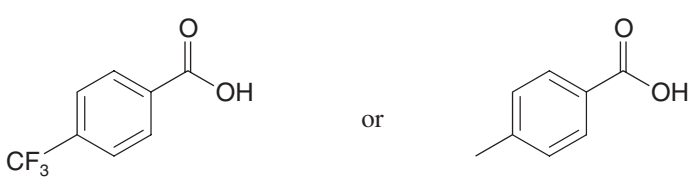
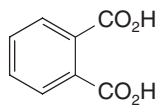
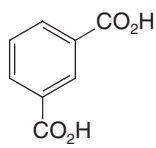
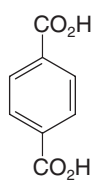


17.2D Dicarboxylic Acids

Dicarboxylic acids are named as **alkanedioic acids** in the IUPAC systematic or substitutive system. Most simple dicarboxylic acids have common names (Table 17.2).

Succinic and fumaric acids are key metabolites in the citric acid pathway. Adipic acid is used in the synthesis of nylon. The isomers of phthalic acid are used in making polyesters. See Special Topic C in *WileyPLUS* for further information on polymers.

TABLE 17.2 DICARBOXYLIC ACIDS

Structure	Common Name	mp (°C)	pK_a (at 25 °C) pK_{a1}	pK_{a2}
HO_2C-CO_2H	Oxalic acid	189 dec	1.2	4.2
$HO_2CCH_2CO_2H$	Malonic acid	136	2.9	5.7
$HO_2C(CH_2)_2CO_2H$	Succinic acid	187	4.2	5.6
$HO_2C(CH_2)_3CO_2H$	Glutaric acid	98	4.3	5.4
$HO_2C(CH_2)_4CO_2H$	Adipic acid	153	4.4	5.6
cis-$HO_2C-CH=CH-CO_2H$	Maleic acid	131	1.9	6.1
trans-$HO_2C-CH=CH-CO_2H$	Fumaric acid	287	3.0	4.4
	Phthalic acid	206–208 dec	2.9	5.4
	Isophthalic acid	345–348	3.5	4.6
	Terephthalic acid	Sublimes	3.5	4.8

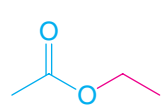
SOLVED PROBLEM 17.3

Suggest explanations for the following. **(a)** The pK_{a1} for all of the dicarboxylic acids in Table 17.2 is smaller than the pK_a for a monocarboxylic acid with the same number of carbon atoms. **(b)** The difference between pK_{a1} and pK_{a2} for dicarboxylic acids of the type $HO_2C(CH_2)_nCO_2H$ decreases as n increases.

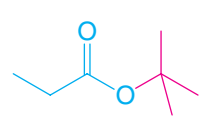
STRATEGY AND ANSWER: **(a)** The carboxyl group is electron-withdrawing; thus, in a dicarboxylic acid such as those in Table 17.2, one carboxylic acid group increases the acidity of the other. **(b)** As the distance between the carboxyl groups increases, the acid-strengthening, inductive effect decreases.

17.2E Esters

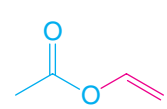
The names of esters are derived from the names of the alcohol (with the ending **-yl**) and the acid (with the ending **-ate** or **-oate**). The portion of the name derived from the alcohol comes first:



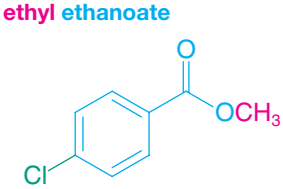
Ethyl acetate or ethyl ethanoate



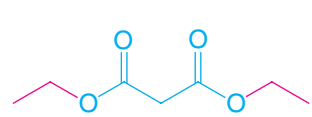
***tert*-Butyl propanoate**



Vinyl acetate or ethenyl ethanoate



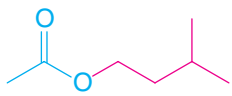
Methyl *p*-chlorobenzoate



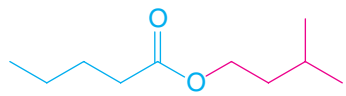
Diethyl malonate

Esters are polar compounds, but, lacking a hydrogen attached to oxygen, their molecules cannot form strong hydrogen bonds to each other. As a result, esters have boiling points that are lower than those of acids and alcohols of comparable molecular weight. The boiling points of esters are about the same as those of comparable aldehydes and ketones.

Unlike the low-molecular-weight acids, esters usually have pleasant odors, some resembling those of fruits, and these are used in the manufacture of synthetic flavors:



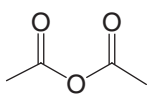
Isopentyl acetate
(used in synthetic banana flavor)



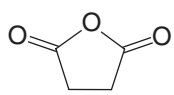
Isopentyl pentanoate
(used in synthetic apple flavor)

17.2F Carboxylic Anhydrides

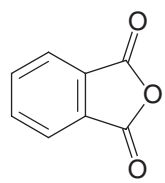
Most anhydrides are named by dropping the word **acid** from the name of the carboxylic acid and then adding the word **anhydride**:



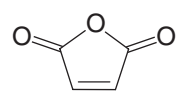
Acetic anhydride
(ethanoic anhydride)
mp –73 °C



Succinic anhydride
mp 121 °C



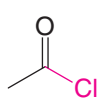
Phthalic anhydride
mp 131 °C



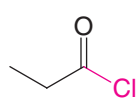
Maleic anhydride
mp 53 °C

17.2G Acyl Chlorides

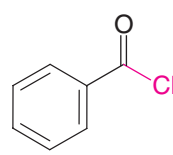
Acyl chlorides are also called **acid chlorides**. They are named by dropping **-ic acid** from the name of the acid and then adding **-yl chloride**. Examples are



Acetyl chloride
(ethanoyl chloride)
mp −112 °C; bp 51 °C



Propanoyl chloride
mp −94 °C; bp 80 °C

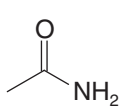


Benzoyl chloride
mp −1 °C; bp 197 °C

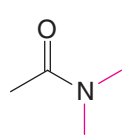
Acyl chlorides and carboxylic anhydrides have boiling points in the same range as esters of comparable molecular weight.

17.2H Amides

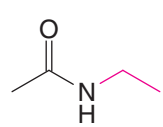
Amides that have no substituent on nitrogen are named by dropping **-ic acid** from the common name of the acid (or *-oic acid* from the substitutive name) and then adding **-amide**. Alkyl groups on the nitrogen atom of amides are named as substituents, and the named substituent is prefaced by *N*- or *N*,*N*-. Examples are



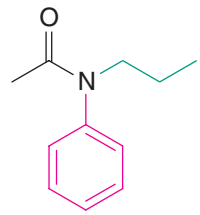
Acetamide
(ethanamide)
mp 82 °C; bp 221 °C



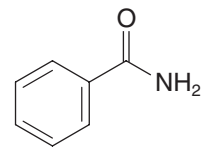
***N*,*N*-Dimethylacetamide**
mp −20 °C; bp 166 °C



***N*-Ethylacetamide**
bp 205 °C



***N*-Phenyl-*N*-propylacetamide**
mp 49 °C; bp 266 °C at 712 torr



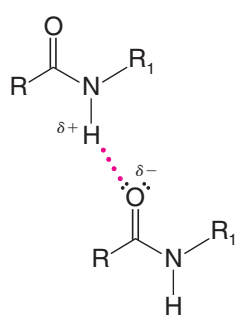
Benzamide
mp 130 °C; bp 290 °C

- Amides with nitrogen atoms bearing one or two hydrogen atoms are able to form strong hydrogen bonds to each other.

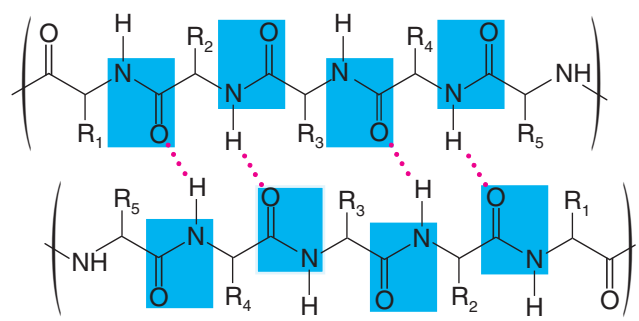
Such amides have high melting points and boiling points. On the other hand, molecules of *N*,*N*-disubstituted amides cannot form strong hydrogen bonds to each other, and they have lower melting points and boiling points. The melting and boiling data given above illustrate this trend.

- Hydrogen bonding between amide groups plays a key role in the way proteins and peptides fold to achieve their overall shape (Chapter 24).

Proteins and peptides (short proteins) are polymers of amino acids joined by amide groups. One feature common to the structure of many proteins is the β sheet, shown below:



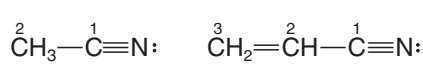
Hydrogen bonding (red dots) between amide molecules



Hydrogen bonding between amide groups of peptide chains. This interaction between chains (called a β sheet) is important to the structure of many proteins.

17.21 Nitriles

Carboxylic acids can be converted to nitriles and vice versa. In IUPAC substitutive nomenclature, acyclic nitriles are named by adding the suffix *-nitrile* to the name of the corresponding hydrocarbon. The carbon atom of the —C≡N group is assigned number 1. Additional examples of nitriles were presented in Section 2.11 with other functional groups of organic molecules. The name acetonitrile is an acceptable common name for CH_3CN, and acrylonitrile is an acceptable common name for $CH_2{=}CHCN$:



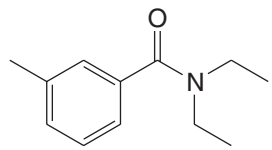
Ethanenitrile (acetonitrile)

Propenenitrile (acrylonitrile)

SOLVED PROBLEM 17.4

N,*N*-Diethyl-3-methylbenzamide (also called *N*,*N*-diethyl-*m*-toluamide, or DEET) is used in many insect repellants. Write its structure.

ANSWER:



DEET

PRACTICE PROBLEM 17.4

Write structural formulas for the following:

(a) Methyl propanoate
(b) Ethyl *p*-nitrobenzoate
(c) Dimethyl malonate
(d) *N*,*N*-Dimethylbenzamide
(e) Pentanenitrile
(f) Dimethyl phthalate
(g) Dipropyl maleate
(h) *N*,*N*-Dimethylformamide
(i) 2-Bromopropanoyl bromide
(j) Diethyl succinate

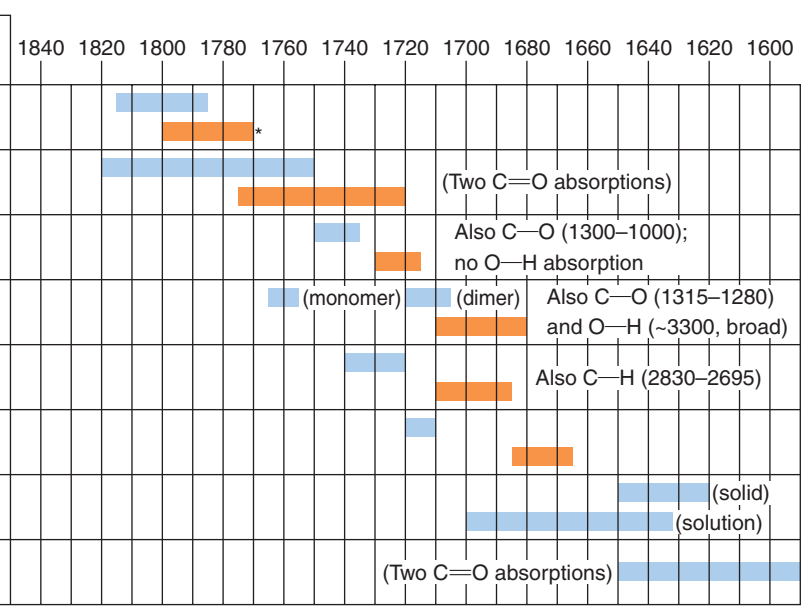
17.2J Spectroscopic Properties of Acyl Compounds

IR Spectra Infrared spectroscopy is of considerable importance in identifying carboxylic acids and their derivatives. The C=O stretching band is one of the most prominent in their IR spectra since it is always a strong band. Figure 17.2 gives the location of this band for most acyl compounds.

- The C=O stretching band occurs at different frequencies for acids, esters, and amides, and its precise location is often helpful in structure determination.
- Conjugation and electron-donating groups bonded to the carbonyl shift the location of the C=O absorption to lower frequencies.

Helpful Hint
Infrared spectroscopy is useful for classifying acyl compounds.

Functional Group	Approximate Frequency Range (cm^{-1})
Acid chloride	1815–1785 1800–1770 (conj.)
Acid anhydride	1820–1750 1775–1720 (conj.)
Ester/lactone	1750–1735 1730–1715 (conj.)
Carboxylic acid	~1760 or 1720–1705 1710–1680 (conj.)
Aldehyde	1740–1720 1710–1685 (conj.)
Ketone	1720–1710 1685–1665 (conj.)
Amide/lactam	1700–1620
Carboxylate salt	1650–1550



*Orange bars represent absorption ranges for conjugated species.

FIGURE 17.2 Approximate carbonyl IR absorption frequencies. (Frequency ranges based on Silverstein and Webster, reprinted with permission of John Wiley & Sons, Inc. from Silverstein, R. and Webster, F. X., *Spectrometric Identification of Organic Compounds*, Sixth Edition. Copyright 1998.)

- Electron-withdrawing groups bonded to the carbonyl shift the C=O absorption to higher frequencies.
- The hydroxyl groups of carboxylic acids also give rise to a broad peak in the 2500–3100-cm^{-1} region arising from O—H stretching vibrations.
- The N—H stretching vibrations of amides absorb between 3140 and 3500 cm^{-1}.

Presence or absence of an O—H or N—H absorption can be an important clue as to which carbonyl functional group is present in an unknown compound.

Figure 17.3 shows an annotated spectrum of propanoic acid. Nitriles show an intense and characteristic infrared absorption band near 2250 cm^{-1} that arises from stretching of the carbon–nitrogen triple bond.

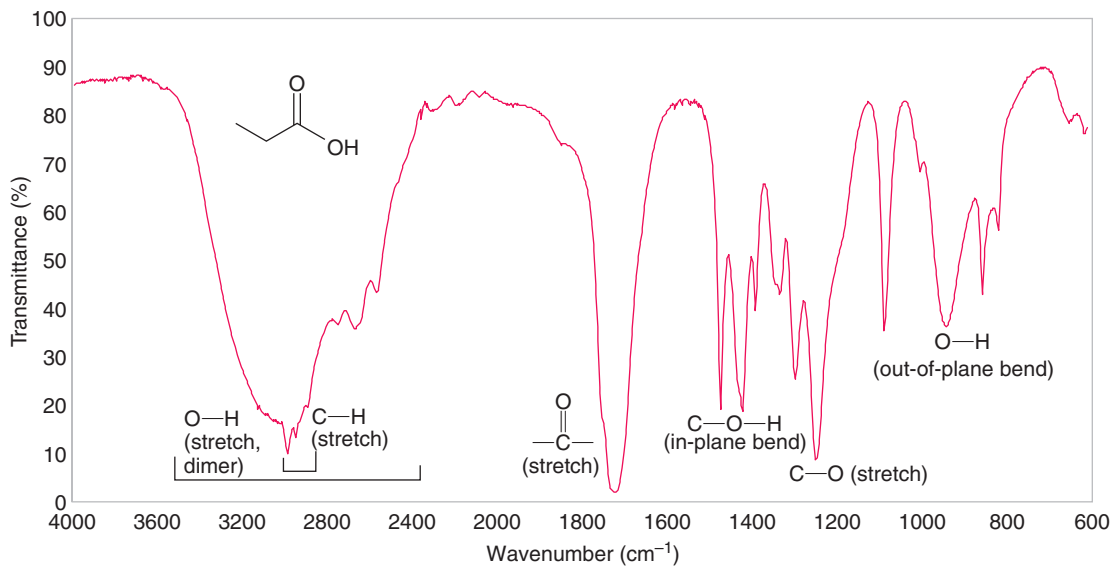


FIGURE 17.3 The infrared spectrum of propanoic acid.

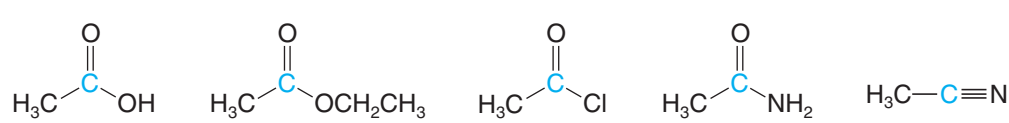
^{1}H NMR Spectra

- The acidic protons of carboxylic acids are highly deshielded and absorb far downfield in the δ 10–12 region.
- The protons of the α carbon of carboxylic acids absorb in the δ 2.0–2.5 region.

Figure 17.4 gives an annotated ^{1}H NMR spectrum of an ester, methyl propanoate; it shows the normal splitting pattern (quartet and triplet) of an ethyl group, and, as we would expect, it shows an unsplit methyl group.

^{13}C NMR Spectra

- The carbonyl carbon of carboxylic acids and their derivatives occurs downfield in the δ 160–180 region (see the following examples), but not as far downfield as for aldehydes and ketones (δ 180–220).
- The nitrile carbon is not shifted so far downfield and absorbs in the δ 115–120 region.



^{13}C NMR chemical shifts for the carbonyl or nitrile carbon atom

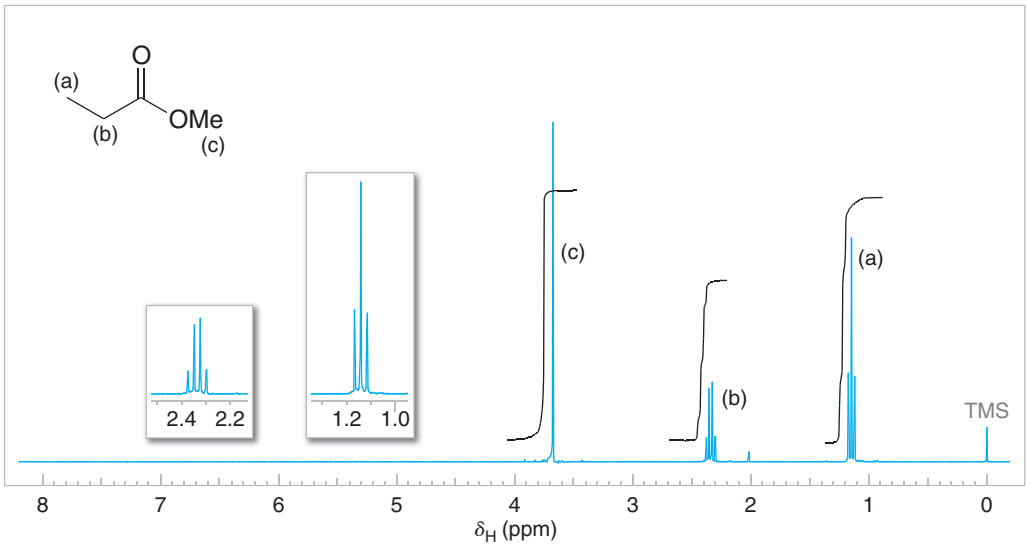
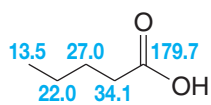


FIGURE 17.4 The 300-MHz ^{1}H NMR spectrum of methyl propanoate. Expansions of the signals are shown in the offset plots.

The carbon atoms of the alkyl groups of carboxylic acids and their derivatives have ^{13}C chemical shifts much further upfield. The chemical shifts for each carbon of pentanoic acid are as follows:

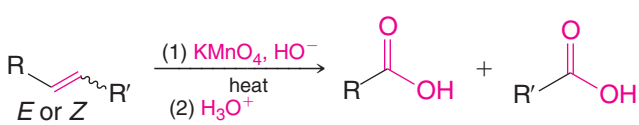


^{13}C NMR chemical shifts (δ)

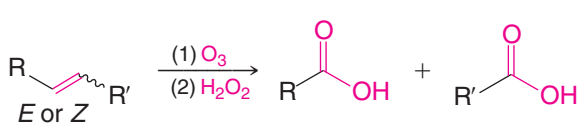
17.3 PREPARATION OF CARBOXYLIC ACIDS

Most of the methods for the preparation of carboxylic acids have been presented previously:

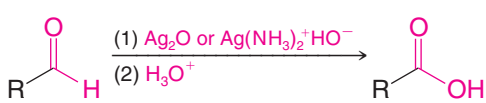
1. **By oxidation of alkenes.** We learned in Section 8.17A that alkenes can be oxidized to carboxylic acids with hot alkaline $KMnO_4$:

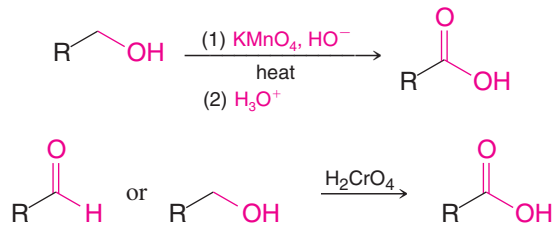


Alternatively, ozonides (Section 8.17B) can be subjected to an oxidative workup that yields carboxylic acids:

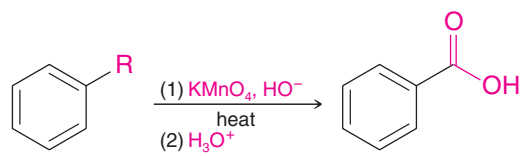


2. **By oxidation of aldehydes and primary alcohols.** Aldehydes can be oxidized to carboxylic acids with mild oxidizing agents such as $Ag(NH_3)_2^+HO^-$ (Section 16.12B). Primary alcohols can be oxidized with $KMnO_4$. Aldehydes and primary alcohols are oxidized to carboxylic acids with chromic acid (H_2CrO_4) in aqueous acetone (the Jones oxidation; Section 12.4C).

