CHAPTER

10

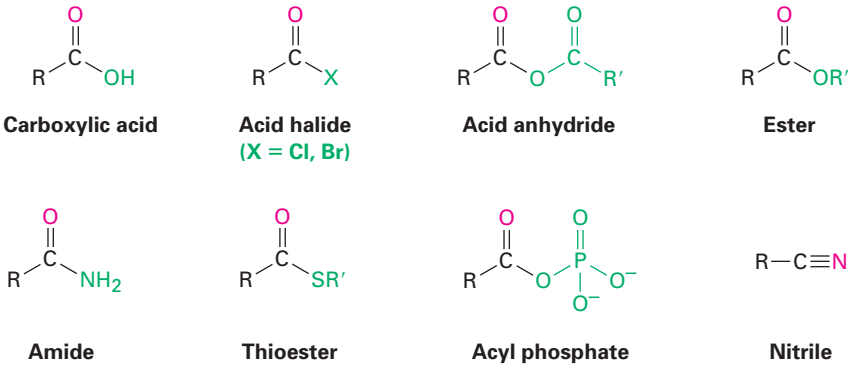
The burning sensation produced by touching or eating chili peppers is due to capsaicin, a carboxylic acid derivative called an amide.

Carboxylic Acids and Derivatives: Nucleophilic Acyl Substitution Reactions

Carboxylic acids and their derivatives are the most abundant of all organic compounds, both in the laboratory and in living organisms. Although there are many different kinds of carboxylic acid derivatives, we'll be concerned only with some of the most common ones: **acid halides**, **acid anhydrides**, **esters, amides**, and related compounds called **nitriles**. In addition, *acyl phosphates* and *thioesters* are acid derivatives of particular importance in numerous biological processes. The common structural feature of all these compounds is that they contain an acyl group bonded to an electronegative atom or substituent that can act as a leaving group in substitution reactions.

OWL

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



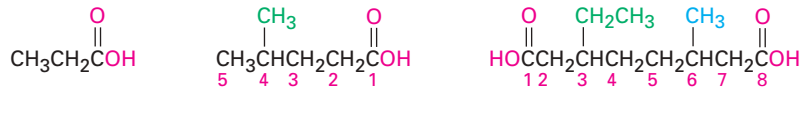
WHY THIS CHAPTER?

Because carboxylic acids and their derivatives are involved in so many industrial processes and most biological pathways, an understanding of their properties and behavior is fundamental to understanding organic and biological chemistry. In this chapter, we'll first discuss carboxylic acids themselves and will then explore in detail the most common reaction of carboxylic acid derivatives—the nucleophilic acyl substitution reaction.

10.1 Naming Carboxylic Acids and Derivatives

Carboxylic Acids: RCO_2H

Simple open-chain carboxylic acids are named by replacing the terminal *-e* of the corresponding alkane name with *-oic acid*. The $-CO_2H$ carbon is numbered C1.

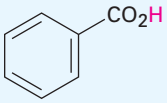


Compounds that have a $-CO_2H$ group (a **carboxyl group**) bonded to a ring are named using the suffix *-carboxylic acid*. The carboxyl carbon is attached to C1 on the ring and is not itself numbered.

Because many carboxylic acids were among the first organic compounds to be isolated and purified, a large number of acids have common names (Table 10.1). We'll use systematic names in this book, with the exception of formic

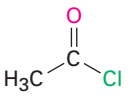
(methanoic) acid, HCO_2H, and acetic (ethanoic) acid, CH_3CO_2H, whose names are so well known that it makes little sense to refer to them in any other way. Also listed in Table 10.1 are the names for acyl groups (R–C=O) derived from the parent acids by removing –OH. Except for the eight acyl groups at the top of Table 10.1, whose common names have a *-yl* ending, all others are named systematically with an *-oyl* ending.

Table 10.1 Some Common Names of Carboxylic Acids and Acyl Groups

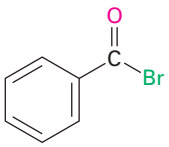
Structure	Name	Acyl group
HCO_2H	Formic	Formyl
CH_3CO_2H	Acetic	Acetyl
$CH_3CH_2CO_2H$	Propionic	Propionyl
$CH_3CH_2CH_2CO_2H$	Butyric	Butyryl
HO_2CCO_2H	Oxalic	Oxalyl
$HO_2CCH_2CO_2H$	Malonic	Malonyl
$HO_2CCH_2CH_2CO_2H$	Succinic	Succinyl
$HO_2CCH_2CH_2CH_2CO_2H$	Glutaric	Glutaryl
$HO_2CCH_2CH_2CH_2CH_2CO_2H$	Adipic	Adipoyl
$H_2C{=}CHCO_2H$	Acrylic	Acryloyl
$HO_2CCH{=}CHCO_2H$	Maleic (cis)	Maleoyl
	Fumaric (trans)	Fumaroyl
	Benzoic	Benzoyl

Acid Halides: RCOX

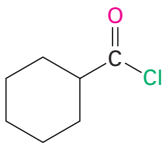
Acid halides are named by identifying first the acyl group, as in Table 10.1, and then the halide. Those cyclic carboxylic acids that take a *-carboxylic acid* ending use *-carbonyl* for the name ending of the corresponding acyl group. For example:



Acetyl chloride (from acetic acid)



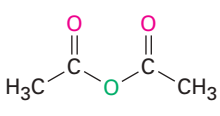
Benzoyl bromide (from benzoic acid)



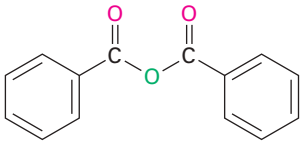
Cyclohexanecarbonyl chloride (from cyclohexanecarboxylic acid)

Acid Anhydrides: RCO_2COR'

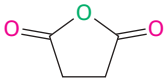
Symmetrical anhydrides from simple carboxylic acids and cyclic anhydrides from dicarboxylic acids are named by replacing the word *acid* with *anhydride.*



Acetic anhydride

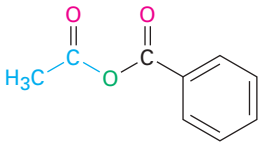


Benzoic anhydride



Succinic anhydride

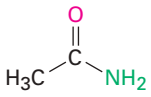
Unsymmetrical anhydrides—those prepared from two different carboxylic acids—are named by citing the two acids alphabetically and then adding *anhydride*.