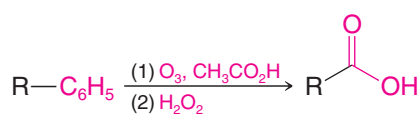




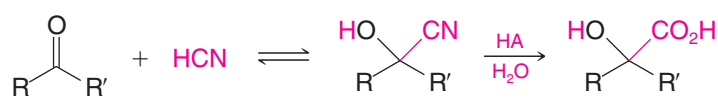
3. **By benzylic oxidation of alkylbenzenes.** Primary and secondary alkyl groups (but not 3° groups) directly attached to a benzene ring are oxidized by $KMnO_4$ to a $-CO_2H$ group (Section 15.13C):



4. **By oxidation of the benzene ring.** The benzene ring of an alkylbenzene can be converted to a carboxyl group by ozonolysis, followed by treatment with hydrogen peroxide (Section 15.13D):

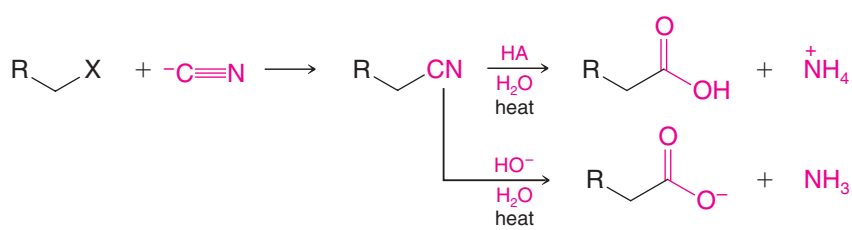


5. **By hydrolysis of cyanohydrins and other nitriles.** We saw, in Section 16.9, that aldehydes and ketones can be converted to **cyanohydrins** and that these can be hydrolyzed to α-hydroxy acids. In the hydrolysis the $-CN$ group is converted to a $-CO_2H$ group. The mechanism of nitrile hydrolysis is discussed in Section 17.8H:

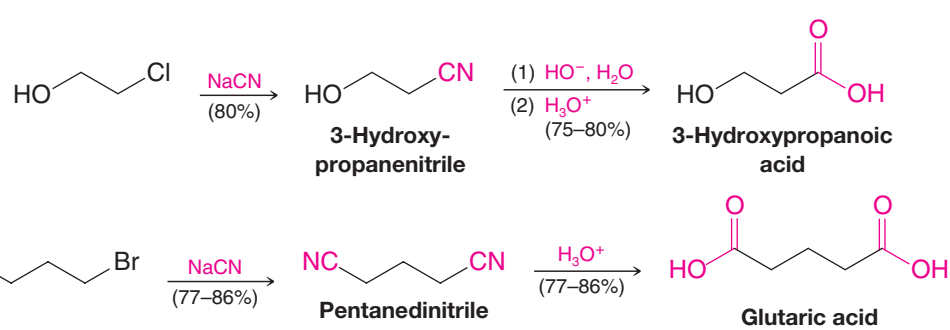


Nitriles can also be prepared by nucleophilic substitution reactions of alkyl halides with sodium cyanide. Hydrolysis of the nitrile yields a carboxylic acid *with a chain one carbon atom longer* than the original alkyl halide:

General Reaction

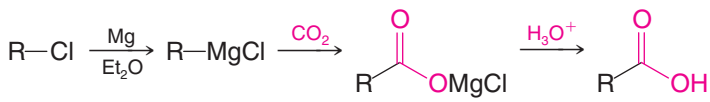


Specific Examples

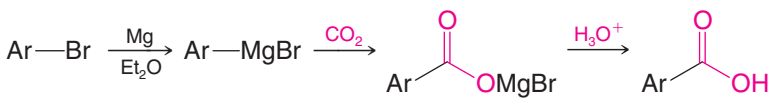


This synthetic method is generally limited to the use of *primary alkyl halides*. The cyanide ion is a relatively strong base, and the use of a secondary or tertiary alkyl halide leads primarily to an alkene (through E2 elimination) rather than to a nitrile (through S_N2 substitution). Aryl halides (except for those with ortho and para nitro groups) do not react with sodium cyanide.

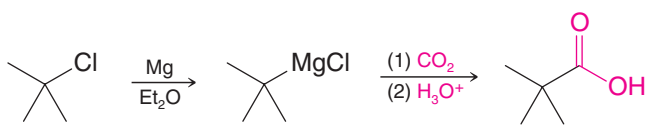
6. **By carbonation of Grignard reagents.** Grignard reagents react with carbon dioxide to yield magnesium carboxylates. Acidification produces carboxylic acids:



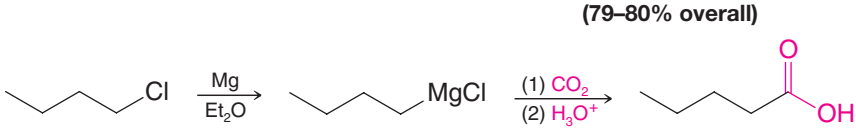
or



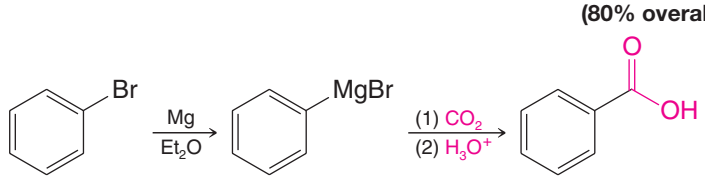
This synthesis of carboxylic acids is applicable to primary, secondary, tertiary, allyl, benzyl, and aryl halides, provided they have no groups incompatible with a Grignard reaction (see Section 12.8B):



***tert*-Butyl chloride** — **2,2-Dimethylpropanoic acid (79–80% overall)**



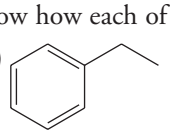
Butyl chloride — **Pentanoic acid (80% overall)**

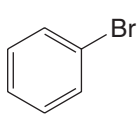


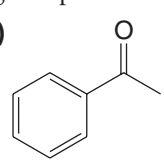
Bromobenzene — **Benzoic acid (85%)**

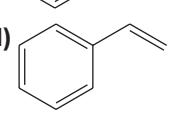
PRACTICE PROBLEM 17.5

Show how each of the following compounds could be converted to benzoic acid:

(a) 

(b) 

(c) 

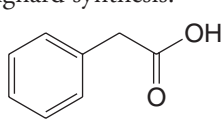
(d) 

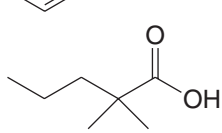
(e) Benzyl alcohol

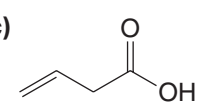
(f) Benzaldehyde

PRACTICE PROBLEM 17.6

Show how you would prepare each of the following carboxylic acids through a Grignard synthesis:

(a) 

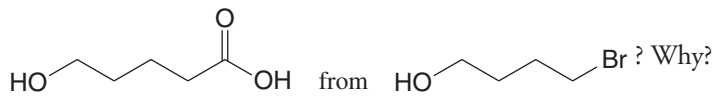
(b) 

(c) 

(d) 4-Methylbenzoic acid

(e) Hexanoic acid

PRACTICE PROBLEM 17.7 **(a)** Which of the carboxylic acids in Practice Problem 17.6 could be prepared by a nitrile synthesis as well? **(b)** Which synthesis, Grignard or nitrile, would you choose to prepare

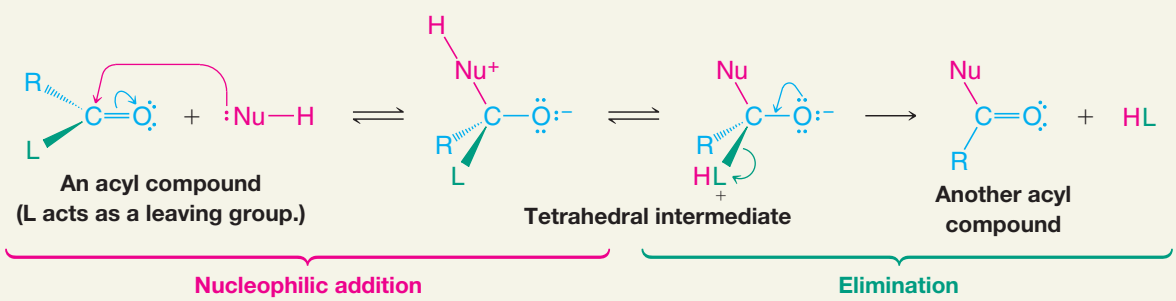


? Why?

17.4 ACYL SUBSTITUTION: NUCLEOPHILIC ADDITION–ELIMINATION AT THE ACYL CARBON

The reactions of carboxylic acids and their derivatives are characterized by **nucleophilic addition–elimination** at their acyl (carbonyl) carbon atoms. The result is a substitution at the acyl carbon. Key to this mechanism is formation of a **tetrahedral intermediate** that returns to a carbonyl group after the elimination of a leaving group. We shall encounter many reactions of this general type, as shown in the following box.

A MECHANISM FOR THE REACTION — Acyl Substitution by Nucleophilic Addition–Elimination



Helpful Hint

If you bear in mind the general mechanism for acyl substitution, you will see the common theme among reactions in this chapter.

Many reactions like this occur in living organisms, and biochemists call them **acyl transfer reactions**. Acetyl-coenzyme A, discussed in Special Topic E in *WileyPLUS*, often serves as a biochemical acyl transfer agent. Acyl **substitution reactions** are of tremendous importance in industry as well, as described in the chapter opening essay and Special Topic C in *WileyPLUS*.

- The initial step in an acyl substitution reaction is nucleophilic addition at the carbonyl carbon atom. This step is facilitated by the relative steric openness of the carbonyl carbon atom and the ability of the carbonyl oxygen atom to accommodate an electron pair of the carbon–oxygen double bond.
- In the second step the tetrahedral intermediate eliminates a leaving group (**L** in the mechanism above); this **elimination** leads to regeneration of the carbon–oxygen double bond and to a substitution product.

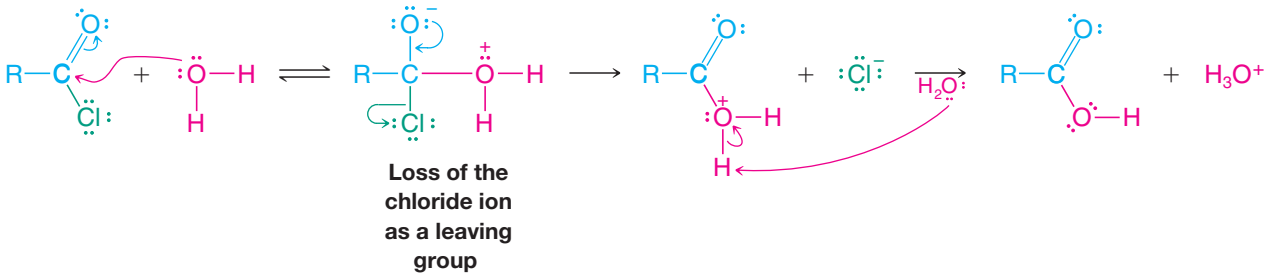
The overall process, therefore, is **acyl substitution** by a **nucleophilic addition–elimination** mechanism.

Acyl compounds react as they do because they all have good, or reasonably good, leaving groups (or they can be protonated to form good leaving groups) attached to the carbonyl carbon atom.

- Acyl substitution requires a leaving group at the carbonyl carbon.

An acyl chloride, for example, generally reacts by losing a *chloride ion*—a very weak base and thus a very good leaving group. The reaction of an acyl chloride with water is an example.

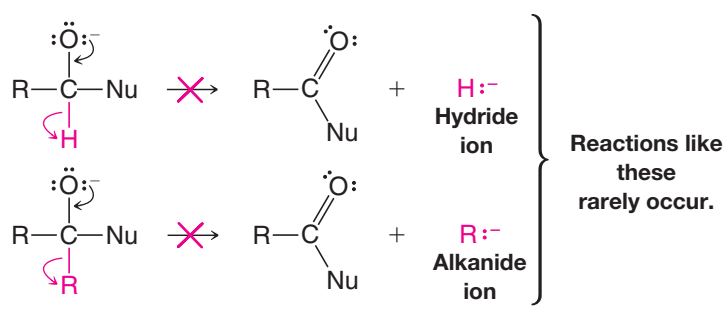
Specific Example



An acid anhydride generally reacts by losing *a carboxylate anion* or a molecule of a *carboxylic acid*—both are weak bases and good leaving groups.

As we shall see later, esters generally undergo nucleophilic addition–elimination by losing a molecule of an *alcohol* (Section 17.7B), acids react by losing a molecule of *water* (Section 17.7A), and amides react by losing a molecule of *ammonia* or of an *amine* (Section 17.8F). All of the molecules lost in these reactions are weak bases and are reasonably good leaving groups.

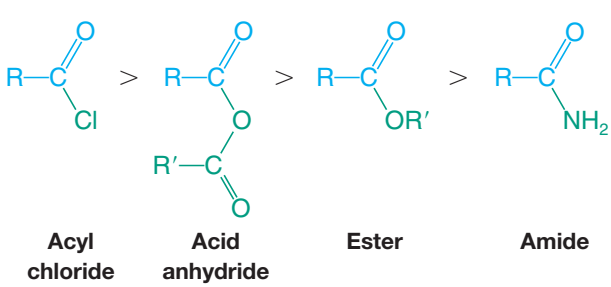
For an aldehyde or ketone to react by nucleophilic addition–elimination, the tetrahedral intermediate would need to eject a hydride ion ($H:^-$) or an alkanide ion ($R:^-$). Both are *very powerful bases*, and both are therefore *very poor leaving groups*:



[The haloform reaction (Section 18.3C) is one of the rare instances in which an alkanide anion can act as a leaving group, but then only, as we shall see, because the leaving group is a weakly basic trihalomethyl anion.]

17.4A Relative Reactivity of Acyl Compounds

Of the acid derivatives that we study in this chapter, acyl chlorides are the most reactive toward nucleophilic addition–elimination, and amides are the least reactive. In general, the overall order of reactivity is



The green groups in the structures above can be related to the green **L** group in the Mechanism for the Reaction box at the beginning of Section 17.4.

- The general order of reactivity of acid derivatives can be explained by taking into account the basicity of the leaving groups.

When acyl chlorides react, the leaving group is a *chloride ion*. When acid anhydrides react, the leaving group is a carboxylic acid or a carboxylate ion. When esters react, the leaving group is an alcohol, and when amides react, the leaving group is an amine (or ammonia). Of all of these bases, chloride ions are the *weakest bases* and acyl chlorides are the *most reactive* acyl compounds. Amines (or ammonia) are the *strongest bases* and so amides are the *least reactive* acyl compounds.

17.4B Synthesis of Acid Derivatives

As we begin now to explore the syntheses of carboxylic acid derivatives, we shall find that in many instances one acid derivative can be synthesized through a nucleophilic addition–elimination reaction of another. The order of reactivities that we have presented gives us a clue as to which syntheses are practical and which are not. In general, ***less reactive acyl compounds can be synthesized from more reactive ones, but the reverse is usually difficult and, when possible, requires special reagents.***

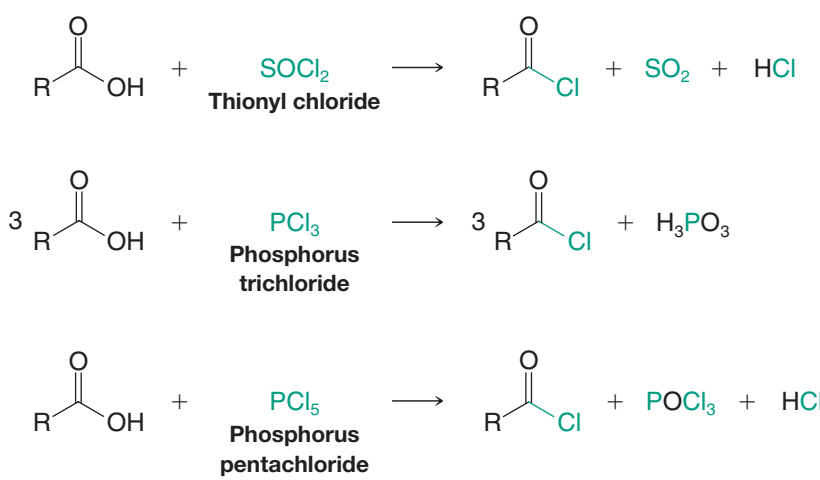
- Synthesis of acid derivatives by acyl substitution requires that the reactant have a better leaving group at the acyl carbon than the product.

17.5 ACYL CHLORIDES

17.5A Synthesis of Acyl Chlorides

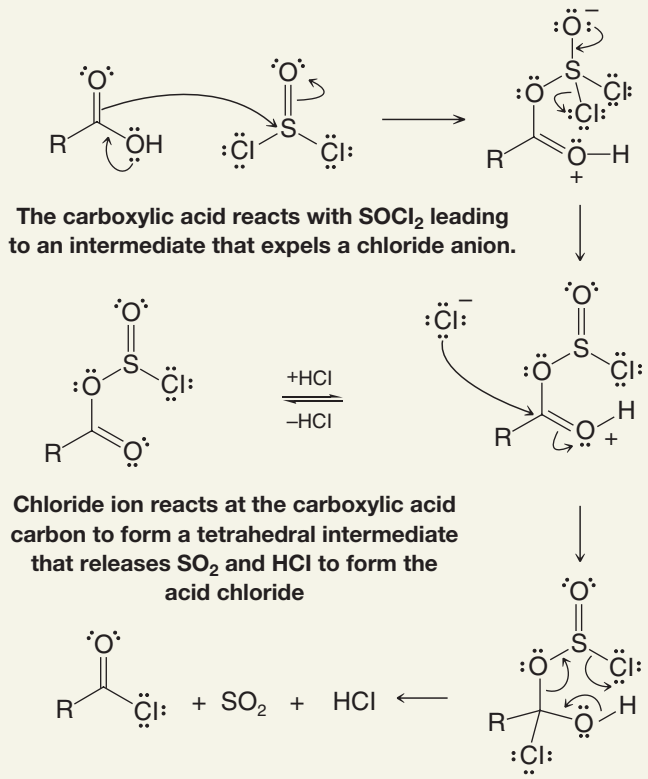
Since acyl chlorides are the most reactive of the acid derivatives, we must use special reagents to prepare them. We use other acid chlorides, *the acid chlorides of inorganic acids*: PCl_5 (an acid chloride of phosphoric acid), PCl_3 (an acid chloride of phosphorous acid), and $SOCl_2$ (an acid chloride of sulfurous acid). All of these reagents react with carboxylic acids to give acyl chlorides in good yield:

General Reactions



These reactions all involve nucleophilic addition–elimination by a chloride ion on a highly reactive intermediate: a protonated acyl chlorosulfite, a protonated acyl chlorophosphite, or a protonated acyl chlorophosphate. These intermediates contain even better acyl leaving groups than the acyl chloride product. Thionyl chloride, for example, reacts with a carboxylic acid in the following way:

A MECHANISM FOR THE REACTION — Synthesis of Acyl Chlorides Using Thionyl Chloride



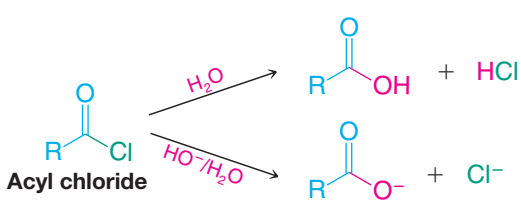
17.5B Reactions of Acyl Chlorides

Because acyl chlorides are the most reactive of the acyl derivatives, they are easily converted to less reactive ones.

- Often the best synthetic route to an anhydride, an ester, or an amide is synthesis of an acyl chloride from the carboxylic acid and then conversion of the acyl chloride to the desired acyl derivative.

The scheme given in Fig. 17.5 illustrates how this can be done. We examine these reactions in detail in Sections 17.6–17.8.