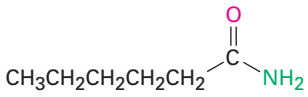
Acetic benzoic anhydride

Amides: $RCONH_2$

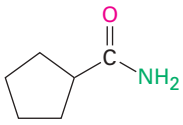
Amides with an unsubstituted $-NH_2$ group are named by replacing the *-oic acid* or *-ic acid* ending with *-amide,* or by replacing the *-carboxylic acid* ending with *-carboxamide*.



Acetamide

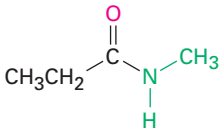


Hexanamide

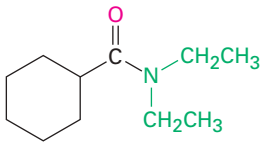


Cyclopentane-carboxamide

If the nitrogen atom is substituted, the amide is named by first identifying the substituent groups and then the parent amide. The substituents are preceded by the letter *N* to identify them as being directly attached to nitrogen.



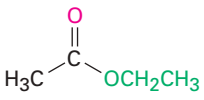
***N*-Methylpropanamide**



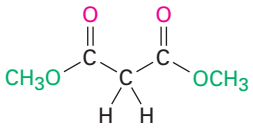
***N,N*-Diethylcyclohexanecarboxamide**

Esters: RCO_2R'

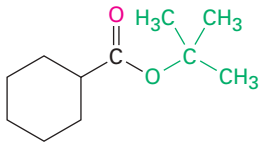
Esters are named by first giving the name of the alkyl group attached to oxygen and then identifying the carboxylic acid, with *-ic acid* replaced by *-ate*.



Ethyl acetate



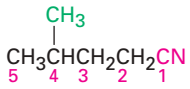
Dimethyl malonate



***tert*-Butyl cyclohexane-carboxylate**

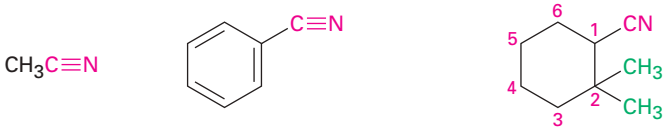
Nitriles: R—C≡N

Compounds containing the $-C{\equiv}N$ functional group are called *nitriles*. Simple acyclic nitriles are named by adding *-nitrile* as a suffix to the alkane name, with the nitrile carbon numbered C1.



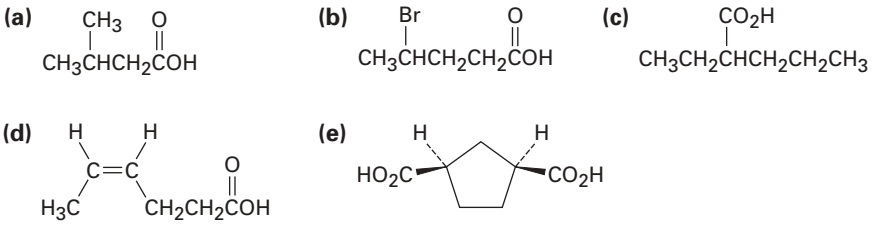
4-Methylpentanenitrile

More complex nitriles are named as derivatives of carboxylic acids by replacing the *-ic acid* or *-oic acid* ending with *-onitrile,* or by replacing the *-carboxylic acid* ending with *-carbonitrile.* In this system, the nitrile carbon atom is attached to C1 but is not itself numbered.



Acetonitrile (from acetic acid) | **Benzonitrile** (from benzoic acid) | **2,2-Dimethylcyclohexanecarbonitrile** (from 2,2-dimethylcyclohexanecarboxylic acid)

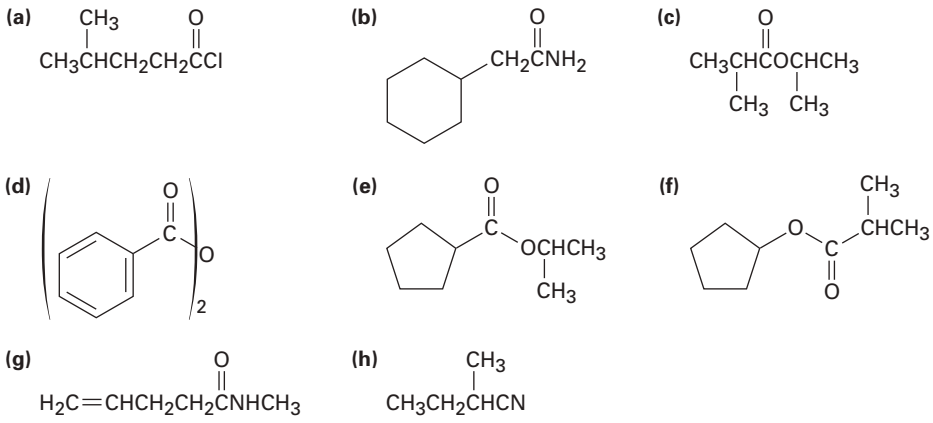
Problem 10.1 Give IUPAC names for the following carboxylic acids:



Problem 10.2 Draw structures corresponding to the following names:

(a) 2,3-Dimethylhexanoic acid
(b) 4-Methylpentanoic acid
(c) *o*-Hydroxybenzoic acid
(d) *trans*-Cyclobutane-1,2-dicarboxylic acid

Problem 10.3 Give IUPAC names for the following acyl derivatives:



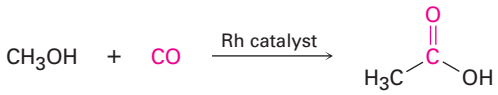
Problem 10.4 Draw structures corresponding to the following names:

(a) 2,2-Dimethylpropanoyl chloride
(b) *N*-Methylbenzamide
(c) 5,5-Dimethylhexanenitrile
(d) *tert*-Butyl butanoate
(e) *trans*-2-Methylcyclohexanecarboxamide
(f) *p*-Methylbenzoic anhydride
(g) *cis*-3-Methylcyclohexanecarbonyl bromide
(h) *p*-Bromobenzonitrile

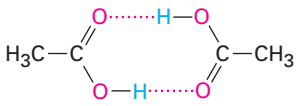
10.2 Occurrence and Properties of Carboxylic Acids and Derivatives

Carboxylic acids are everywhere in nature. Acetic acid, CH_3CO_2H, for instance, is the principal organic component of vinegar; butanoic acid, $CH_3CH_2CH_2CO_2H$, is responsible for the rancid odor of sour butter; and hexanoic acid (caproic acid), $CH_3(CH_2)_4CO_2H$, is responsible for the aroma of goats (Latin *caper,* meaning "goat") and dirty socks.

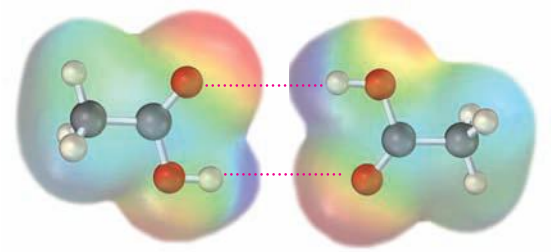
Approximately 5 million tons of acetic acid are produced each year worldwide for a variety of purposes, including preparation of the vinyl acetate polymer used in paints and adhesives. About 20% of the acetic acid synthesized industrially is obtained by oxidation of acetaldehyde. Much of the remaining 80% is prepared by the rhodium-catalyzed reaction of methanol with carbon monoxide.



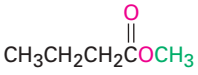
Like alcohols, carboxylic acids form strong intermolecular hydrogen bonds. Most carboxylic acids, in fact, exist as *dimers* held together by two hydrogen bonds. This strong hydrogen bonding has a noticeable effect on boiling points, making carboxylic acids boil at substantially higher temperatures than alkanes or alcohols of similar molecular weight. Acetic acid, for instance has a boiling point of 117.9 °C, versus 78.3 °C for ethanol.



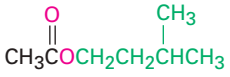
Acetic acid dimer



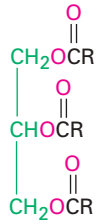
Esters, like carboxylic acids, are widespread in nature. Many simple esters are pleasant-smelling liquids that are responsible for the fragrant odors of fruits and flowers. For example, methyl butanoate is found in pineapple oil, and isopentyl acetate is a constituent of banana oil. The ester linkage is also present in animal fats and in many other biologically important molecules.



Methyl butanoate (from pineapples)

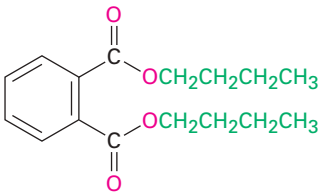


Isopentyl acetate (from bananas)



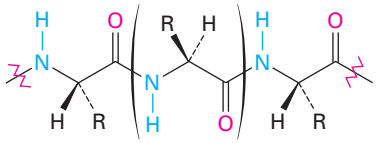
A fat (R = $C_{11–17}$ chains)

The chemical industry uses esters for a variety of purposes: ethyl acetate is a commonly used solvent, and dialkyl phthalates are used as plasticizers to keep polymers from becoming brittle. You might be aware that there is current concern about possible toxicity of phthalates at high concentrations, although a recent assessment by the U.S. Food and Drug Administration found the risk to be minimal for most people, with the possible exception of male infants.

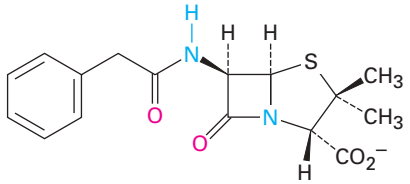


Dibutyl phthalate
(a plasticizer)

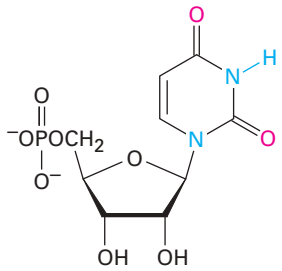
Amides, like acids and esters, are abundant in living organisms—proteins, nucleic acids, and many pharmaceuticals have amide functional groups. The reason for this abundance of amides is that they are the least reactive of the common acid derivatives and are thus stable to the temperatures and aqueous conditions found in living organisms.



A protein segment



Benzylpenicillin
(penicillin G)



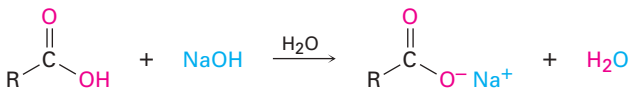
Uridine 5′-phosphate
(a ribonucleotide)

Acid chlorides and anhydrides are frequently used in chemical laboratories but are not found in nature because of their high reactivity.

10.3 Acidity of Carboxylic Acids

The most obvious property of carboxylic acids is implied by their name: carboxylic acids are *acidic*. Acetic acid, for example, has $K_a = 1.75 \times 10^{-5}$ ($pK_a = 4.76$). In practical terms, a K_a value near 10^{-5} means that only about

1% of the molecules in a 0.1 M aqueous solution are dissociated. Because of their acidity, carboxylic acids react with bases such as NaOH to give water-soluble metal **carboxylates**, $RCO_2^-\ Na^+$.