Acyl chlorides also react with water and (even more rapidly) with aqueous base, but these reactions are usually not carried out deliberately because they destroy the useful acyl chloride reactant by regenerating either the carboxylic acid or its salt:



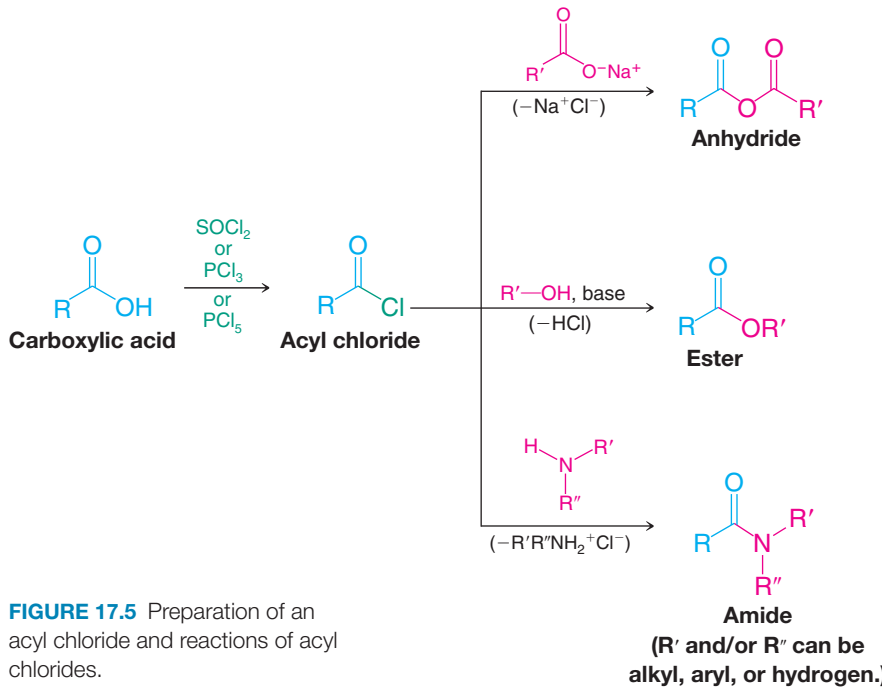
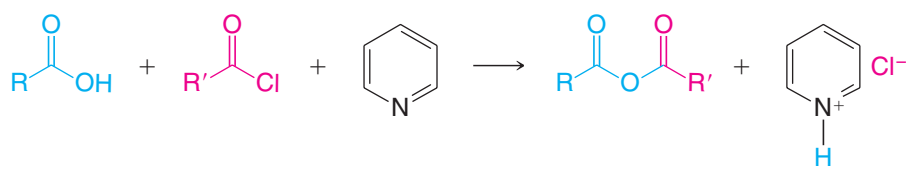


FIGURE 17.5 Preparation of an acyl chloride and reactions of acyl chlorides.

17.6 CARBOXYLIC ACID ANHYDRIDES

17.6A Synthesis of Carboxylic Acid Anhydrides

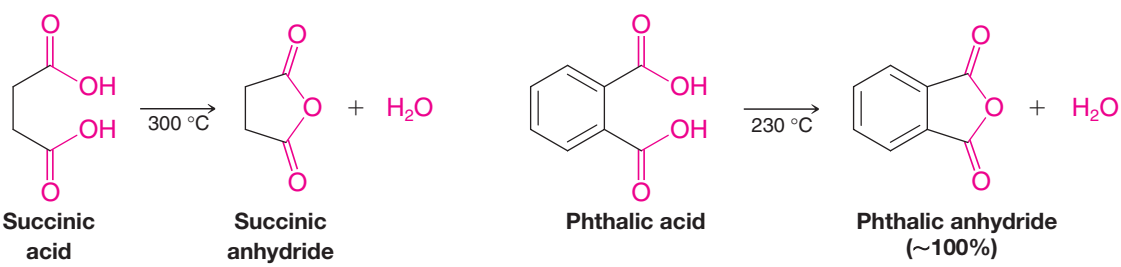
Carboxylic acids react with acyl chlorides in the presence of pyridine to give carboxylic acid anhydrides. Pyridine deprotonates the carboxylic acid, enhancing its nucleophilicity.



This method is frequently used in the laboratory for the preparation of anhydrides. The method is quite general and can be used to prepare mixed anhydrides ($R \neq R'$) or symmetric anhydrides ($R = R'$).

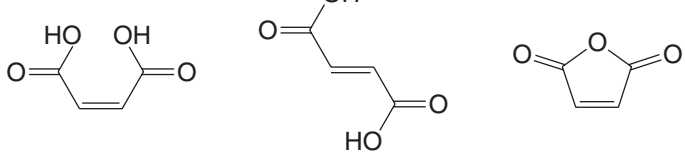
Sodium salts of carboxylic acids also react with acyl chlorides to give anhydrides:

Cyclic anhydrides can sometimes be prepared simply by heating the appropriate dicarboxylic acid. This method succeeds, however, only when anhydride formation leads to a five- or six-membered ring:



PRACTICE PROBLEM 17.8

When maleic acid is heated to 200 °C, it loses water and becomes maleic anhydride. Fumaric acid, a diastereomer of maleic acid, requires a much higher temperature before it dehydrates; when it does, it also yields maleic anhydride. Provide an explanation for these observations.



Maleic acid | Fumaric acid | Maleic anhydride

17.6B Reactions of Carboxylic Acid Anhydrides

Because carboxylic acid anhydrides are highly reactive, they can be used to prepare esters and amides (Fig. 17.6). We study these reactions in detail in Sections 17.7 and 17.8.

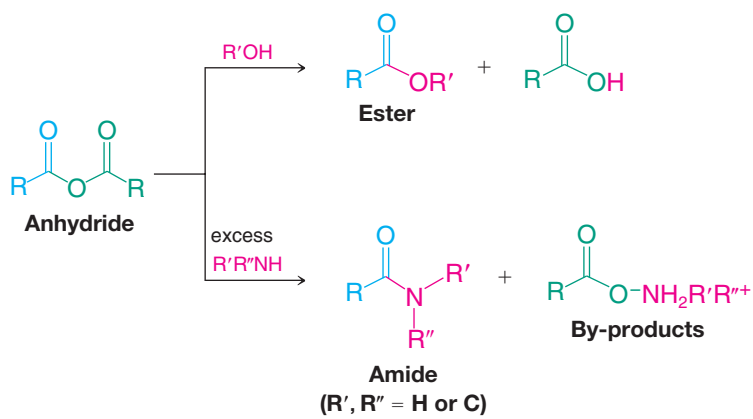
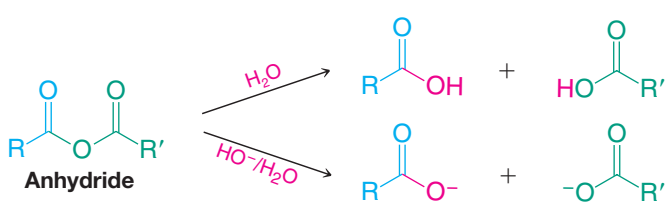


FIGURE 17.6 Reactions of carboxylic acid anhydrides.

Carboxylic acid anhydrides also undergo hydrolysis:

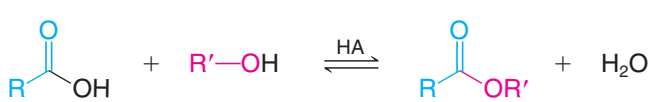


17.7 ESTERS

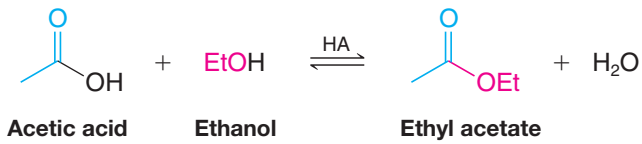
17.7A Synthesis of Esters: Esterification

Carboxylic acids react with alcohols to form esters through a condensation reaction known as **esterification**:

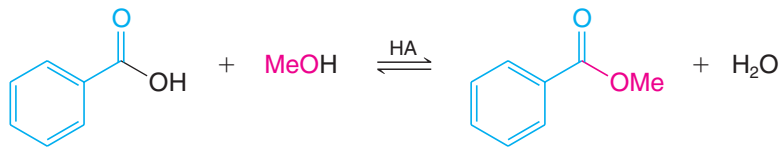
General Reaction



Specific Examples



Acetic acid **Ethanol** **Ethyl acetate**

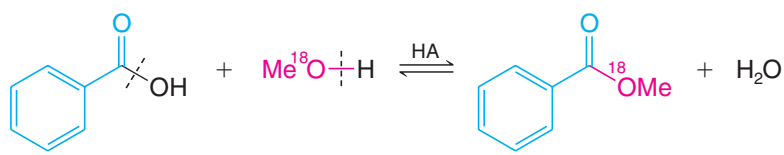


Benzoic acid **Methanol** **Methyl benzoate**

- Acid-catalyzed esterifications, such as these examples, are called Fischer esterifications.

Fischer esterifications proceed very slowly in the absence of strong acids, but they reach equilibrium within a matter of a few hours when an acid and an alcohol are refluxed with a small amount of concentrated sulfuric acid or hydrogen chloride. Since the position of equilibrium controls the amount of the ester formed, the use of an excess of either the carboxylic acid or the alcohol increases the yield based on the limiting reagent. Just which component we choose to use in excess will depend on its availability and cost. The yield of an esterification reaction can also be increased by removing water from the reaction mixture as it is formed.

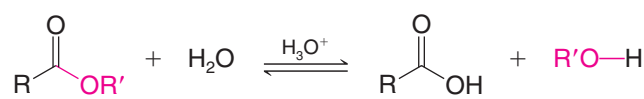
When benzoic acid reacts with methanol that has been labeled with ^{18}O, the labeled oxygen appears in the ester. This result reveals just which bonds break in the esterification:



The results of the labeling experiment and the fact that esterifications are acid catalyzed are both consistent with the mechanism that follows. This mechanism is typical of acid-catalyzed nucleophilic addition–elimination reactions at acyl carbon atoms.

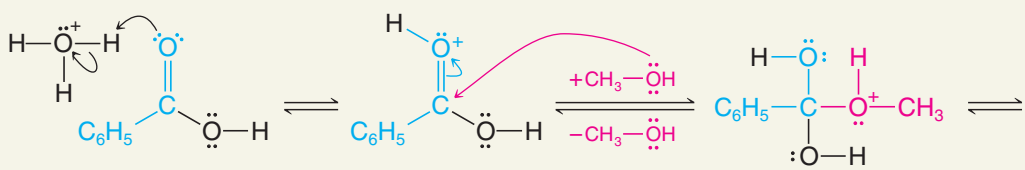
If we follow the forward reactions in this mechanism, we have the mechanism for the *acid-catalyzed esterification of an acid*. If, however, we follow the reverse reactions, we have the mechanism for the *acid-catalyzed hydrolysis of an ester*:

Acid-Catalyzed Ester Hydrolysis



Which result we obtain will depend on the conditions we choose. If we want to esterify an acid, we use an excess of the alcohol and, if possible, remove the water as it is formed. If we want to hydrolyze an ester, we use a large excess of water; that is, we reflux the ester with dilute aqueous HCl or dilute aqueous H_2SO_4.

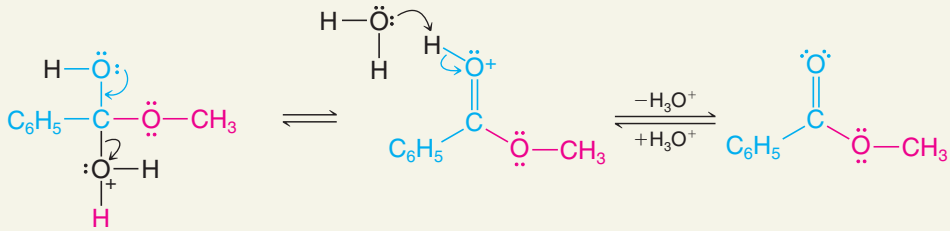
A MECHANISM FOR THE REACTION — Acid-Catalyzed Esterification



The carboxylic acid accepts a proton from the strong acid catalyst.

The alcohol attacks the protonated carbonyl group to give a tetrahedral intermediate.

A proton is lost at one oxygen atom and gained at another.



Loss of a molecule of water gives a protonated ester.

Transfer of a proton to a base leads to the ester.

PRACTICE PROBLEM 17.9

Where would you expect to find the labeled oxygen if you carried out an acid-catalyzed hydrolysis of methyl benzoate in ^{18}O-labeled water? Write a detailed mechanism to support your answer.

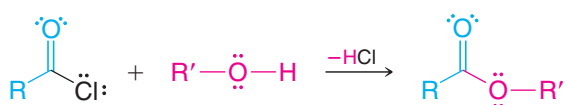
Steric factors strongly affect the rates of acid-catalyzed hydrolyses of esters. Large groups near the reaction site, whether in the alcohol component or the acid component, slow both reactions markedly. Tertiary alcohols, for example, react so slowly in acid-catalyzed esterifications that they usually undergo elimination instead. However, they can be converted to esters safely through the use of acyl chlorides and anhydrides in the ways that follow.

Esters from Acyl Chlorides

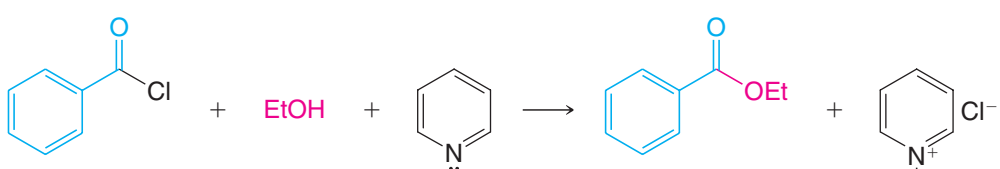
- The reaction of acyl chlorides with alcohols is one of the best ways to synthesize an ester.

The reaction of an acyl chloride with an alcohol to form an ester occurs rapidly and does not require an acid catalyst. Pyridine is often added to the reaction mixture to react with the HCl that forms. (Pyridine may also react with the acyl chloride to form an acylpyridinium ion, an intermediate that is even more reactive toward the nucleophile than the acyl chloride.)

General Reaction



Specific Example



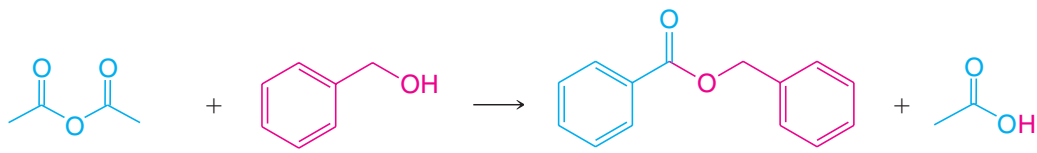
Benzoyl chloride

Ethyl benzoate (80%)

Esters from Carboxylic Acid Anhydrides Carboxylic acid anhydrides also react with alcohols to form esters in the absence of an acid catalyst.

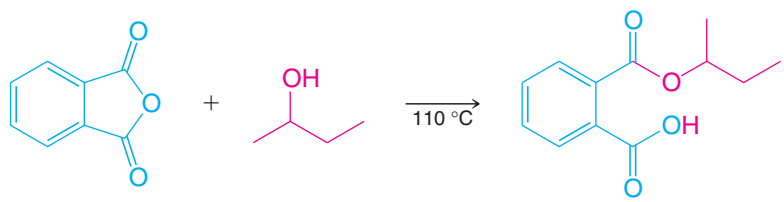
General Reaction

Specific Example

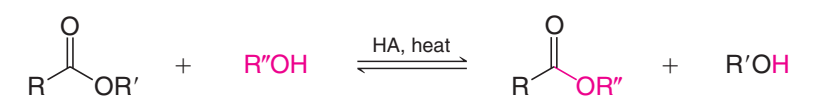


- Ester synthesis is often accomplished best by the reaction of an alcohol with an acyl chloride or anhydride. These reagents avoid the use of a strong acid, as is needed for acid-catalyzed esterification. A strong acid may cause side reactions depending on what other functional groups are present.

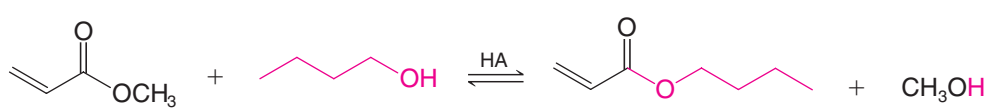
Cyclic anhydrides react with one molar equivalent of an alcohol to form compounds that are *both esters and acids*:



PRACTICE PROBLEM 17.10 Esters can also be synthesized by **transesterification**:



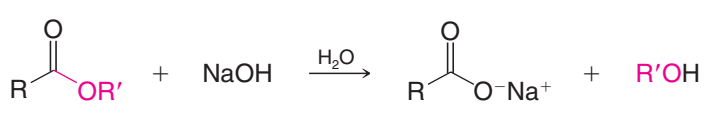
In this procedure we shift the equilibrium to the right by allowing the low-boiling alcohol to distill from the reaction mixture. The mechanism for transesterification is similar to that for an acid-catalyzed esterification (or an acid-catalyzed ester hydrolysis). Write a detailed mechanism for the following transesterification:



17.7B Base-Promoted Hydrolysis of Esters: Saponification

- Esters undergo *base-promoted hydrolysis* as well as acid hydrolysis.

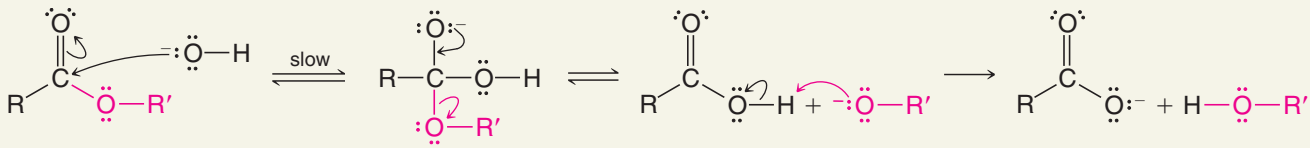
Base-promoted hydrolysis is called **saponification**, from the Latin word *sapo*, for soap (see Section 23.2C). Refluxing an ester with aqueous sodium hydroxide, for example, produces an alcohol and the sodium salt of the acid:



The carboxylate ion is very unreactive toward nucleophilic substitution because it is negatively charged. Base-promoted hydrolysis of an ester, as a result, is an essentially irreversible reaction.

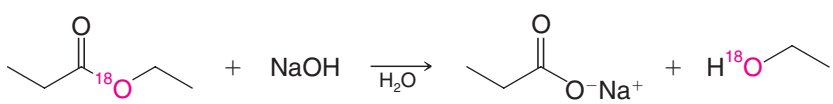
The mechanism for base-promoted hydrolysis of an ester also involves a nucleophilic addition–elimination at the acyl carbon.

A MECHANISM FOR THE REACTION — Base-Promoted Hydrolysis of an Ester

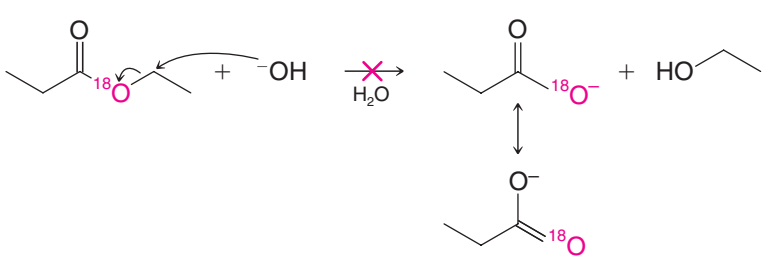


A hydroxide ion attacks the carbonyl carbon atom. **The tetrahedral intermediate expels an alkoxide ion.** **Transfer of a proton leads to the products of the reaction.**

Evidence for this mechanism comes from studies done with isotopically labeled esters. When ethyl propanoate labeled with ^{18}O in the ether-type oxygen of the ester (below) is subjected to hydrolysis with aqueous NaOH, all of the ^{18}O shows up in the ethanol that is produced. None of the ^{18}O appears in the propanoate ion:

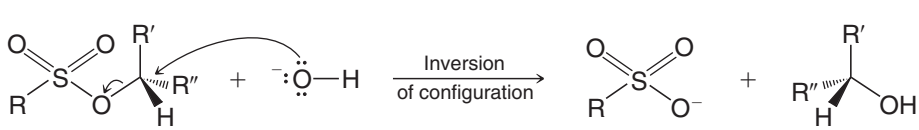


This labeling result is completely consistent with the mechanism given above (outline the steps for yourself and follow the labeled oxygen through to the products). If the hydroxide ion had attacked the alkyl carbon instead of the acyl carbon, the alcohol obtained would not have been labeled. Attack at the alkyl carbon is almost never observed. (For one exception see Practice Problem 17.12.)



These products are not formed.

Although nucleophilic attack at the alkyl carbon seldom occurs with esters of carboxylic acids, it is the preferred mode of attack with esters of sulfonic acids (e.g., tosylates, mesylates, and triflates; Section 11.10).