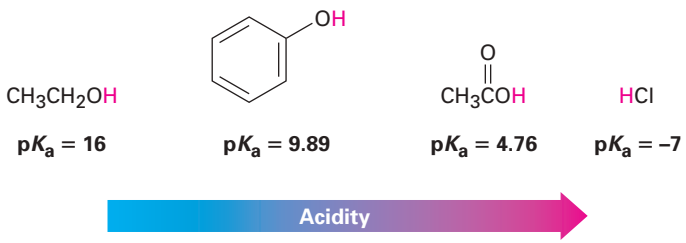
A carboxylic acid (water-insoluble) **A carboxylic acid salt (water-soluble)**

As indicated by the list of K_a values in Table 10.2, there is a considerable range in the strengths of various carboxylic acids. For most, K_a is in the range 10^{-4} to 10^{-5}, but some, such as trifluoroacetic acid ($K_a = 0.59$) are much stronger. The electron-withdrawing fluorine substituents stabilize the carboxylate ion by sharing the negative charge and thus favor dissociation of the acid.

Table 10.2 Acid Strengths of Some Carboxylic Acids

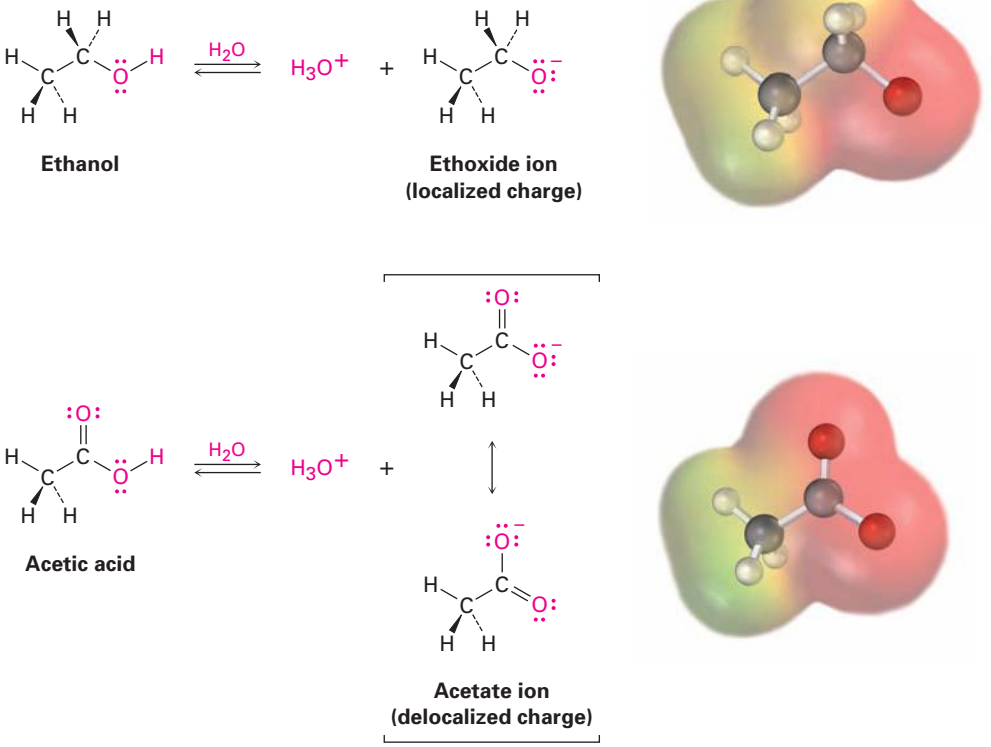
Structure	K_a	pK_a	
CF_3CO_2H	0.59	0.23	Stronger acid
HCO_2H	1.77×10^{-4}	3.75	
$HOCH_2CO_2H$	1.5×10^{-4}	3.84	
$C_6H_5CO_2H$	6.46×10^{-5}	4.19	
$H_2C{=}CHCO_2H$	5.6×10^{-5}	4.25	
CH_3CO_2H	1.75×10^{-5}	4.76	
$CH_3CH_2CO_2H$	1.34×10^{-5}	4.87	
CH_3CH_2OH (ethanol)	(1.00×10^{-16})	(16.00)	Weaker acid

Although much weaker than mineral acids, carboxylic acids are nevertheless much stronger acids than alcohols and phenols. The K_a of ethanol, for example, is approximately 10^{-16}, making ethanol a weaker acid than acetic acid by a factor of 10^{11}.



Why are carboxylic acids so much more acidic than alcohols even though both contain –OH groups? To answer this question, compare the relative stabilities of carboxylate anions versus alkoxide anions (Figure 10.1). In an alkoxide ion, the negative charge is localized on one oxygen atom, but in a carboxylate ion, the negative charge is spread out over both oxygen atoms because a carboxylate anion is a resonance hybrid of two equivalent structures (Section 4.10). Because a carboxylate ion is more stable than an alkoxide ion, it is lower in energy and is present to a greater extent at equilibrium.

Figure 10.1 An alkoxide ion has its charge localized on one oxygen atom and is less stable, while a carboxylate ion has the charge spread equally over both oxygens and is therefore more stable.



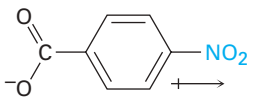
Worked Example 10.1

Predicting Acid Strength

Which would you expect to be the stronger acid, benzoic acid or *p*-nitrobenzoic acid?

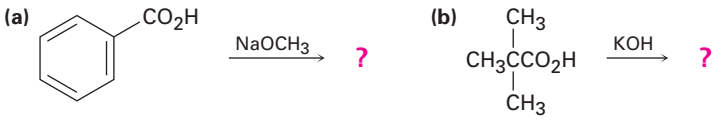
Solution

The more stabilized the carboxylate anion, the stronger the acid. We know from its effect on aromatic substitution (Section 5.7) that a nitro group is electron-withdrawing and can stabilize a negative charge. Thus, a *p*-nitrobenzoate ion is more stable than a benzoate ion, and *p*-nitrobenzoic acid is stronger than benzoic acid.



Nitro group withdraws electrons from ring and stabilizes negative charge.