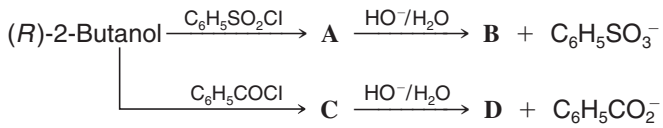


An alkyl sulfonate

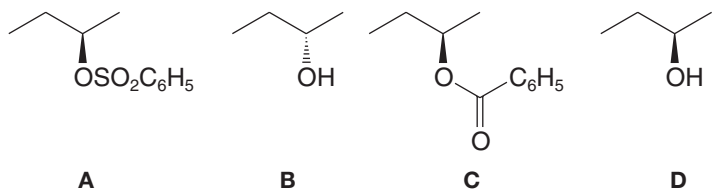
This mechanism is preferred with alkyl sulfonates.

SOLVED PROBLEM 17.5

Give stereochemical formulas for **A–D**. [*Hint*: **B** and **D** are enantiomers of each other.]



STRATEGY AND ANSWER: Compound **A** is a benzenesulfonate ester, which forms with retention of configuration from (*R*)-2-butanol. **B** is the S_N2 product formed by reaction with hydroxide, which occurs with **inversion** of configuration. **C** is a benzoate ester, formation of which does not affect the configuration at the chirality center. Saponification of **C** to form **D** does not affect the chirality center either, since it is an acyl substitution reaction.



A **B** **C** **D**

PRACTICE PROBLEM 17.11

(a) Write stereochemical formulas for compounds **A–F**:

1. *cis*-3-Methylcyclopentanol + $C_6H_5SO_2Cl$ ⟶ **A** $\xrightarrow[\text{heat}]{HO^-}$ **B** + $C_6H_5SO_3^-$

2. *cis*-3-Methylcyclopentanol + $C_6H_5C(=O)Cl$ ⟶ **C** $\xrightarrow[\text{reflux}]{HO^-}$ **D** + $C_6H_5CO_2^-$

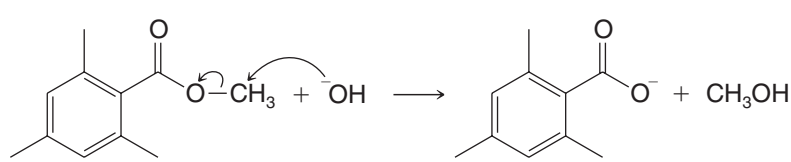
3. (*R*)-2-Bromooctane + $CH_3CO_2^-Na^+$ ⟶ **E** + NaBr $\xrightarrow[\text{(reflux)}]{HO^-,\ H_2O}$ **F**

4. (*R*)-2-Bromooctane + HO^- $\xrightarrow[\text{acetone}]{}$ **F** + Br^-

(b) Which of the last two methods, **3** or **4**, would you expect to give a higher yield of **F**? Why?

PRACTICE PROBLEM 17.12

Base-promoted hydrolysis of methyl mesitoate occurs through an attack on the alcohol carbon instead of the acyl carbon:

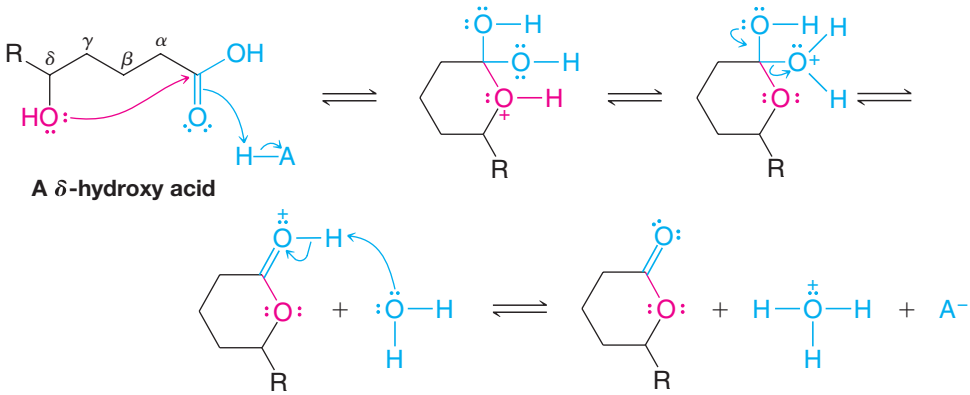


Methyl mesitoate

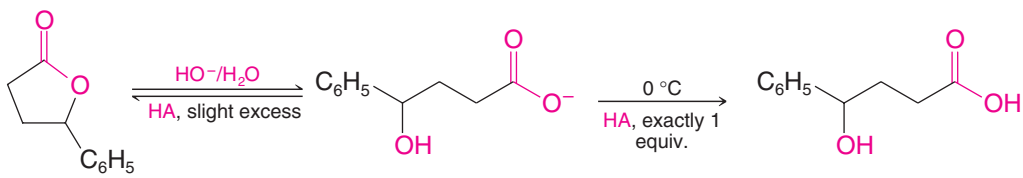
(a) Can you suggest a reason that accounts for this unusual behavior? **(b)** Suggest an experiment with labeled compounds that would confirm this mode of attack.

17.7C Lactones

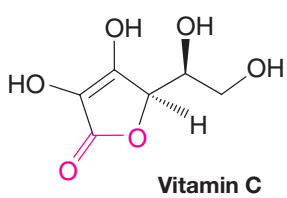
Carboxylic acids whose molecules have a hydroxyl group on a γ or δ carbon undergo an intramolecular esterification to give cyclic esters known as γ- or δ-*lactones*. The reaction is acid catalyzed:

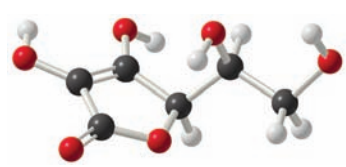


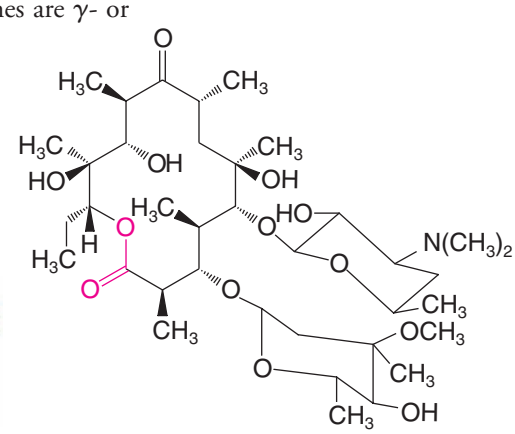
Lactones are hydrolyzed by aqueous base just as other esters are. Acidification of the sodium salt, however, may lead spontaneously back to the γ- or δ-lactone, particularly if excess acid is used:



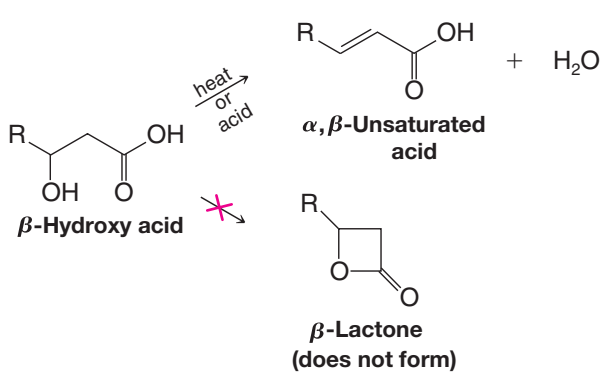
Many lactones occur in nature. Vitamin C (below), for example, is a γ-lactone. Some antibiotics, such as erythromycin and nonactin (Section 11.16), are lactones with very large rings (called macrocyclic lactones), but most naturally occurring lactones are γ- or δ-lactones; that is, most contain five- or six-membered rings.


Vitamin C
(ascorbic acid)




Erythromycin A

β-Lactones (lactones with four-membered rings) have been detected as intermediates in some reactions, and several have been isolated. They are highly reactive, however. If one attempts to prepare a β-lactone from a β-hydroxy acid, β elimination usually occurs instead:



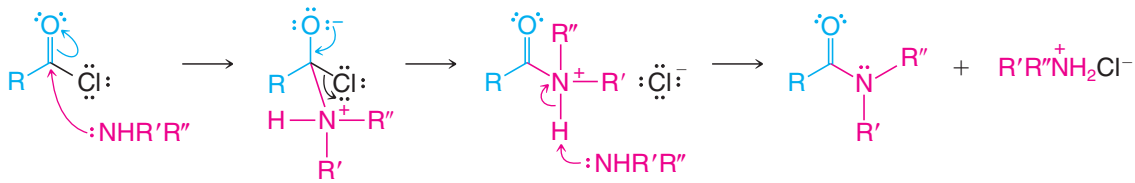
17.8 AMIDES

17.8A Synthesis of Amides

Amides can be prepared in a variety of ways, starting with acyl chlorides, acid anhydrides, esters, carboxylic acids, and carboxylate salts. All of these methods involve nucleophilic addition–elimination reactions by ammonia or an amine at an acyl carbon. As we might expect, acid chlorides are the most reactive and carboxylate anions are the least.

17.8B Amides from Acyl Chlorides

Primary amines, secondary amines, and ammonia all react rapidly with acid chlorides to form amides. An excess of ammonia or amine is used to neutralize the HCl that would be formed otherwise:



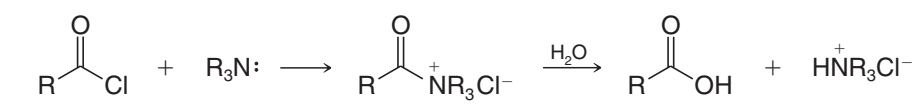
Reactant
Ammonia; R′, R″ = H
1° Amine; R′ = H, R″ = alkyl, aryl
2° Amine; R′, R″ = alkyl, aryl

Product
Unsubstituted amide; R′, R″ = H
***N*-Substituted amide; R′ = H, R″ = alkyl, aryl**
***N,N*-Disubstituted amide; R′, R″ = alkyl, aryl**

- The reaction of an amine with an acyl chloride is one of the most widely used laboratory methods for the synthesis of amides, because acyl chlorides are themselves easily prepared from carboxylic acids.

The reaction between an acyl chloride and an amine (or ammonia) usually takes place at room temperature (or below) and produces the amide in high yield.

Acyl chlorides also react with tertiary amines by a nucleophilic addition–elimination reaction. The acylammonium ion that forms, however, is not stable in the presence of water or any hydroxylic solvent:

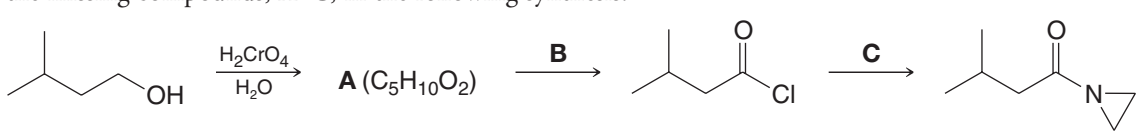


Acyl chloride **3° Amine** **Acylammonium chloride**

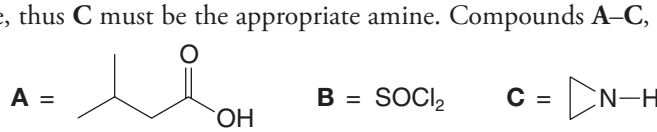
Acylpyridinium ions are probably involved as intermediates in those reactions of acyl chlorides that are carried out in the presence of pyridine.

SOLVED PROBLEM 17.6

Provide the missing compounds, **A**–**C**, in the following synthesis.

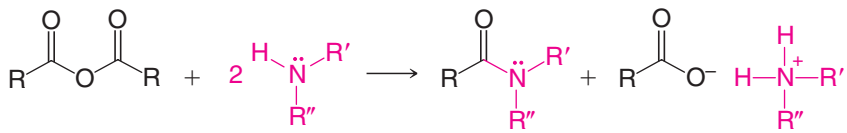


STRATEGY AND ANSWER: The first reaction is a chromic acid oxidation, leading to $C_5H_{10}O_2$, which is consistent with the carboxylic acid derived from 3-methyl-1-butanol. **B** must be a reagent by which we can prepare an acid chloride. The final product is an amide, thus **C** must be the appropriate amine. Compounds **A**–**C**, therefore, are as follows:



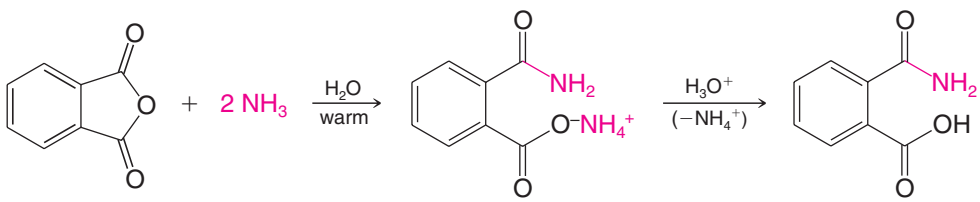
17.8C Amides from Carboxylic Anhydrides

Acid anhydrides react with ammonia and with primary and secondary amines to form amides through reactions that are analogous to those of acyl chlorides:

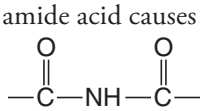


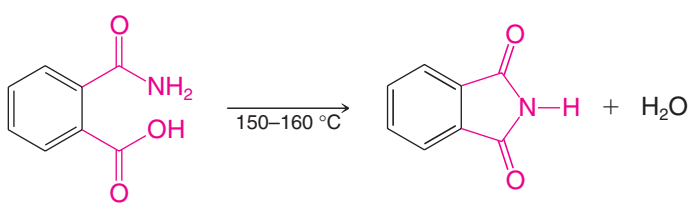
R′, R″ can be H, alkyl, or aryl.

Cyclic anhydrides react with ammonia or an amine in the same general way as acyclic anhydrides; however, the reaction yields a product that is both an amide and an ammonium salt. Acidifying the ammonium salt gives a compound that is both an amide and an acid:



Phthalic anhydride | **Ammonium phthalamate (94%)** | **Phthalamic acid (81%)**

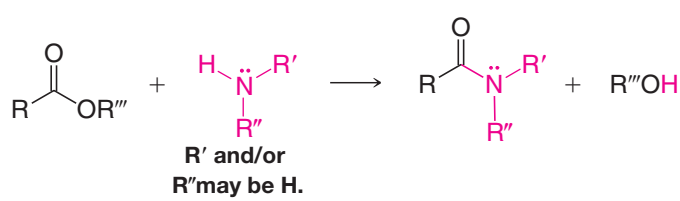
Heating the amide acid causes dehydration to occur and gives an *imide*. Imides contain the linkage  .



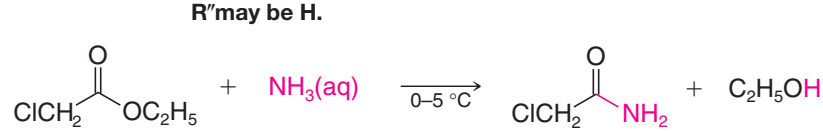
Phthalamic acid | **Phthalimide (~100%)**

17.8D Amides from Esters

Esters undergo nucleophilic addition–elimination at their acyl carbon atoms when they are treated with ammonia (called *ammonolysis*) or with primary and secondary amines. These reactions take place much more slowly than those of acyl chlorides and anhydrides, but they can still be synthetically useful:



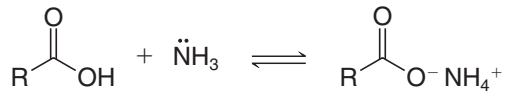
R′ and/or R″may be H.



Ethyl chloroacetate | **Chloroacetamide (62–87%)**

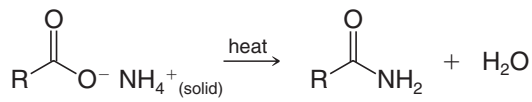
17.8E Amides from Carboxylic Acids and Ammonium Carboxylates

Carboxylic acids react with aqueous ammonia to form ammonium salts:



An ammonium carboxylate

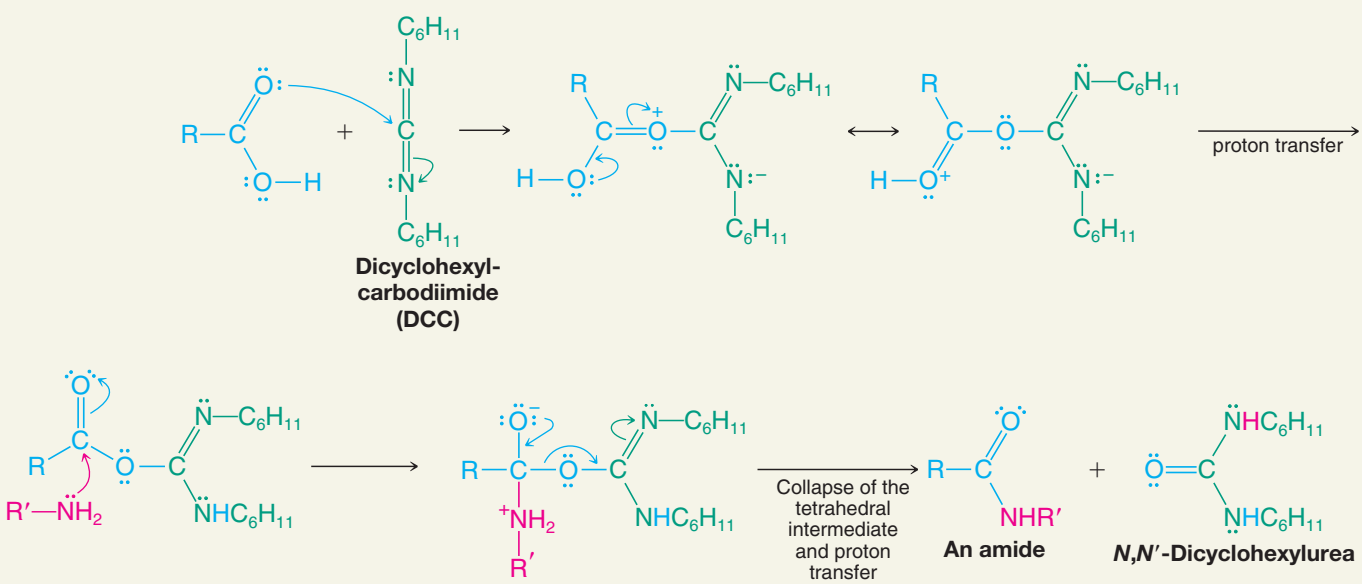
Because of the low reactivity of the carboxylate ion toward nucleophilic addition–elimination, further reaction does not usually take place in aqueous solution. However, if we evaporate the water and subsequently heat the dry salt, dehydration produces an amide:



This is generally a poor method for preparing amides. A much better method is to convert the acid to an acyl chloride and then treat the acyl chloride with ammonia or an amine (Section 17.8B).

Amides are of great importance in biochemistry. The linkages that join individual amino acids together to form proteins are primarily amide linkages. As a consequence, much research has been done to find convenient and mild ways for amide synthesis. Dialkylcarbodiimides (R—N═C═N—R), such as diisopropylcarbodiimide and dicyclohexylcarbodiimide (DCC), are especially useful reagents for amide synthesis. Dialkylcarbodiimides promote amide formation by reacting with the carboxyl group of an acid and activating it toward nucleophilic addition–elimination.

A MECHANISM FOR THE REACTION — DCC-Promoted Amide Synthesis

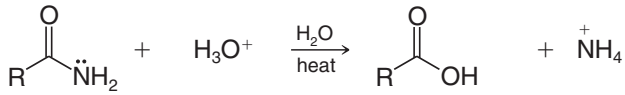


The intermediate in this synthesis does not need to be isolated, and both steps take place at room temperature. Amides are produced in very high yield. In Chapter 24 we shall see how diisopropylcarbodiimide is used in an automated synthesis of peptides.

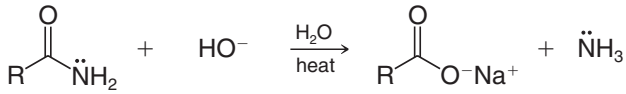
17.8F Hydrolysis of Amides

- Amides undergo hydrolysis when they are heated with aqueous acid or aqueous base.

Acidic Hydrolysis



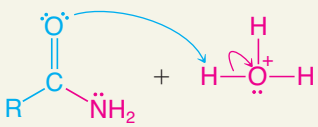
Basic Hydrolysis



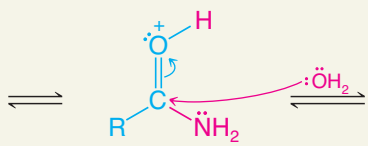
N-Substituted amides and *N*,*N*-disubstituted amides also undergo hydrolysis in aqueous acid or base. Amide hydrolysis by either method takes place more slowly than the corresponding hydrolysis of an ester. Thus, amide hydrolyses generally require the forcing conditions of heat and strong acid or base.

The mechanism for acid hydrolysis of an amide is similar to that given in Section 17.7A for the acid hydrolysis of an ester. Water acts as a nucleophile and attacks the protonated amide. The leaving group in the acidic hydrolysis of an amide is ammonia (or an amine).