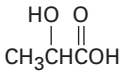
Problem 10.5 Draw structures for the products of the following reactions:



Problem 10.6 Rank the following compounds in order of increasing acidity:

(a) Sulfuric acid, methanol, phenol, *p*-nitrophenol, acetic acid
(b) Benzoic acid, ethanol, *p*-cyanobenzoic acid

Problem 10.7 Which would you expect to be a stronger acid, the lactic acid found in tired muscles or acetic acid? Explain.

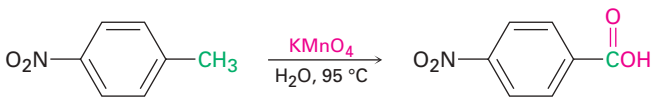


Lactic acid

10.4 Synthesis of Carboxylic Acids

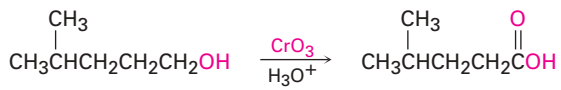
Let's review briefly several methods for preparing carboxylic acids that we've seen in past chapters.

- A substituted alkylbenzene can be oxidized with $KMnO_4$ to give a substituted benzoic acid (Section 5.8).

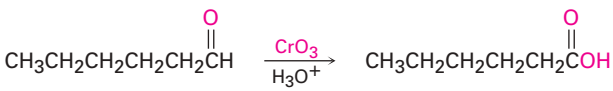


***p*-Nitrotoluene** ***p*-Nitrobenzoic acid (88%)**

- Primary alcohols and aldehydes can be oxidized with aqueous CrO_3 or $Na_2Cr_2O_7$ to give carboxylic acids (Sections 8.4 and 9.4).



4-Methylpentan-1-ol **4-Methylpentanoic acid**

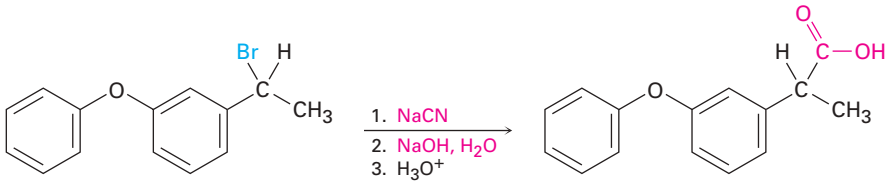


Hexanal **Hexanoic acid**

In addition to the preceding two methods, there are numerous other ways to prepare carboxylic acids. For instance, carboxylic acids can be prepared from nitriles, R—C≡N, by a *hydrolysis* reaction with hot aqueous acid or base. Since nitriles themselves are usually prepared by an S_N2 reaction between an alkyl halide and cyanide ion, CN^-, the two-step sequence of cyanide ion

displacement followed by nitrile hydrolysis is a good method for converting an alkyl halide into a carboxylic acid: RBr → RC≡N → RCO_2H. As with all S_N2 reactions, the method works best with primary alkyl halides, although secondary alkyl halides can sometimes be used (Section 7.5).

An example of nitrile hydrolysis occurs in the commercial synthesis of the antiarthritis drug fenoprofen, a nonsteroidal anti-inflammatory agent (see Chapter 5 *Interlude*) marketed under the name Nalfon.



Fenoprofen
(an antiarthritis agent)

Problem 10.8 Show the steps in the conversion of iodomethane to acetic acid by the nitrile hydrolysis route. Would a similar route work for the conversion of iodobenzene to benzoic acid? Explain.

10.5 Nucleophilic Acyl Substitution Reactions

We saw in Chapter 9 that the addition of a nucleophile to the polar C=O bond is a general feature of aldehyde and ketone chemistry. Carboxylic acids and their derivatives also react with nucleophiles, but the ultimate product is different from that of the aldehyde/ketone reaction. Instead of undergoing protonation to yield an alcohol, the initially formed alkoxide intermediate expels one of the substituents originally bonded to the carbonyl carbon, leading to the formation of a new carbonyl compound by a **nucleophilic acyl substitution reaction** (Figure 10.2).

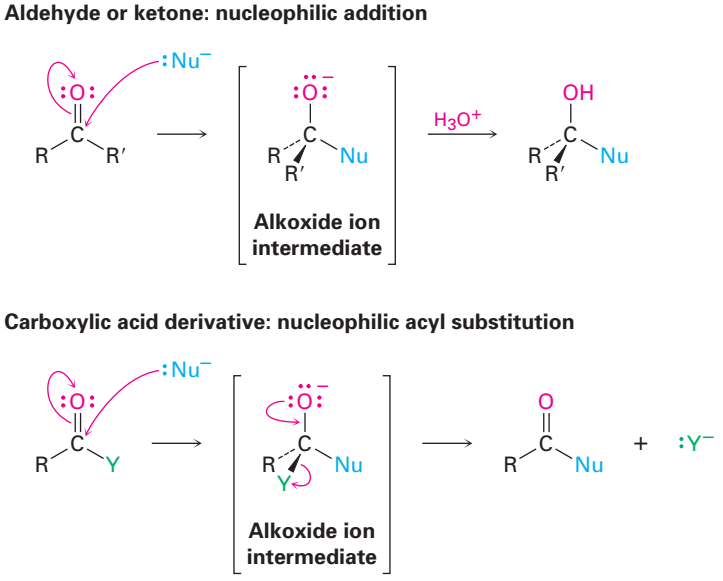
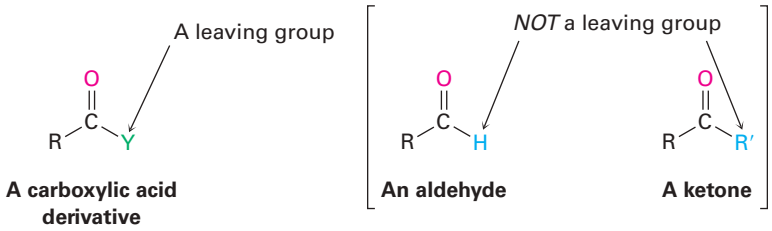