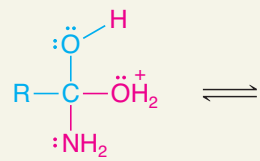
A MECHANISM FOR THE REACTION — Acidic Hydrolysis of an Amide



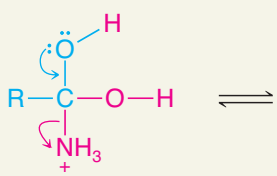
The amide carbonyl accepts a proton from the aqueous acid.



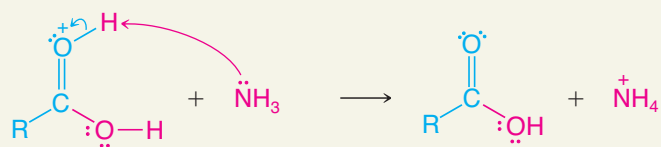
A water molecule attacks the protonated carbonyl to give a tetrahedral intermediate.



A proton is lost at one oxygen and gained at the nitrogen.



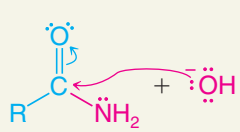
Loss of a molecule of ammonia gives a protonated carboxylic acid.



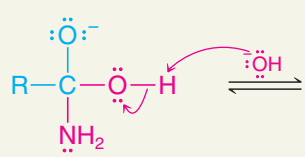
Transfer of a proton to ammonia leads to the carboxylic acid and an ammonium ion.

There is evidence that in basic hydrolyses of amides, hydroxide ions act both as nucleophiles and as bases.

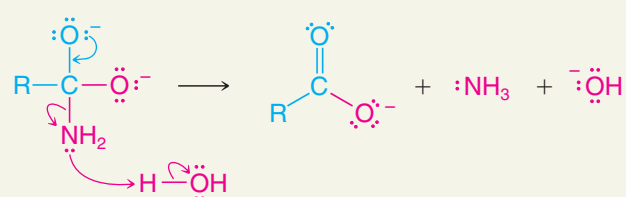
A MECHANISM FOR THE REACTION — Basic Hydrolysis of an Amide



A hydroxide ion attacks the acyl carbon of the amide.



A hydroxide ion removes a proton to give a dianion.

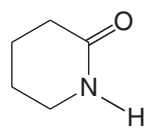


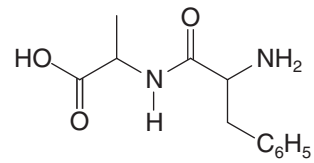
The dianion loses a molecule of ammonia (or an amine); this step is synchronized with a proton transfer from water due to the basicity of NH_2^-.

Hydrolysis of amides by enzymes is central to the digestion of proteins. The mechanism for protein hydrolysis by the enzyme chymotrypsin is presented in Section 24.11.

PRACTICE PROBLEM 17.13 What products would you obtain from acidic and basic hydrolysis of each of the following amides?

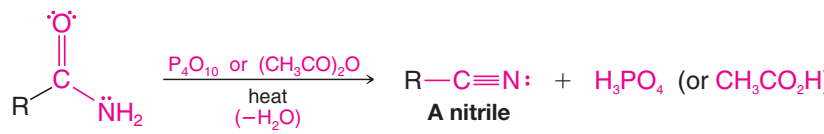
(a) *N*,*N*-Diethylbenzamide

(b) 

(c)  (a dipeptide)

17.8G Nitriles from the Dehydration of Amides

Amides react with P_4O_{10} (a compound that is often called phosphorus pentoxide and written P_2O_5) or with boiling acetic anhydride to form nitriles:

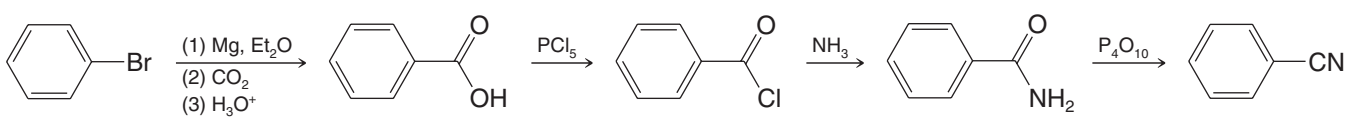


This is a useful synthetic method for preparing nitriles that are not available by nucleophilic substitution reactions between alkyl halides and cyanide ion.

SOLVED PROBLEM 17.7

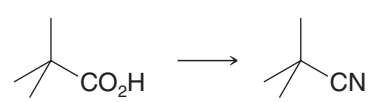
At first glance the conversion of bromobenzene to benzenenitrile looks simple—just carry out a nucleophilic substitution using cyanide ion as the nucleophile. Then we remember that bromobenzene does not undergo either an S_N1 or an S_N2 reaction (Section 6.14A). The conversion can be accomplished, however, though it involves several steps. Outline possible steps.

ANSWER:

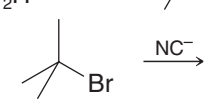


PRACTICE PROBLEM 17.14

(a) Provide the reagents required to accomplish the following transformation.

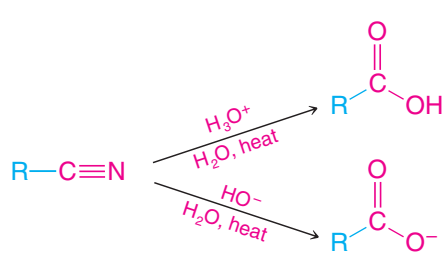


(b) What product would you likely obtain if you attempted to synthesize the nitrile above by the following method?



17.8H Hydrolysis of Nitriles

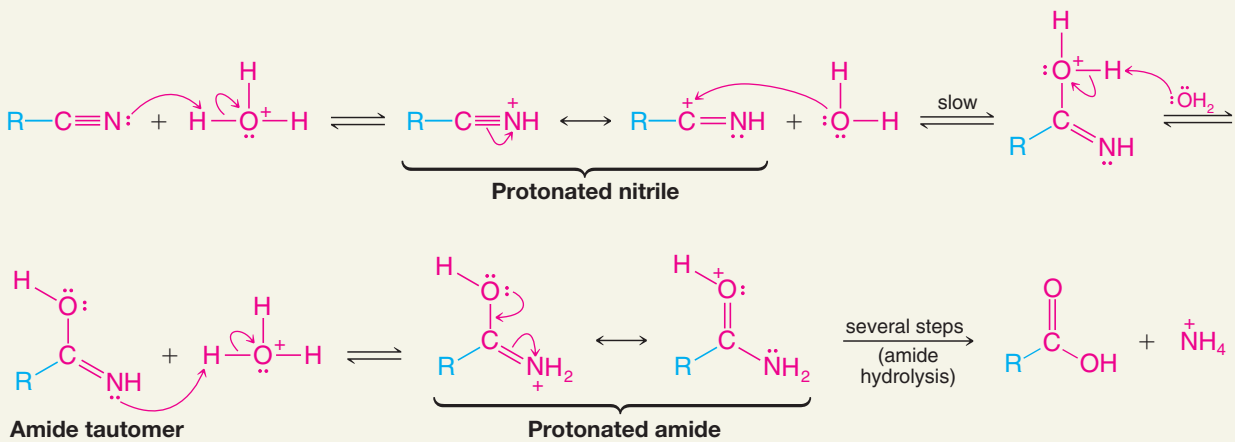
- Nitriles are related to carboxylic acids because complete hydrolysis of a nitrile produces a carboxylic acid or a carboxylate anion (Sections 16.9 and 17.3):



The mechanisms for these hydrolyses are related to those for the acidic and basic hydrolyses of amides.

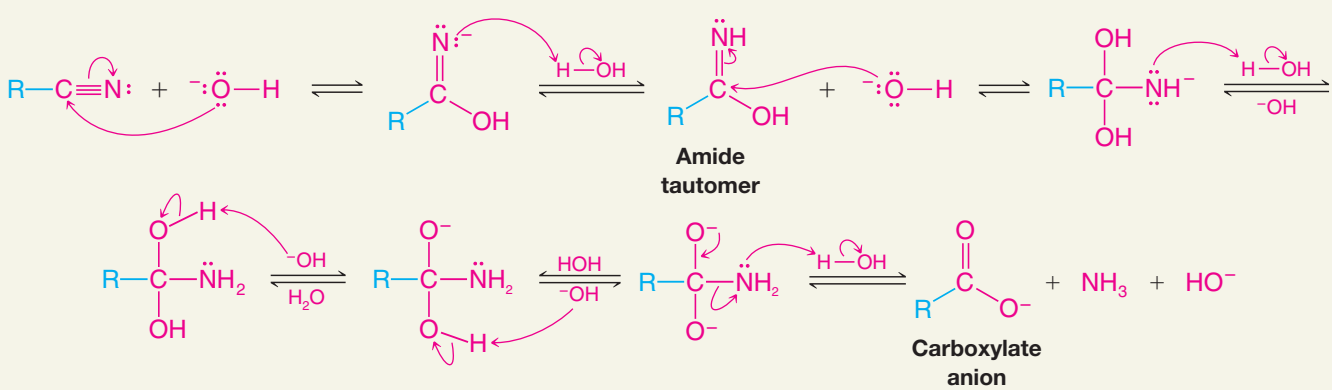
In **acidic hydrolysis** of a nitrile the first step is protonation of the nitrogen atom. This protonation (in the following sequence) enhances polarization of the nitrile group and makes the carbon atom more susceptible to nucleophilic attack by the weak nucleophile, water. The loss of a proton from the oxygen atom then produces a tautomeric form of an amide. Gain of a proton at the nitrogen atom gives a **protonated amide**, and from this point on the steps are the same as those given for the acidic hydrolysis of an amide in Section 17.8F. (In concentrated H_2SO_4 the reaction stops at the protonated amide, and this is a useful way of making amides from nitriles.)

A MECHANISM FOR THE REACTION — Acidic Hydrolysis of a Nitrile



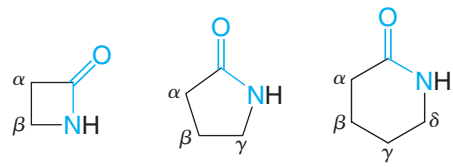
In **basic hydrolysis**, a hydroxide ion attacks the nitrile carbon atom, and subsequent protonation leads to the amide tautomer. Further attack by the hydroxide ion leads to hydrolysis in a manner analogous to that for the basic hydrolysis of an amide (Section 17.8F). (Under the appropriate conditions, amides can be isolated when nitriles are hydrolyzed.)

A MECHANISM FOR THE REACTION — Basic Hydrolysis of a Nitrile



17.8I Lactams

Cyclic amides are called **lactams**. The size of the lactam ring is designated by Greek letters in a way that is analogous to lactone nomenclature (Section 17.7C):

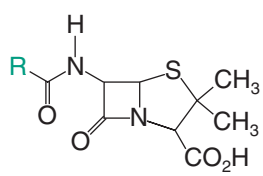


A β-lactam **A γ-lactam** **A δ-lactam**

γ-Lactams and δ-lactams often form spontaneously from γ- and δ-amino acids. β-Lactams, however, are highly reactive; their strained four-membered rings open easily in the presence of nucleophilic reagents.

THE CHEMISTRY OF... Penicillins

The penicillin antibiotics (see the following structures) contain a β-lactam ring:

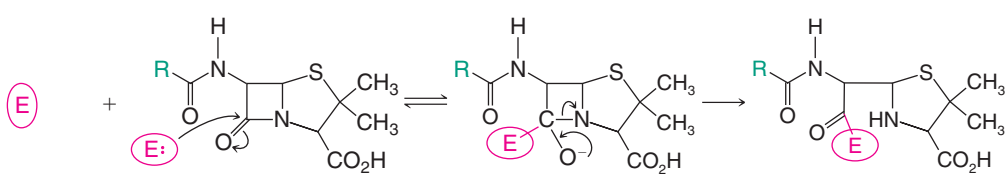


R = $C_6H_5CH_2$— **Penicillin G**

R = $C_6H_5CH(NH_2)$— **Ampicillin**

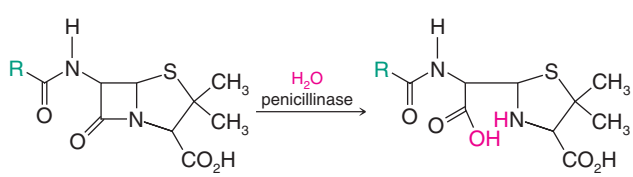
R = $C_6H_5OCH_2$— **Penicillin V**

The penicillins apparently act by interfering with the synthesis of bacterial cell walls. It is thought that they do this by reacting with an amino group of an essential enzyme of the cell wall biosynthetic pathway. This reaction involves ring opening of the β-lactam and acylation of the enzyme, inactivating it.



Active enzyme **A penicillin** **Inactive enzyme** **Inactive enzyme**

Bacterial resistance to the penicillin antibiotics is a serious problem for the treatment of infections. Bacteria that have developed resistance to penicillin produce an enzyme called penicillinase. Penicillinase hydrolyzes the β-lactam ring of penicillin, resulting in penicilloic acid. Because penicilloic acid cannot act as an acylating agent, it is incapable of blocking bacterial cell wall synthesis by the mechanism shown above.

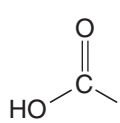


A penicillin **Penicilloic acid**

Michael Rosenfeld/Stone/Getty Images

An industrial-scale reactor for preparation of an antibiotic.

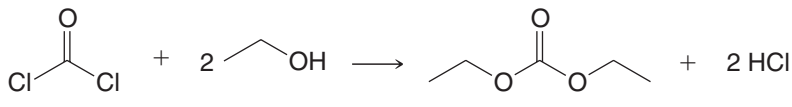
17.9 DERIVATIVES OF CARBONIC ACID



Carbonic acid, , is an unstable compound that decomposes spontaneously to produce carbon dioxide and water and, therefore, cannot be isolated. However,

many acyl chlorides, esters, and amides that are derived from carbonic acid are stable compounds that have important applications.

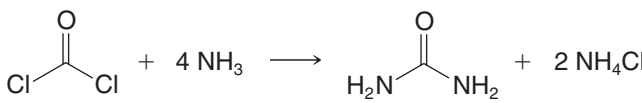
Carbonyl dichloride (ClCOCl), a highly toxic compound that is also called *phosgene*, can be thought of as the diacyl chloride of carbonic acid. Carbonyl dichloride reacts by nucleophilic addition–elimination with two molar equivalents of an alcohol to yield a **dialkyl carbonate**:



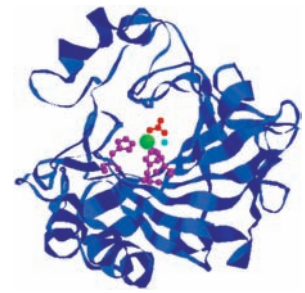
Carbonyl dichloride — **Diethyl carbonate**

A tertiary amine is usually added to the reaction to neutralize the hydrogen chloride that is produced.

Carbonyl dichloride reacts with ammonia to yield **urea** (Section 1.1A):



Urea is the end product of the metabolism of nitrogen-containing compounds in most mammals and is excreted in the urine.



Carbonic anhydrase

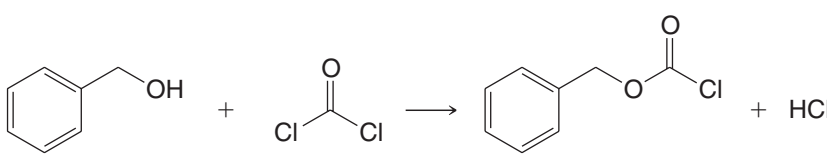
Carbonic anhydrase is an enzyme that interconverts water and carbon dioxide with carbonic acid. A carbonate dianion is shown in red within the structure of carbonic anhydrase above.

17.9A Alkyl Chloroformates and Carbamates (Urethanes)

Treating carbonyl dichloride with one molar equivalent of an alcohol leads to the formation of an alkyl chloroformate:

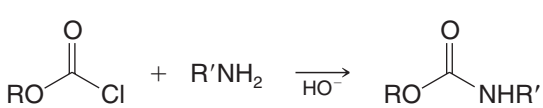
Alkyl chloroformate

Specific Example



Benzyl chloroformate

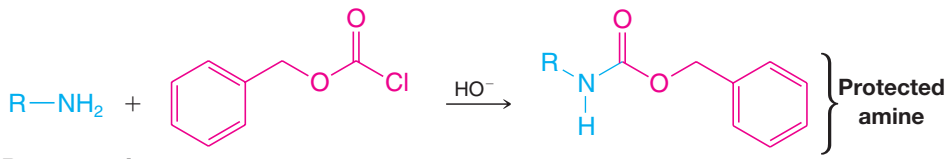
Alkyl chloroformates react with ammonia or amines to yield compounds called *carbamates* or *urethanes*:



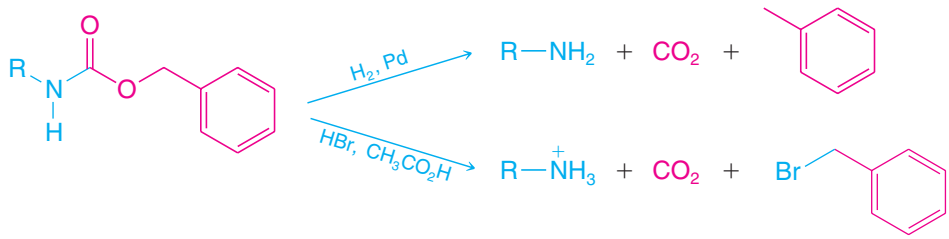
A carbamate (or urethane)

Benzyl chloroformate is used to install an amino protecting (blocking) group called the benzyloxycarbonyl group. We shall see in Section 24.7A how this protecting group is used in the synthesis of peptides and proteins. One advantage of the benzyloxycarbonyl group is that it can be removed under mild conditions. Treating the benzyloxycarbonyl derivative with hydrogen and a catalyst or with cold HBr in acetic acid removes the protecting group:

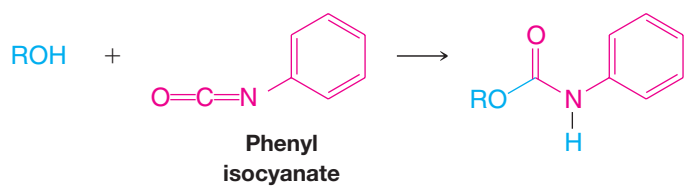
Protection



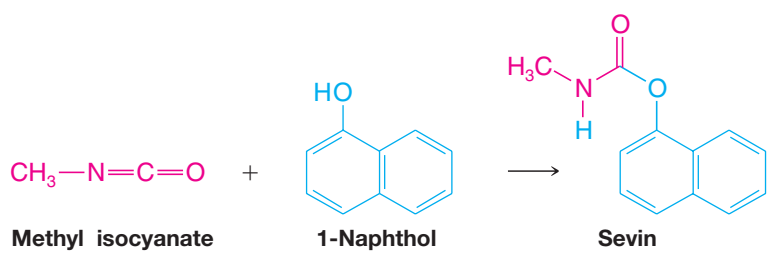
Deprotection



Carbamates can also be synthesized by allowing an alcohol to react with an isocyanate, R—N=C=O. (Carbamates tend to be nicely crystalline solids and are useful derivatives for identifying alcohols.) The reaction is an example of nucleophilic addition to the acyl carbon:



The insecticide called *Sevin* is a carbamate made by allowing 1-naphthol to react with methyl isocyanate:



A tragic accident that occurred at Bhopal, India, in 1984 was caused by leakage of methyl isocyanate from a manufacturing plant. Methyl isocyanate is a highly toxic gas, and more than 1800 people living near the plant lost their lives.