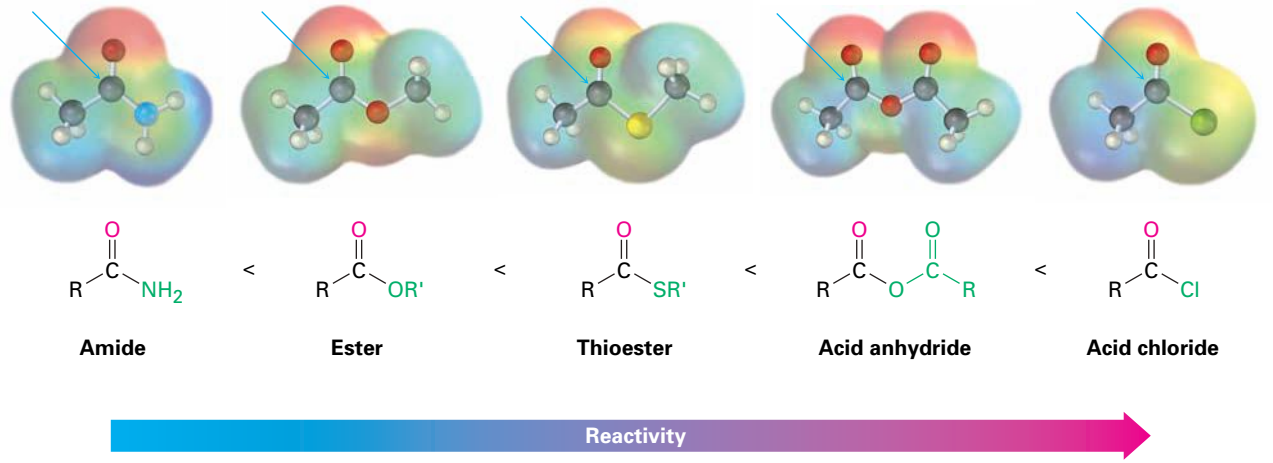
Figure 10.2 The general mechanisms of nucleophilic addition and nucleophilic acyl substitution reactions. Both reactions begin with the addition of a nucleophile to a polar C=O bond to give a tetrahedral, alkoxide ion intermediate. The intermediate formed from an aldehyde or ketone is protonated to give an alcohol, but the intermediate formed from a carboxylic acid derivative expels a leaving group to give a new carbonyl compound.

The different behavior toward nucleophiles of aldehydes/ketones and carboxylic acid derivatives is a consequence of structure. Carboxylic acid derivatives have an acyl carbon bonded to a group –Y that can leave as a stable anion. As soon as addition of a nucleophile occurs, the group leaves and a new carbonyl compound forms. Aldehydes and ketones have no such leaving group, however, and therefore don't undergo substitution.



Both the initial addition step and the subsequent elimination step can affect the overall rate of a nucleophilic acyl substitution reaction, but the addition step is generally the rate-limiting one. Thus, any factor that makes the carbonyl group more reactive toward nucleophiles favors the substitution process.

As a general rule, the more electron-poor the C=O carbon, the more readily the compound reacts with nucleophiles. Thus, acid chlorides are the most reactive compounds because the electronegative chlorine atom strongly withdraws electrons from the carbonyl carbon, whereas amides are the least reactive compounds. Although the differences are subtle, electrostatic potential maps indicate the relative reactivities of various carboxylic acid derivatives by the relative blueness on the C=O carbons. Note that thioesters, RCOSR′, which are commonly found in biological molecules, have a reactivity intermediate between that of esters and acid anhydrides. Thioesters are thus stable enough to exist in living organisms but are reactive enough to be useful.



A consequence of these reactivity differences is that it's usually possible to convert a more reactive acid derivative into a less reactive one. Acid chlorides, for example, can be converted into esters and amides, but amides and

esters can't be converted into acid chlorides. Remembering the reactivity order is therefore a useful way to keep track of a large number of reactions (Figure 10.3).

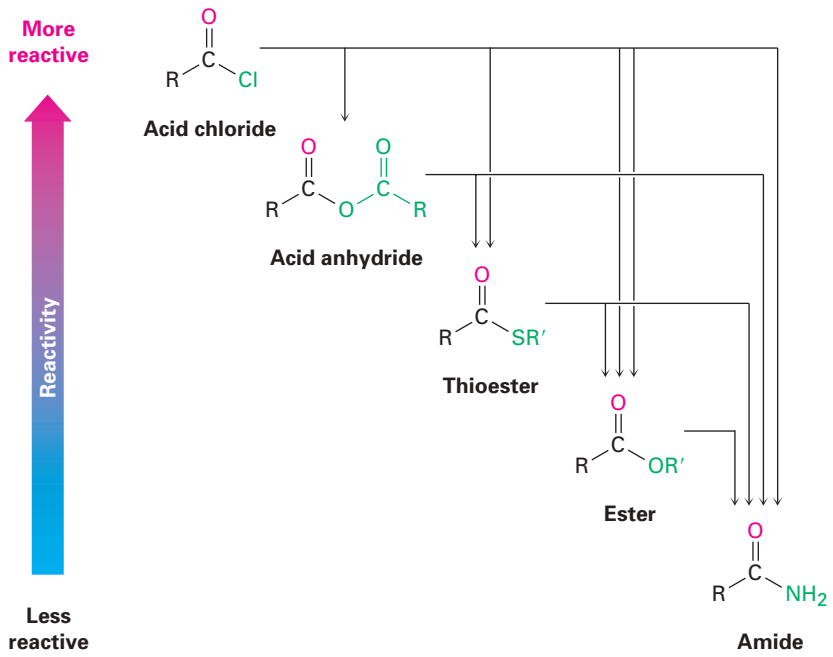


Figure 10.3 Interconversions of carboxylic acid derivatives. More reactive compounds can be converted into less reactive ones, but not vice versa.

In studying the chemistry of carboxylic acids and derivatives in the next few sections, we'll be concerned largely with the reactions of just a few nucleophiles and will see that the same kinds of reactions keep occurring (Figure 10.4).

- **Hydrolysis:** Reaction with water to yield a carboxylic acid
- **Alcoholysis:** Reaction with an alcohol to yield an ester
- **Aminolysis:** Reaction with ammonia or an amine to yield an amide
- **Reduction:** Reaction with a hydride reducing agent to yield an alcohol
- **Grignard reaction:** Reaction with an organomagnesium reagent to yield an alcohol

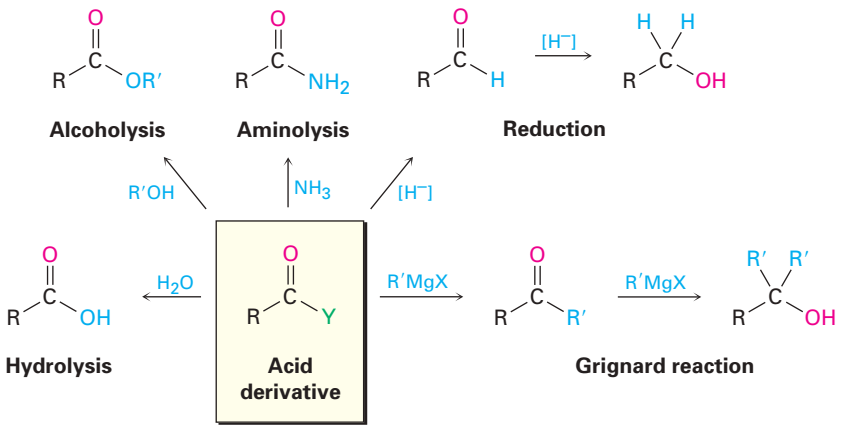
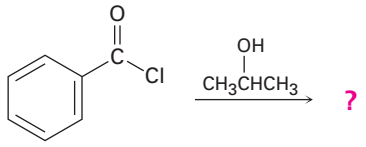


Figure 10.4 Some general reactions of carboxylic acid derivatives.

Worked Example 10.2 Predicting the Product of a Nucleophilic Acyl Substitution Reaction

Predict the product of the following nucleophilic acyl substitution reaction of benzoyl chloride with propan-2-ol:

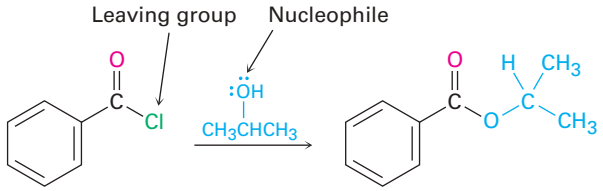


Benzoyl chloride

Strategy

A nucleophilic acyl substitution reaction involves the substitution of a nucleophile for a leaving group in a carboxylic acid derivative. Identify the leaving group (Cl^- in the case of an acid chloride) and the nucleophile (an alcohol in this case), and replace one by the other. The product is the ester isopropyl benzoate.

Solution

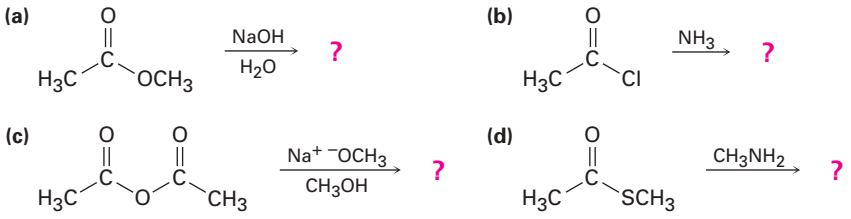


Benzoyl chloride **Isopropyl benzoate**

Problem 10.9 Which compound in each of the following sets is more reactive in nucleophilic acyl substitution reactions?

(a) CH_3COCl or $CH_3CO_2CH_3$
(b) $(CH_3)_2CHCONH_2$ or $CH_3CH_2CO_2CH_3$
(c) $CH_3CO_2CH_3$ or $CH_3CO_2COCH_3$
(d) $CH_3CO_2CH_3$ or CH_3CHO

Problem 10.10 Predict the products of the following nucleophilic acyl substitution reactions:

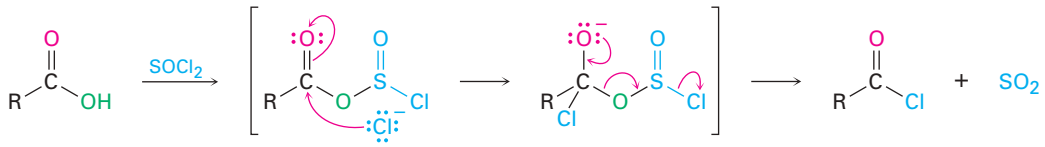


10.6 Carboxylic Acids and Their Reactions

The direct nucleophilic acyl substitution of a carboxylic acid is difficult because −OH is a poor leaving group (Section 7.5). Thus, it's usually necessary to enhance the reactivity of the acid, either by using a strong acid catalyst to protonate the carboxyl and make it a better acceptor or by converting the −OH into a better leaving group. Under the right conditions, however, acid chlorides, anhydrides, esters, and amides can all be prepared from carboxylic acids.

Conversion of Acids into Acid Chlorides ($RCO_2H \rightarrow RCOCl$)

Carboxylic acids are converted into acid chlorides by treatment with thionyl chloride, $SOCl_2$. The reaction occurs by a nucleophilic acyl substitution pathway in which the carboxylic acid is first converted into an acyl chlorosulfite intermediate, thereby replacing the −OH of the acid with a much better leaving group. The chlorosulfite then reacts with a nucleophilic chloride ion.