PRACTICE PROBLEM 17.15 Write structures for the products of the following reactions:

(a) $C_6H_5CH_2OH + C_6H_5N{=}C{=}O \longrightarrow$

(b) $ClCOCl$ + excess $CH_3NH_2 \longrightarrow$

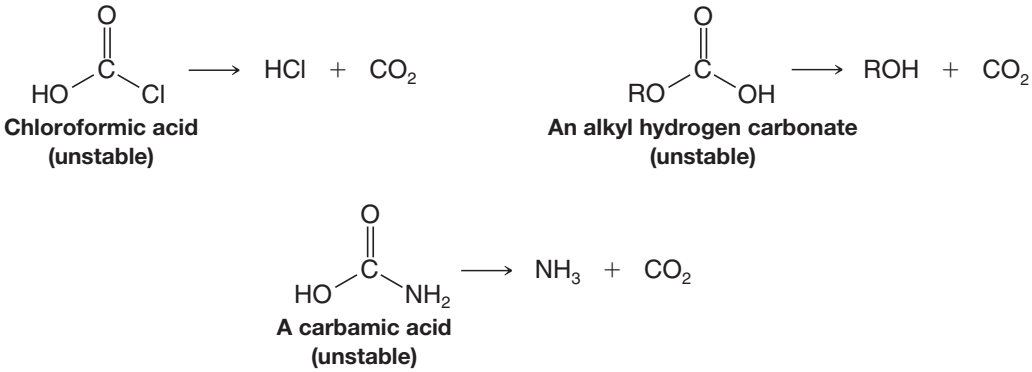
(c) Glycine ($H_3\overset{+}{N}CH_2CO_2^-$) + $C_6H_5CH_2OCOCl \xrightarrow{HO^-}$

(d) Product of (c) + H_2, Pd $\longrightarrow$

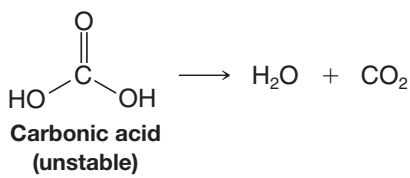
(e) Product of (c) + cold HBr, $CH_3CO_2H \longrightarrow$

(f) Urea + HO^-, H_2O, heat

Although alkyl chloroformates (ROCOCl), dialkyl carbonates (ROCOOR), and carbamates ($ROCONH_2$, ROCONHR, etc.) are stable, chloroformic acid (HOCOCl), alkyl hydrogen carbonates (ROCOOH), and carbamic acid ($HOCONH_2$) are not. These latter compounds decompose spontaneously to liberate carbon dioxide:

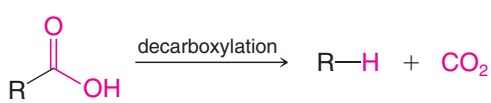


This instability is a characteristic that these compounds share with their functional parent, carbonic acid:



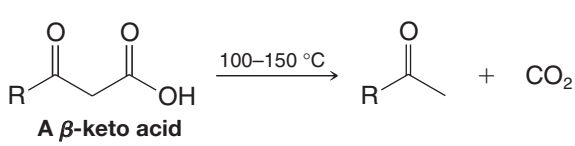
17.10 DECARBOXYLATION OF CARBOXYLIC ACIDS

The reaction whereby a carboxylic acid loses CO_2 is called a **decarboxylation**:



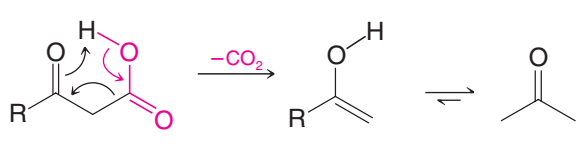
Although the unusual stability of carbon dioxide means that decarboxylation of most acids is exothermic, in practice the reaction is not always easy to carry out because the reaction is very slow. Special groups usually have to be present in the molecule for decarboxylation to be rapid enough to be synthetically useful.

- Carboxylic acids that have a carbonyl group one carbon removed from the carboxylic acid group, called **β-keto acids**, decarboxylate readily when they are heated to 100–150 °C. Some β-keto acids even decarboxylate slowly at room temperature.



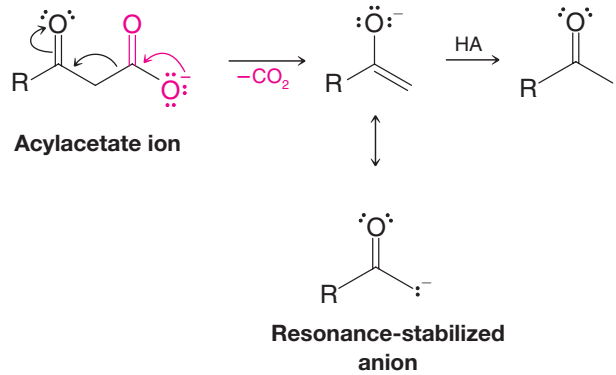
There are two reasons for this ease of decarboxylation:

1. When the acid itself decarboxylates, it can do so through a six-membered cyclic transition state:



This reaction produces an enol (alk**en**e-alcoh**ol**) directly and avoids an anionic intermediate. The enol then tautomerizes to a methyl ketone.

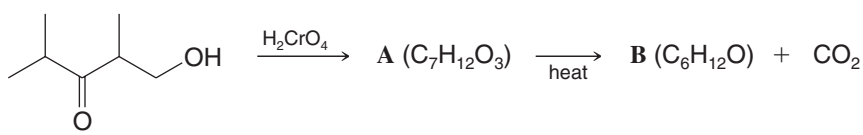
2. When the carboxylate anion decarboxylates, it forms a resonance-stabilized anion:



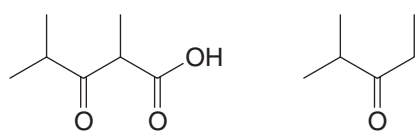
This type of anion, which we shall study further in Chapter 19, is much more stable than simply $RCH_2:^-$, the anion that would have been produced by decarboxylation in the absence of a β-carbonyl group. It is known as an enolate.

SOLVED PROBLEM 17.8

Provide structures for **A** and **B**.

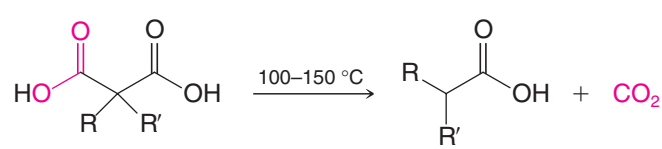


STRATEGY AND ANSWER: H_2CrO_4 oxidizes a primary alcohol to a carboxylic acid, which is consistent with the formula provided for **A**. Because **A** is a β-ketocarboxylic acid, it decarboxylates on heating to form **B**.



A **B**

β-Dicarboxylic acids (1,3-dicarboxylic acids, also called malonic acids) decarboxylate readily for reasons similar to β-keto acids.



A β-dicarboxylic acid

β-Dicarboxylic acids undergo decarboxylation so readily that they do not form cyclic anhydrides (Section 17.6A).

We shall see in Sections 18.6 and 18.7 how decarboxylation of β-keto acids and malonic acids is synthetically useful.

17.10A Decarboxylation of Carboxyl Radicals

Although the carboxylate ions (RCO_2^-) of simple aliphatic acids do not decarboxylate readily, carboxyl radicals ($RCO_2\cdot$) do. They decarboxylate by losing CO_2 and producing alkyl radicals:

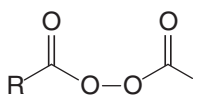
$$RCO_2\cdot \longrightarrow R\cdot + CO_2$$

PRACTICE PROBLEM 17.16

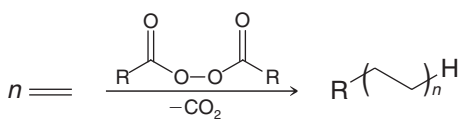
Using decarboxylation reactions, outline a synthesis of each of the following from appropriate starting materials:

(a) 2-Hexanone
(b) 2-Methylbutanoic acid
(c) Cyclohexanone
(d) Pentanoic acid

PRACTICE PROBLEM 17.17

Diacyl peroxides,  , decompose readily when heated.

(a) What factor accounts for this instability?
(b) The decomposition of a diacyl peroxide produces CO_2. How is it formed?
(c) Diacyl peroxides are often used to initiate radical reactions, for example, the polymerization of an alkene:



Show the steps involved.

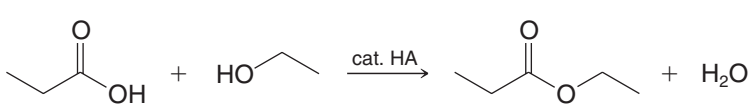
17.11 CHEMICAL TESTS FOR ACYL COMPOUNDS

Carboxylic acids are weak acids, and their acidity helps us to detect them.

- Aqueous solutions of water-soluble carboxylic acids give an acid test with blue litmus paper.
- Water-insoluble carboxylic acids dissolve in aqueous sodium hydroxide and aqueous sodium bicarbonate (see Section 17.2C).
- Sodium bicarbonate helps us distinguish carboxylic acids from most phenols. Except for the di- and trinitrophenols, phenols do not dissolve in aqueous sodium bicarbonate. When carboxylic acids dissolve in aqueous sodium bicarbonate, they also cause the evolution of carbon dioxide.

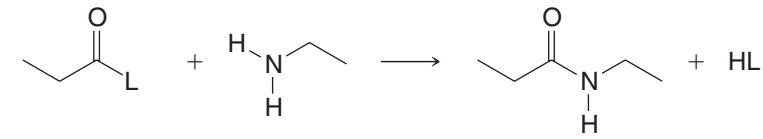
17.12 POLYESTERS AND POLYAMIDES: STEP-GROWTH POLYMERS

We have seen in Section 17.7A that carboxylic acids react with alcohols to form esters.



Carboxylic acid **Alcohol** **Ester**

In a similar way carboxylic acid derivatives (L is a leaving group) react with amines (Section 17.8) to form amides.

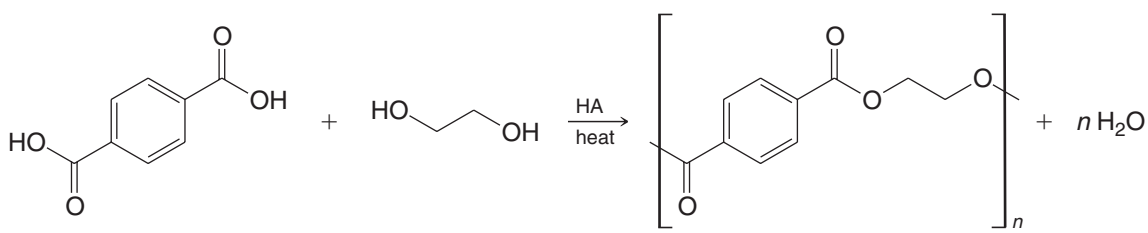


Carboxylic acid derivative **Amine** **Amide**

In each reaction the two reactants become joined and a small molecule is lost. Such reactions are often called **condensation reactions**.

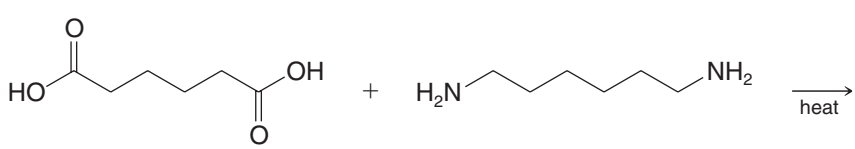
Similar condensation reactions beginning with dicarboxylic acids and either diols or diamines can be used to form polymers that are either **polyesters** or **polyamides**. These polymers are called **step-growth polymers**. [Recall that in Section 10.10 and Special Topic B in *WileyPLUS*, we studied another group of polymers called *chain-growth polymers* (also called *addition polymers*), which are formed by radicals undergoing chain-reactions.]

- **Polyesters.** When a dicarboxylic acid reacts with a diol under the appropriate conditions, the product is a polyester. For example, the reaction of 1,4-benzenedicarboxylic acid (terephthalic acid) with 1,2-ethanediol leads to the formation of the familiar polyesters called Dacron, Terelene or Mylar, and systemically called poly(ethylene terephthalate).

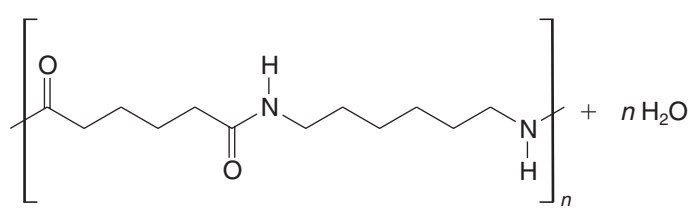


Terephthalic acid **1,2-Ethanediol** **Poly(ethylene terephthalate) (a polyester)**

- **Polyamides.** When a dicarboxylic acid or acid chloride or anhydride reacts with a diamine under the appropriate conditions, the product is a polyamide. For example, 1,6-hexanedioic acid (adipic acid) can react with 1,6-hexanediamine with heat in an industrial process to form a familiar polyamide called Nylon. This example of nylon is called nylon 6,6 because both components of the polymer have six carbon atoms. Other nylons can be made in a similar way.



1,6-Hexanedioic acid **1,6-Hexanediamine**



Nylon 6,6 (A polyamide)

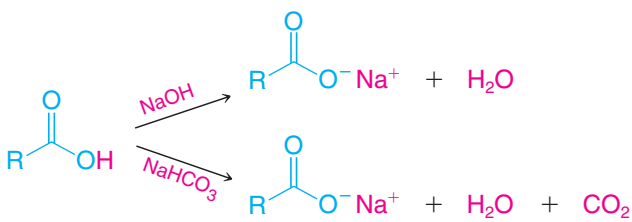
Special Topic C in *WileyPLUS* continues our discussion of Step-Growth Polymers.

17.13 SUMMARY OF THE REACTIONS OF CARBOXYLIC ACIDS AND THEIR DERIVATIVES

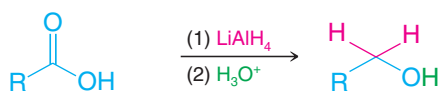
The reactions of carboxylic acids and their derivatives are summarized here. Many (but not all) of the reactions in this summary are acyl substitution reactions (they are principally the reactions referenced to Sections 17.5 and beyond). As you use this summary, you will find it helpful to also review Section 17.4, which presents the general nucleophilic addition–elimination mechanism for acyl substitution. It is instructive to relate aspects of the specific acyl substitution reactions below to this general mechanism. In some cases proton transfer steps are also involved, such as to make a leaving group more suitable by prior protonation or to transfer a proton to a stronger base at some point in a reaction, but in all acyl substitution the essential nucleophilic addition–elimination steps are identifiable.

REACTIONS OF CARBOXYLIC ACIDS

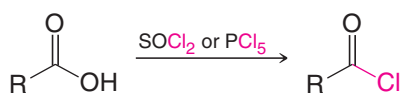
1. As acids (discussed in Sections 3.11 and 17.2C):



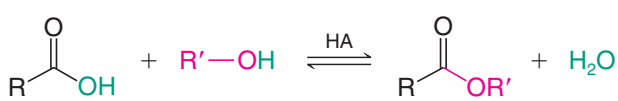
2. Reduction (discussed in Section 12.3):



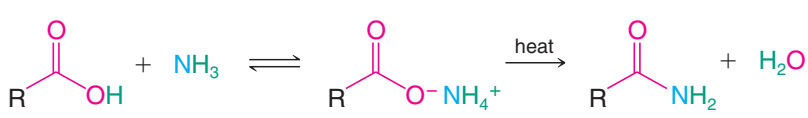
3. Conversion to acyl chlorides (discussed in Section 17.5):



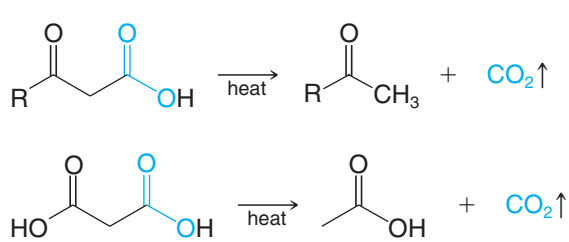
4. Conversion to esters (Fischer esterification) or lactones (discussed in Section 17.7A):



5. Conversion to amides (discussed in Section 17.8E, but a very limited method):



6. Decarboxylation (discussed in Section 17.10):

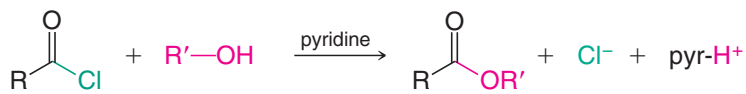


REACTIONS OF ACYL CHLORIDES

1. Conversion (hydrolysis) to acids (discussed in Section 17.5B):

2. Conversion to anhydrides (discussed in Section 17.6A):

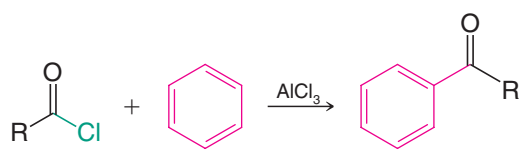
3. Conversion to esters (discussed in Section 17.7A):



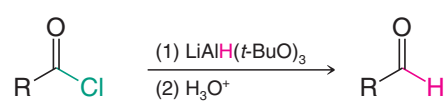
4. Conversion to amides (discussed in Section 17.8B):

R′ and/or R″ may be H.

5. Conversion to ketones (Friedel–Crafts acylation, Sections 15.7–15.9):

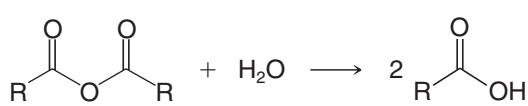


6. Conversion to aldehydes (discussed in Section 16.4C):

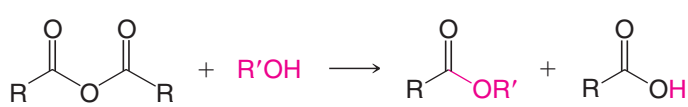


REACTIONS OF ACID ANHYDRIDES

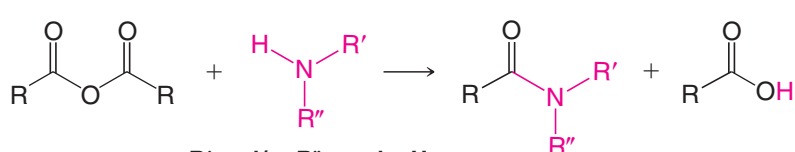
1. Conversion (hydrolysis) to acids (discussed in Section 17.6B):



2. Conversion to esters (discussed in Sections 17.6B and 17.7A):

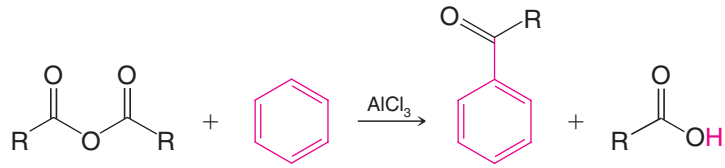


3. Conversion to amides (discussed in Section 17.8C):



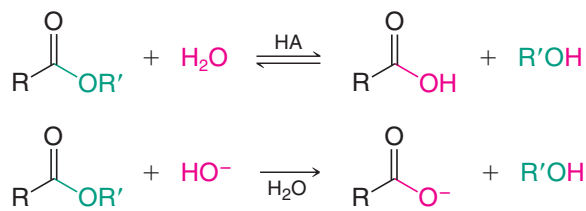
R′ and/or R″ may be H.

4. Conversion to aryl ketones (Friedel–Crafts acylation, Sections 15.7–15.9):

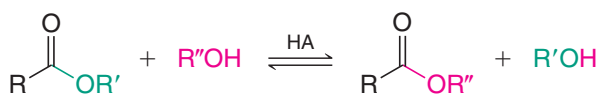


REACTIONS OF ESTERS

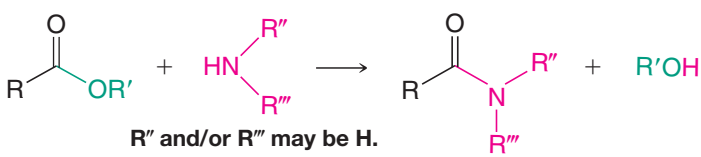
1. Hydrolysis (discussed in Section 17.7B):



2. Conversion to other esters: transesterification (discussed in Practice Problem 17.10):

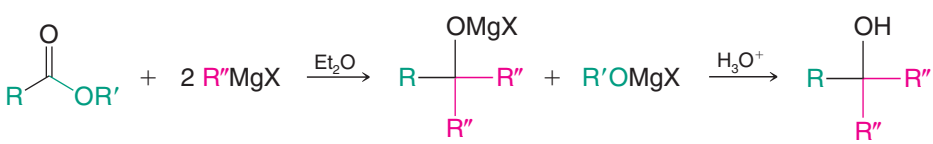


3. Conversion to amides (discussed in Section 17.8D):

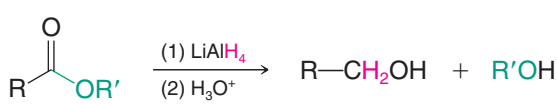


R″ and/or R‴ may be H.

4. Reaction with Grignard reagents (discussed in Section 12.8):

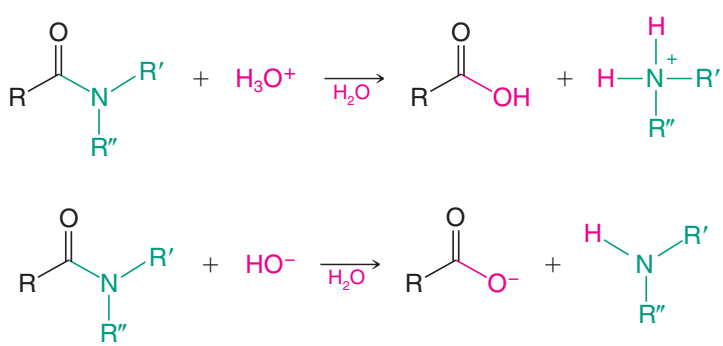


5. Reduction (discussed in Section 12.3):



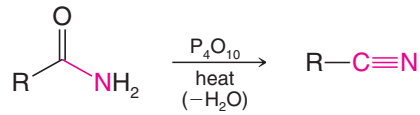
REACTIONS OF AMIDES

1. Hydrolysis (discussed in Section 17.8F):



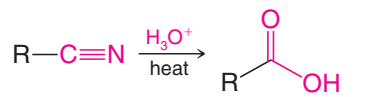
R, R′, and/or R″ may be H.

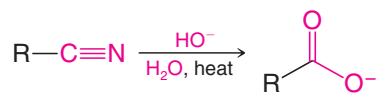
2. Conversion to nitriles: dehydration (discussed in Section 17.8G):



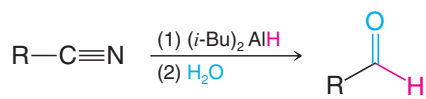
REACTIONS OF NITRILES

1. Hydrolysis to a carboxylic acid or carboxylate anion (Section 17.8H):

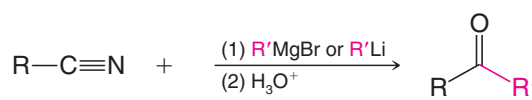




2. Reduction to an aldehyde with $(i\text{-Bu})_2$AlH (DIBAL-H, Section 16.4C):



3. Conversion to a ketone by a Grignard or organolithium reagent (Section 16.5B):



WHY Do These Topics Matter?]

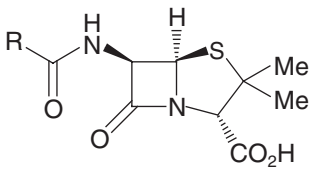
FORGING THE UNIQUE, STRAINED AMIDE OF THE PENICILLINS

The saying that necessity is the mother of invention often rings true for organic chemists, particularly when they are trying to synthesize unique structures. Indeed, efforts to make particular bonds form in the presence of many potentially reactive groups often require the development of new and more selective reagents. Such was the case with the penicillins, a family of molecules whose structural determination was discussed at the end of Chapter 9 and whose unique lactam structures were presented earlier in this chapter.

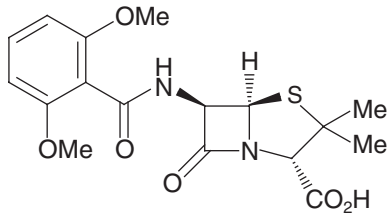
In 1945, the year when their structures were finally established, chemists knew several ways to make amides, including the use of acid halides and amines through nucleophilic acyl substitution reactions that you learned about in this chapter. None of the known processes, however, was mild enough to permit the formation of the needed bond within a highly strained system because they produce acidic by-products and/or require high temperatures that can readily rupture such a fragile bond. Indeed, as noted by John C. Sheehan of MIT, who ultimately solved the problem, attempting to forge such an amide using methods available at the time was "like attempting to repair a fine watch with a blacksmith's sledge and anvil." In fact, it is that same lability and strain in their lactam rings which, as mentioned earlier in "The Chemistry of... Penicillins," is the basis for how these antibiotics act and how bacterial resistance has developed around them.

What was needed chemically was the ability to turn a carboxylic acid into a more activated species for nucleophilic acyl substition and effect its merger with an amine at low temperatures and neutral pH; otherwise, once formed, the strained amide bond would simply hydrolyze back to the starting carboxylic acid and amine. It ultimately took Sheehan and his research team over a decade to find a solution in the form of the reagent dicyclohexylcarbodiimide (DCC), introduced in Section 17.8E. The importance of this discovery cannot be understated. Not only did it allow for the production of penicillins in greater quantities, it also allowed

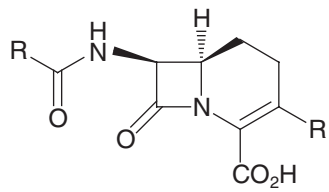
chemists to create new penicillin analogs such as methicillin that have superior and/or distinct properties from the original structures found in nature. It also provided access to other classes of antibiotics that possess strained lactam rings such as the cephalosporins and the carbapenems. And, it provided insights into how to create even milder and more powerful amide-bond-forming reagents, tools that have now led to the automated synthesis of peptides (see Chapter 24) as well as a number of peptide-based drugs used by hundreds of thousands of patients, including several treatments for the human immunodeficiency virus.



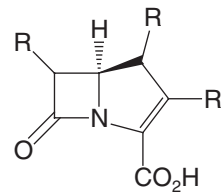
Penicillins
[R = variable group]



Methicillin



Cephalosporins
[R = variable group]



Carbapenems
[R = variable group]

To learn more about these topics, see:

1. Sheehan, J. C. *The Enchanted Ring: The Untold Story of Penicillin*. MIT Press: Cambridge, **1984**, p. 224.
2. "Penicillin Synthesis" in *Time* magazine. March 18, 1957.
3. Nicolaou, K. C.; Montagnon, T. *Molecules that Changed the World*. Wiley-VCH: Weinheim, **2008**, pp. 97–106..

SUMMARY AND REVIEW TOOLS

The study aids for this chapter include key terms and concepts (which are hyperlinked to the Glossary from the bold, blue terms in the *WileyPLUS* version of the book at wileyplus.com) and the Summary of Reactions of Carboxylic Acids and Their Derivatives found in Section 17.13.

PROBLEMS

Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

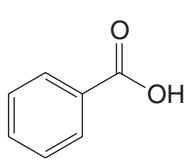
STRUCTURE AND NOMENCLATURE

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

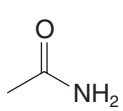
(a) Octanoic acid
(b) Propanamide
(c) *N*,*N*-Diethylhexanamide
(d) 2-Methyl-4-hexenoic acid
(e) Butanedioic acid
(f) 1,2-Benzenedioic acid (phthalic acid)
(g) 1,4-Benzenedioic acid (terephthalic acid)
(h) Acetic anhydride
(i) Isobutyl propanoate
(j) Benzyl acetate
(k) Ethanoyl chloride (acetyl chloride)
(l) 2-Methylpropanenitrile
(m) Ethyl 3-oxobutanoate (ethyl acetoacetate)
(n) Diethyl propanedioate (diethyl malonate)

17.19 Give an IUPAC systematic or common name for each of the following compounds:

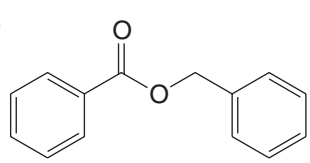
(a)



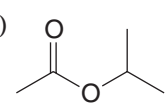
(c)



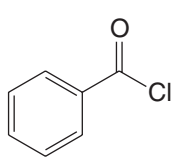
(e)



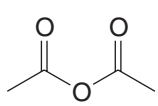
(g)



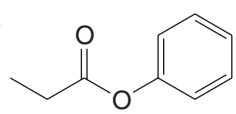
(b)



(d)



(f)

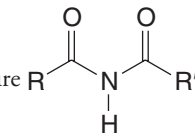


(h) CH_3CN

17.20 Amides are weaker bases than corresponding amines. For example, most water-insoluble amines (RNH_2) will dissolve in dilute aqueous acids (aqueous HCl, H_2SO_4, etc.) by forming water-soluble alkylaminium salts ($RNH_3^+X^-$). Corresponding amides ($RCONH_2$) *do not dissolve in dilute aqueous acids*, however. Propose an explanation for the much lower basicity of amides when compared to amines.

17.21 While amides are much less basic than amines, they are much stronger acids. Amides have pK_a values in the range 14–16, whereas for amines, pK_a = 33–35.

(a) What factor accounts for the much greater acidity of amides?

(b) Imides, that is, compounds with the structure  , are even stronger acids than amides.

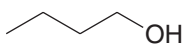
For imides, pK_a = 9–10, and as a consequence, water-insoluble imides dissolve in aqueous NaOH by forming soluble sodium salts. What extra factor accounts for the greater acidity of imides?

FUNCTIONAL GROUP TRANSFORMATIONS

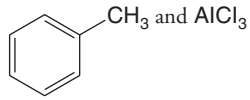
17.22 What major organic product would you expect to obtain when acetyl chloride reacts with each of the following?

(a) H_2O

(b) BuLi (excess)

(c)  and pyridine

(d) NH_3 (excess)

(e) 

(f) LiAlH(t-BuO)$_3$

(g) NaOH/H_2O

(h) CH_3NH_2 (excess)

(i) $(CH_3)_2NH$ (excess)

(j) EtOH and pyridine

(k) $CH_3CO_2^-Na^+$

(l) CH_3CO_2H and pyridine

17.23 What major organic product would you expect to obtain when acetic anhydride reacts with each of the following?

(a) NH_3 (excess) **(c)** $CH_3CH_2CH_2OH$ **(e)** $CH_3CH_2NH_2$ (excess)

(b) H_2O **(d)** $C_6H_6 + AlCl_3$ **(f)** $(CH_3CH_2)_2NH$ (excess)

17.24 What major organic product would you expect to obtain when succinic anhydride reacts with each of the reagents given in Problem 17.23?

17.25 What products would you expect to obtain when ethyl propanoate reacts with each of the following?

(a) H_3O^+, H_2O **(c)** 1-Octanol, HCl **(e)** $LiAlH_4$, then H_2O

(b) HO^-, H_2O **(d)** CH_3NH_2 **(f)** Excess C_6H_5MgBr, then H_2O, NH_4Cl

17.26 What products would you expect to obtain when propanamide reacts with each of the following?

(a) H_3O^+, H_2O **(b)** HO^-, H_2O **(c)** P_4O_{10} and heat

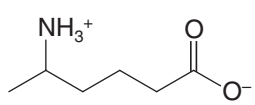
17.27 What products would you expect to obtain when each of the following compounds is heated?

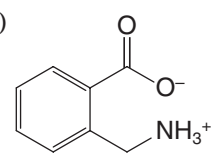
(a) 4-Hydroxybutanoic acid

(b) 3-Hydroxybutanoic acid

(c) 2-Hydroxybutanoic acid

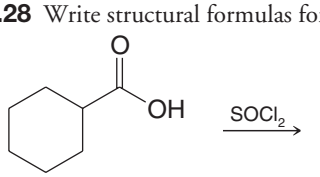
(d) Glutaric acid

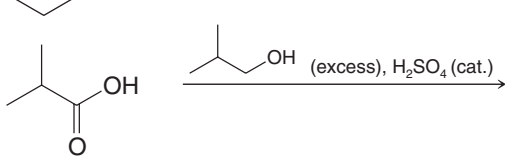
(e) 

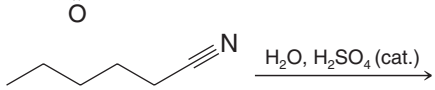
(f) 

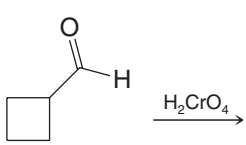
GENERAL PROBLEMS

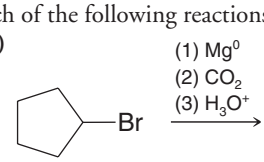
17.28 Write structural formulas for the major organic products from each of the following reactions.

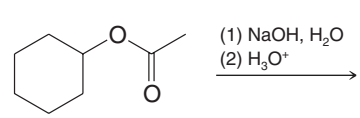
(a) 

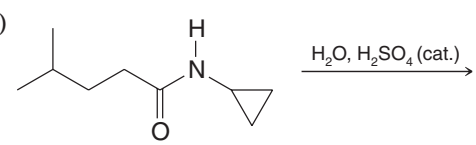
(b) 

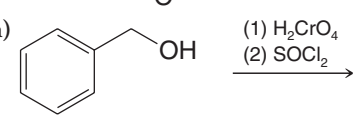
(c) 

(d) 

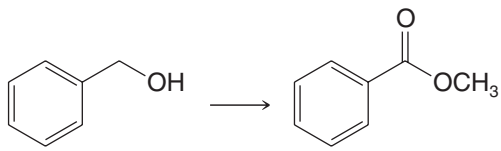
(e) 

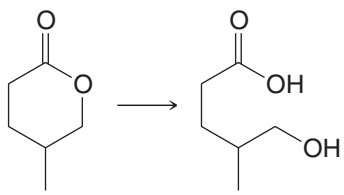
(f) 

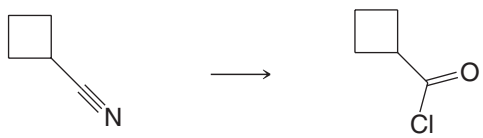
(g) 

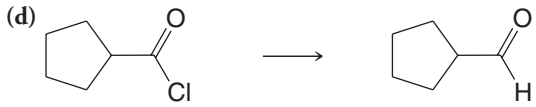
(h) 

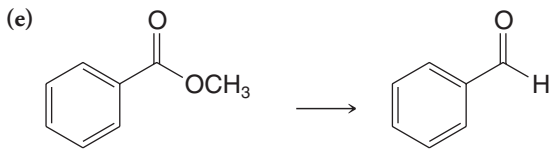
17.29 Indicate reagents that would accomplish each of following transformations. More than one reaction may be necessary in some cases.

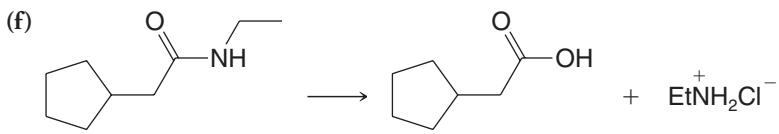
(a) 

(b) 

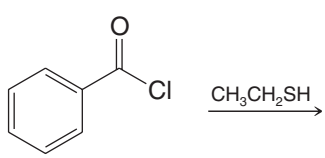
(c) 

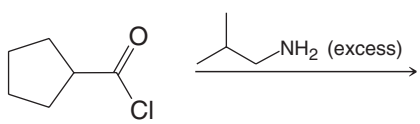
(d) 

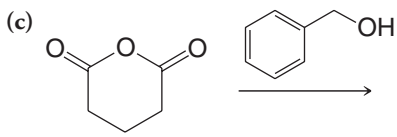
(e) 

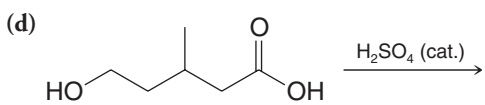
(f) 

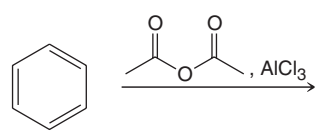
17.30 Write structural formulas for the major organic products from each of the following reactions.

(a) 

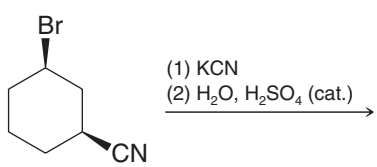
(b) 

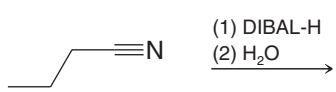
(c) 

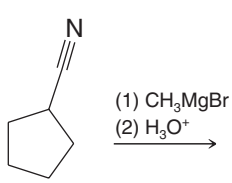
(d) 

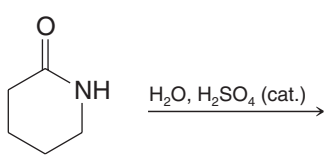
(e) 

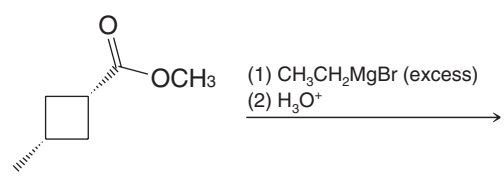
17.31 Write structural formulas for the major organic products from each of the following reactions.

(a) 

(b) 

(c) 

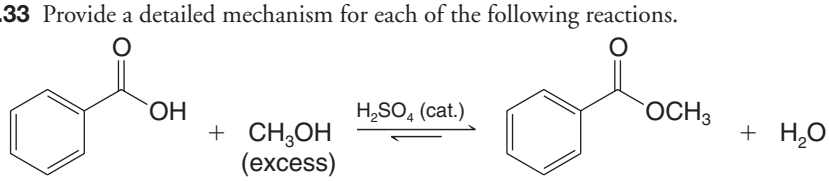
(d) 

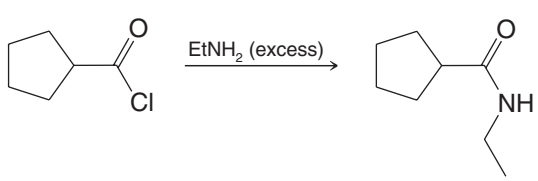
(e) 

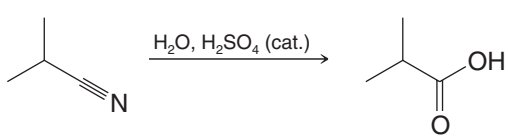
MECHANISMS

17.32 Write detailed mechanisms for the acidic and basic hydrolysis of propanamide.

17.33 Provide a detailed mechanism for each of the following reactions.

(a) 

(b) 

(c) 

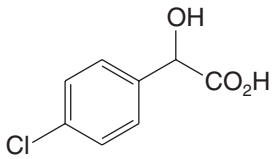
17.34 On heating, *cis*-4-hydroxycyclohexanecarboxylic acid forms a lactone but *trans*-4-hydroxycyclohexanecarboxylic acid does not. Explain.

SYNTHESIS

17.35 Show how *p*-chlorotoluene could be converted to each of the following:

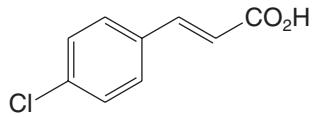
(a) *p*-Chlorobenzoic acid

(b)



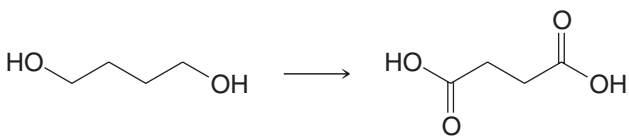
(c) *p*-Chlorophenylacetic acid

(d)

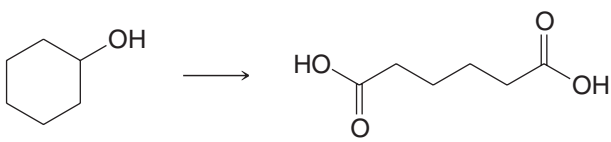


17.36 Indicate the reagents needed for each of the following syntheses. More than one step may be needed.

(a)



(b)



17.37 Show how pentanoic acid can be prepared from each of the following:

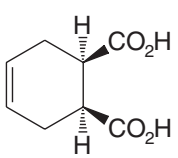
(a) 1-Pentanol **(b)** 1-Bromobutane (two ways) **(c)** 5-Decene **(d)** Pentanal

17.38 The active ingredient of the insect repellent Off is *N*,*N*-diethyl-*m*-toluamide, *m*-$CH_3C_6H_4CON(CH_2CH_3)_2$. Outline a synthesis of this compound starting with 3-methylbenzoic acid (*m*-toluic acid).

17.39 Starting with benzene and succinic anhydride and using any other needed reagents, outline a synthesis of 1-phenylnaphthalene.

17.40 Starting with either *cis*- or *trans*-$HO_2C-CH=CH-CO_2H$ (i.e., either maleic or fumaric acid) and using any other needed compounds, outline syntheses of each of the following:

(a)



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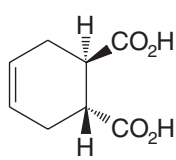
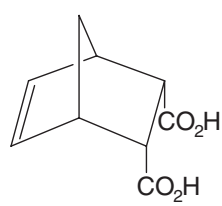


(c)



17.41 Give stereochemical formulas for compounds **A–Q**:

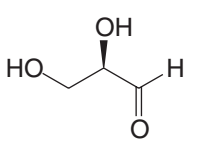
(a) (*R*)-(−)-2-Butanol $\xrightarrow[\text{pyridine}]{\text{p-toluenesulfonyl chloride (TsCl)}}$ **A** $\xrightarrow{^-C\equiv N}$ **B** (C_5H_9N) $\xrightarrow[H_2O]{H_2SO_4}$ (+)-**C** ($C_5H_{10}O_2$) $\xrightarrow[(2)\ H_2O]{(1)\ LiAlH_4}$ (−)-**D** ($C_5H_{12}O$)

(b) (*R*)-(−)-2-Butanol $\xrightarrow[\text{pyridine}]{PBr_3}$ **E** (C_4H_9Br) $\xrightarrow{^-C\equiv N}$ **F** (C_5H_9N) $\xrightarrow[H_2O]{H_2SO_4}$ (−)-**C** ($C_5H_{10}O_2$) $\xrightarrow[(2)\ H_2O]{(1)\ LiAlH_4}$ (+)-**D** ($C_5H_{12}O$)

(c) **A** $\xrightarrow{CH_3CO_2^-}$ **G** ($C_6H_{12}O_2$) $\xrightarrow{HO^-}$ (+)-**H** ($C_4H_{10}O$) + $CH_3CO_2^-$

(d) (−)-**D** $\xrightarrow{PBr_3}$ **J** ($C_5H_{11}Br$) $\xrightarrow[Et_2O]{Mg}$ **K** ($C_5H_{11}MgBr$) $\xrightarrow[(2)\ H_3O^+]{(1)\ CO_2}$ **L** ($C_6H_{12}O_2$)

(e)



(*R*)-(+)-Glyceraldehyde

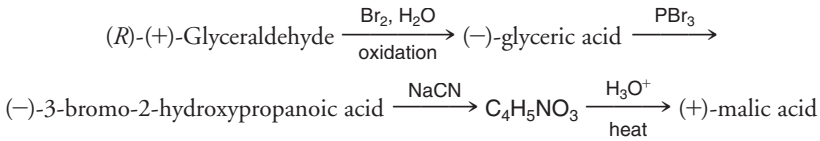
$\xrightarrow{HCN}$ **M** ($C_4H_7NO_3$) + **N** ($C_4H_7NO_3$)

Diastereomers, separated by fractional crystallization

(f) **M** $\xrightarrow[H_2O]{H_2SO_4}$ **P** ($C_4H_8O_5$) $\xrightarrow[HNO_3]{[O]}$ *meso*-tartaric acid

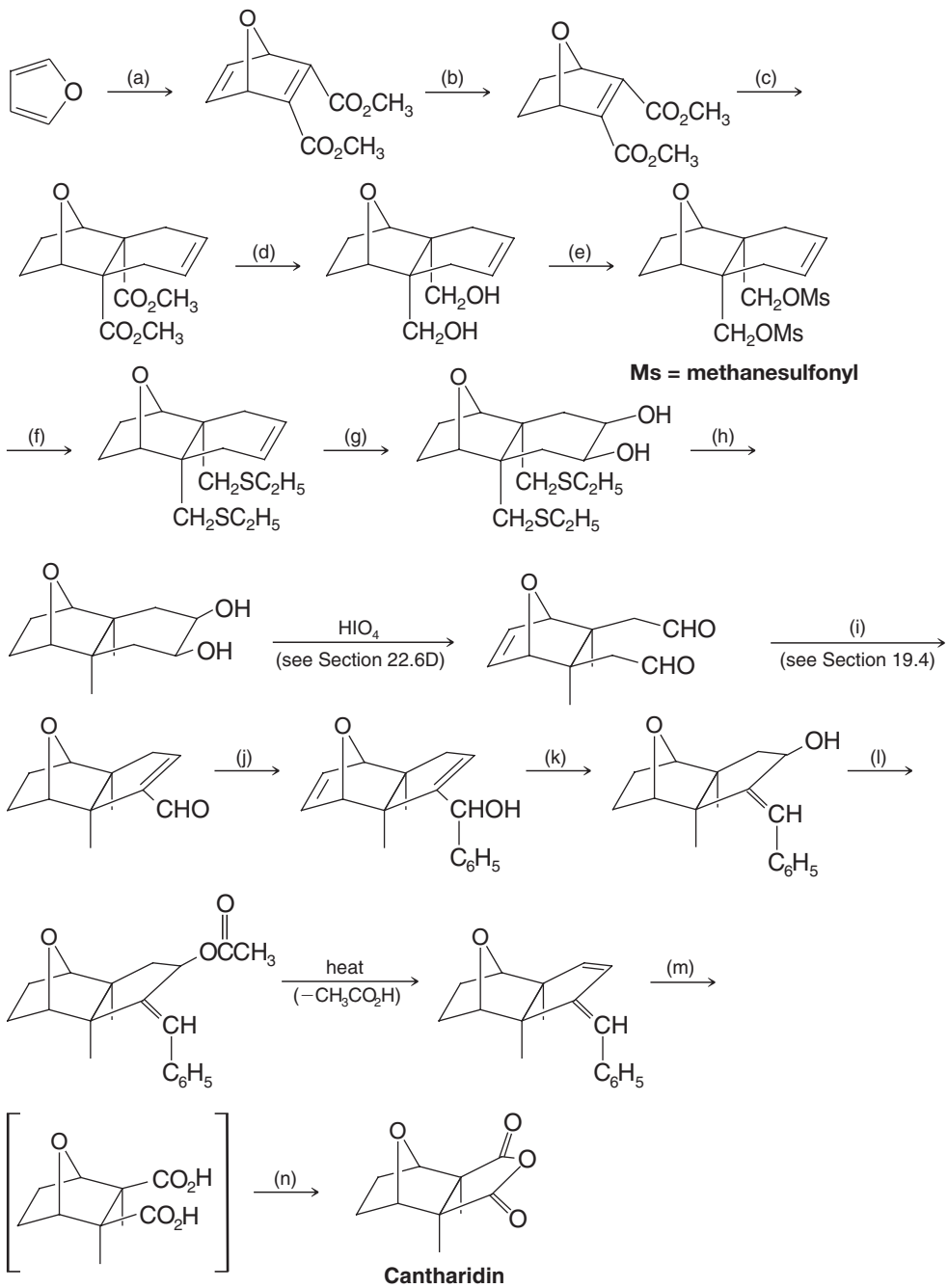
(g) **N** $\xrightarrow[H_2O]{H_2SO_4}$ **Q** ($C_4H_8O_5$) $\xrightarrow[HNO_3]{[O]}$ (−)-tartaric acid

17.42 (*R*)-(+)-Glyceraldehyde can be transformed into (+)-malic acid by the following synthetic route. Give stereochemical structures for the products of each step.



17.43 (*R*)-(+)-Glyceraldehyde can also be transformed into (−)-malic acid. This synthesis begins with the conversion of (*R*)-(+)-glyceraldehyde into (−)-tartaric acid, as shown in Problem 17.41, parts (e) and (g). Then (−)-tartaric acid is allowed to react with phosphorus tribromide in order to replace one alcoholic —OH group with —Br. This step takes place with inversion of configuration at the carbon that undergoes attack. Treating the product of this reaction with dimethyl sulfide produces (−)-malic acid. **(a)** Outline all steps in this synthesis by writing stereochemical structures for each intermediate. **(b)** The step in which (−)-tartaric acid is treated with phosphorus tribromide produces only one stereoisomer, even though there are two replaceable —OH groups. How is this possible? **(c)** Suppose that the step in which (−)-tartaric acid is treated with phosphorus tribromide had taken place with "mixed" stereochemistry, that is, with both inversion and retention at the carbon under attack. How many stereoisomers would have been produced? **(d)** What difference would this have made to the overall outcome of the synthesis?

17.44 Cantharidin is a powerful vesicant that can be isolated from dried beetles (*Cantharis vesicatoria,* or "Spanish fly"). Outlined here is the stereospecific synthesis of cantharidin reported by Gilbert Stork (Columbia University). Supply the missing reagents (a)–(n).



SPECTROSCOPY

17.45 The IR and ^{1}H NMR spectra of phenacetin ($C_{10}H_{13}NO_2$) are given in Fig. 17.7. Phenacetin is an analgesic and antipyretic compound and was the P of A–P–C tablets (aspirin–phenacetin–caffeine). (Because of its toxicity, phenacetin is no longer used medically.) When phenacetin is heated with aqueous sodium hydroxide, it yields phenetidine ($C_8H_{11}NO$) and sodium acetate. Propose structures for phenacetin and phenetidine.

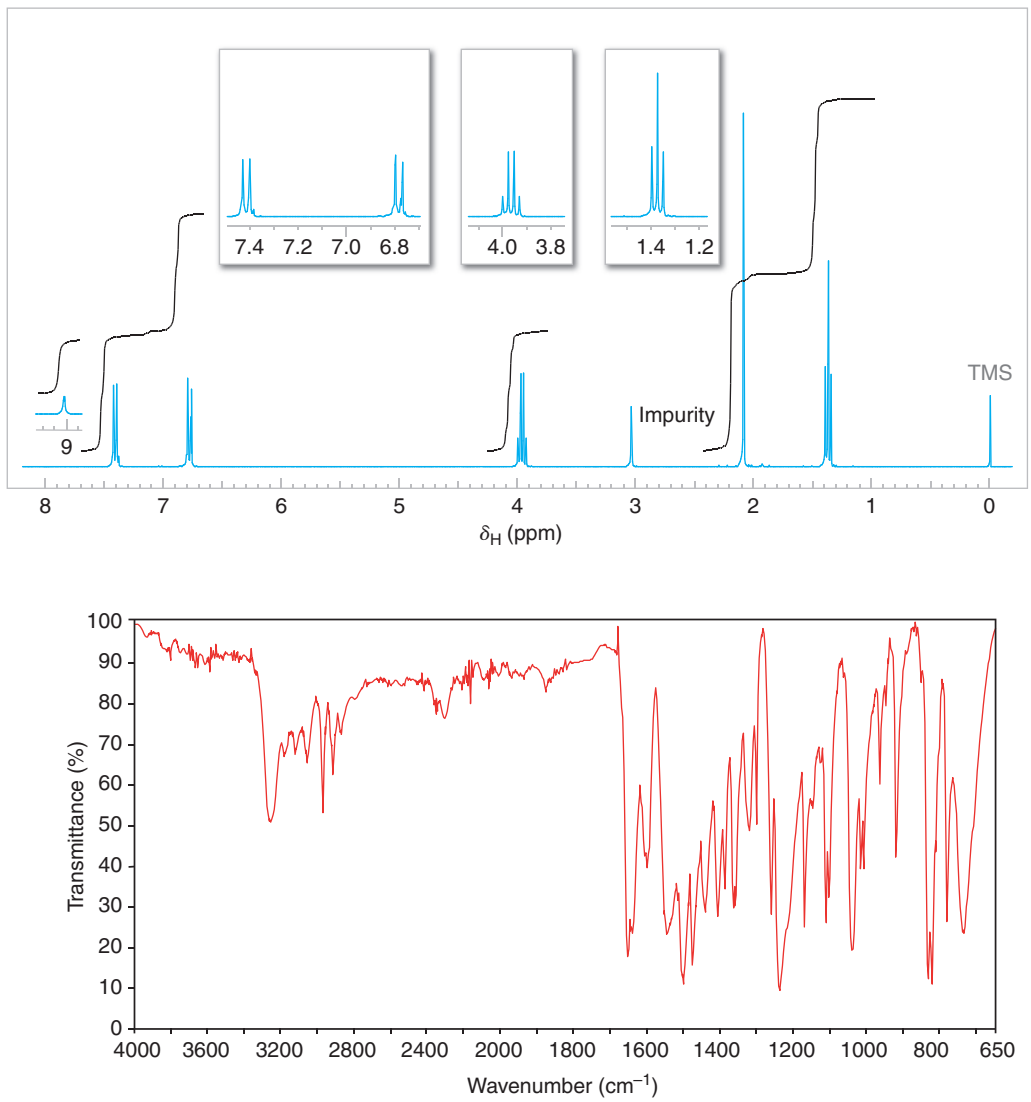


FIGURE 17.7 The 300-MHz ^{1}H NMR and IR spectra of phenacetin. Expansions of the ^{1}H NMR signals are shown in the offset plots.

17.46 Given here are the ^{1}H NMR spectra and carbonyl IR absorption peaks of five acyl compounds. Propose a structure for each.

(a) $C_8H_{14}O_4$	^{1}H NMR Spectrum		IR Spectrum
	Triplet	δ 1.2 (6H)	1740 cm^{-1}
	Singlet	δ 2.5 (4H)	
	Quartet	δ 4.1 (4H)	
(b) $C_{11}H_{14}O_2$	^{1}H NMR Spectrum		IR Spectrum
	Doublet	δ 1.0 (6H)	1720 cm^{-1}
	Multiplet	δ 2.1 (1H)	
	Doublet	δ 4.1 (2H)	
	Multiplet	δ 7.8 (5H)	
(c) $C_{10}H_{12}O_2$	^{1}H NMR Spectrum		IR Spectrum
	Triplet	δ 1.2 (3H)	1740 cm^{-1}
	Singlet	δ 3.5 (2H)	
	Quartet	δ 4.1 (2H)	
	Multiplet	δ 7.3 (5H)	

(d) $C_2H_2Cl_2O_2$	^{1}H NMR Spectrum		IR Spectrum
	Singlet	δ 6.0	Broad peak 2500–2700 cm^{-1}
	Singlet	δ 11.70	1705 cm^{-1}
(e) $C_4H_7ClO_2$	^{1}H NMR Spectrum		IR Spectrum
	Triplet	δ 1.3	1745 cm^{-1}
	Singlet	δ 4.0	
	Quartet	δ 4.2	

17.47 Compound **X** ($C_7H_{12}O_4$) is insoluble in aqueous sodium bicarbonate. The IR spectrum of **X** has a strong absorption peak near 1740 cm^{-1}, and its broadband proton-decoupled ^{13}C spectrum is given in Fig. 17.8. Propose a structure for **X**.

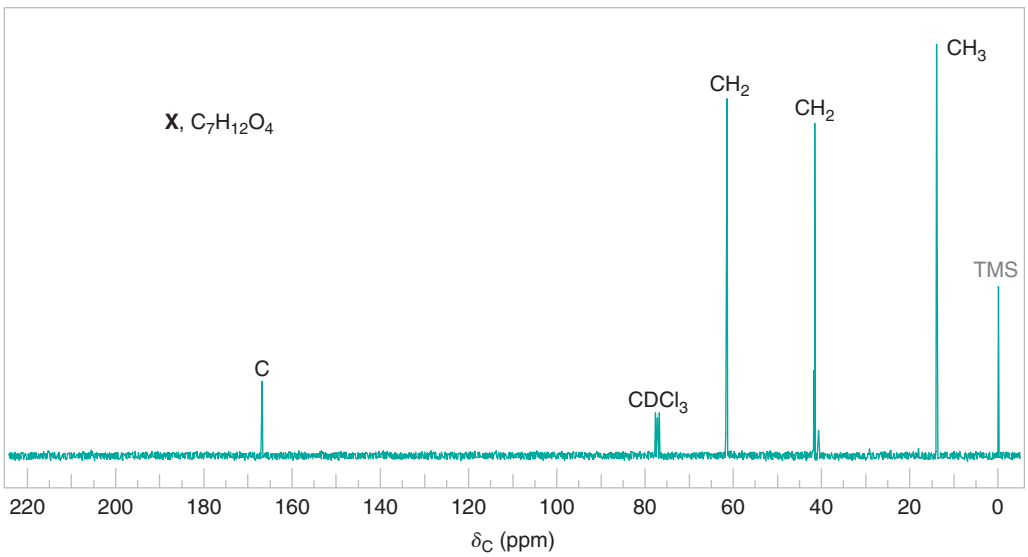


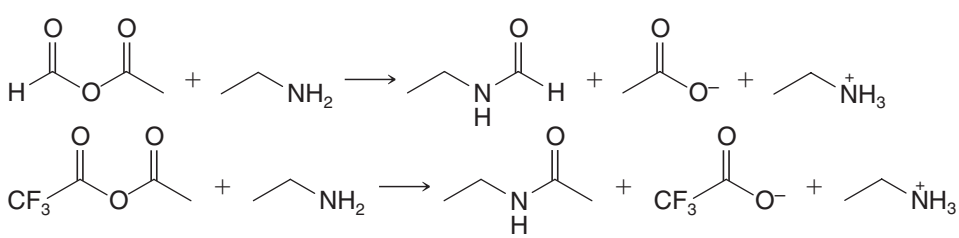
FIGURE 17.8 Broadband proton-decoupled ^{13}C NMR spectrum of compound X, Problem 17.47. Information from the DEPT ^{13}C NMR spectra is given above each peak.

17.48 Compound **Y** ($C_8H_4O_3$) dissolves slowly when warmed with aqueous sodium bicarbonate. The IR spectrum of **Y** has strong peaks at 1779 and at 1854 cm^{-1}. The broadband proton-decoupled ^{13}C spectrum of **Y** exhibits signals at δ 125 (CH), 130 (C), 136 (CH), and 162 (C). Acidification of the bicarbonate solution of **Y** gave compound **Z**. The proton-decoupled ^{13}C NMR spectrum of **Z** showed four signals. When **Y** was warmed in ethanol, compound **AA** was produced. The ^{13}C NMR spectrum of **AA** displayed 10 signals. Propose structures for **Y**, **Z**, and **AA**.

CHALLENGE PROBLEMS

17.49 Ketene, $H_2C{=}C{=}O$, is an important industrial chemical. Predict the products that would be formed when ketene reacts with (**a**) ethanol, (**b**) acetic acid, and (**c**) ethylamine. (*Hint*: Markovnikov addition occurs.)

17.50 Two unsymmetrical anhydrides react with ethylamine as follows:

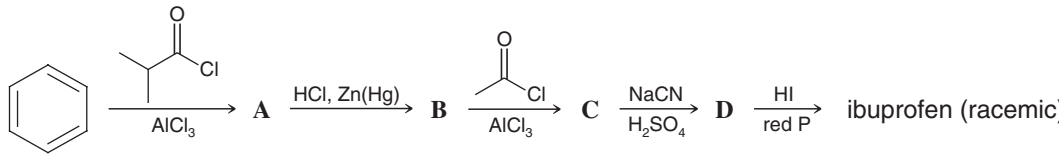


Explain the factors that might account for the formation of the products in each reaction.

17.51 Starting with 1-naphthol, suggest an alternative synthesis of the insecticide Sevin to the one given in Section 17.9A.

17.52 Suggest a synthesis of ibuprofen (Section 5.11) from benzene, employing **chloromethylation** as one step. Chloromethylation is a special case of the Friedel–Crafts reaction in which a mixture of HCHO and HCl, in the presence of $ZnCl_2$, introduces a —CH_2Cl group into an aromatic ring.

17.53 An alternative synthesis of ibuprofen is given below. Supply the structural formulas for compounds **A–D**:



17.54 As a method for the synthesis of cinnamaldehyde (3-phenyl-2-propenal), a chemist treated 3-phenyl-2-propen-1-ol with $K_2Cr_2O_7$ in sulfuric acid. The product obtained from the reaction gave a signal at δ 164.5 in its ^{13}C NMR spectrum. Alternatively, when the chemist treated 3-phenyl-2-propen-1-ol with PCC in CH_2Cl_2, the ^{13}C NMR spectrum of the product displayed a signal at δ 193.8. (All other signals in the spectra of both compounds appeared at similar chemical shifts.) **(a)** Which reaction produced cinnamaldehyde? **(b)** What was the other product?

LEARNING GROUP PROBLEMS

The Chemical Synthesis of Peptides Carboxylic acids and acyl derivatives of the carboxyl functional group are very important in biochemistry. For example, the carboxylic acid functional group is present in the family of lipids called fatty acids. Lipids called glycerides contain the ester functional group, a derivative of carboxylic acids. Furthermore, the entire class of biopolymers called proteins contain repeating amide functional group linkages. Amides are also derivatives of carboxylic acids. Both laboratory and biochemical syntheses of proteins require reactions that involve substitution at activated acyl carbons.

This Learning Group Problem focuses on the chemical synthesis of small proteins, called peptides. The essence of peptide or protein synthesis is formation of the amide functional group by reaction of an activated carboxylic acid derivative with an amine.

First we shall consider reactions for traditional chemical synthesis of peptides and then we look at reactions used in automated solid-phase peptide synthesis. The method for solid-phase peptide synthesis was invented by R. B. Merrifield (Rockefeller University), for which he earned the 1984 Nobel Prize in Chemistry. Solid-phase peptide synthesis reactions are so reliable that they have been incorporated into machines called peptide synthesizers (Section 24.7D).

1. The first step in peptide synthesis is blocking (protection) of the amine functional group of an amino acid (a compound that contains both amine and carboxylic acid functional groups). Such a reaction is shown in Section 24.7C in the reaction between Ala (alanine) and benzyl chloroformate. The functional group formed in the structure labeled Z-Ala is called a carbamate (or urethane).

(Z is a benzyloxycarbonyl group, $C_6H_5CH_2OC(=O)-$).

(a) Write a detailed mechanism for formation of Z-Ala from Ala and benzyl chloroformate in the presence of hydroxide.

(b) In the reaction of part (a), why does the amino group act as the nucleophile preferentially over the carboxylate anion?

(c) Another widely used amino protecting group is the 9-fluorenylmethoxycarbonyl (Fmoc) group. Fmoc is the protecting group most often used in automated solid-phase peptide synthesis (see part 4 below). Write a detailed mechanism for formation of an Fmoc-protected amino acid under the conditions given in Section 24.7A.

2. The second step in the reactions of Section 24.7C is the formation of a mixed anhydride. Write a detailed mechanism for the reaction between Z-Ala and ethyl chloroformate ($ClCO_2C_2H_5$) in the presence of triethylamine to form the mixed anhydride. What is the purpose of this step?

3. The third step in the sequence of reactions in Section 24.7C is the one that actually joins the new amino acid (in this case leucine, abbreviated Leu) by another amide functional group. Write a detailed mechanism for this step (from the mixed anhydride of Z-Ala to Z-Ala-Leu). Show how CO_2 and ethanol are formed in the course of this mechanism.

4. A sequence of reactions commonly used for solid-phase peptide synthesis is shown in Section 24.7D.

(a) Write a detailed mechanism for step 1, in which diisopropylcarbodiimide is used to join the carboxyl group of the first amino acid (in Fmoc-protected form) to a hydroxyl group on the polymer solid support.

(b) Step 3 of the automated synthesis involves removal of the Fmoc group by reaction with piperidine (a reaction also shown in Section 24.7A). Write a detailed mechanism for this step.