Carboxylic acid **A chlorosulfite** **Acid chloride**

Conversion of Acids into Esters ($RCO_2H \rightarrow RCO_2R'$)

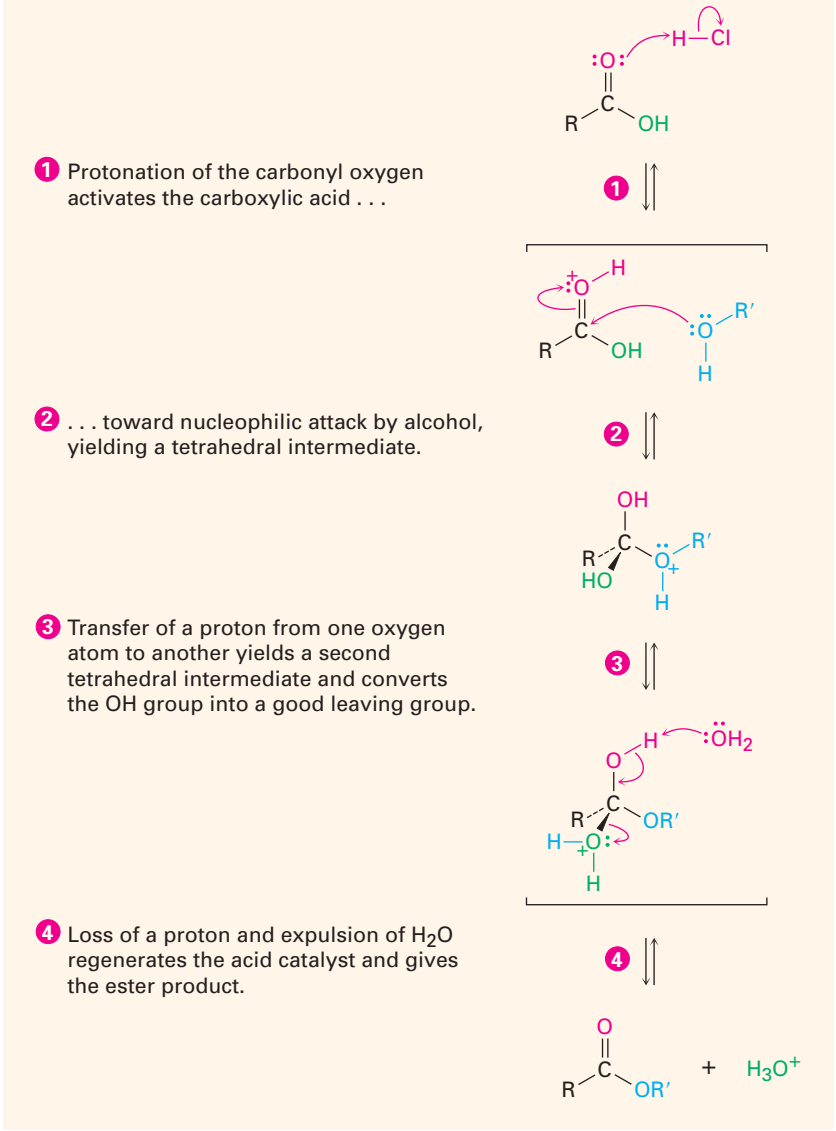
Perhaps the most useful reaction of carboxylic acids is their conversion into esters by reaction with an alcohol—the substitution of −OH by −OR. Called the **Fischer esterification reaction**, the simplest method involves heating the carboxylic acid with an acid catalyst in an alcohol solvent.

Benzoic acid **Ethyl benzoate (91%)**

As shown in Figure 10.5, the acid catalyst first protonates an oxygen atom of the $-CO_2H$ group, which gives the carboxylic acid a positive charge and makes it more reactive toward nucleophiles. An alcohol molecule then adds to the protonated carboxylic acid, and subsequent loss of water yields the ester product.

MECHANISM

Figure 10.5 Mechanism of the Fischer esterification reaction of a carboxylic acid to yield an ester. The reaction is an acid-catalyzed nucleophilic acyl substitution.

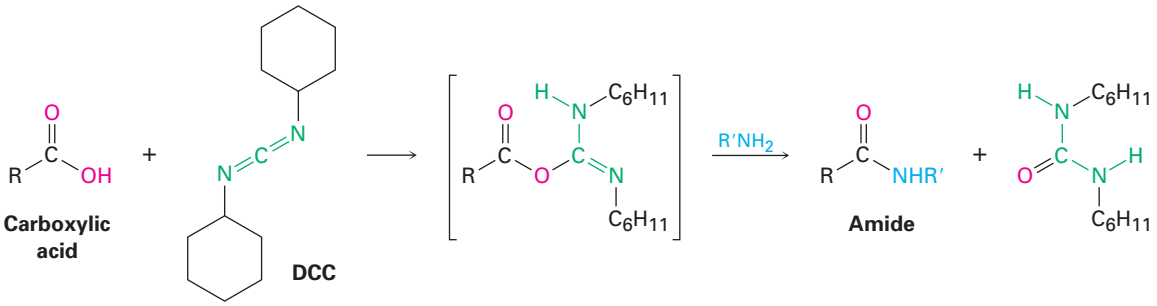


All steps in the Fischer esterification reaction are reversible, and the position of the equilibrium can be driven either forward or backward depending on the reaction conditions. Ester formation is favored when alcohol is used as the solvent, but carboxylic acid is favored when the solvent is water.

Conversion of Acids into Amides ($RCO_2H \rightarrow RCONH_2$)

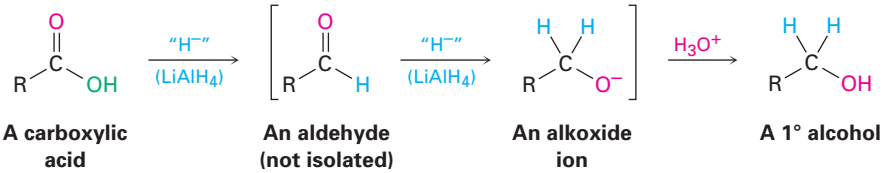
Amides are carboxylic acid derivatives in which the acid –OH group has been replaced by a nitrogen substituent, $–NH_2$, –NHR, or $–NR_2$. Amides are difficult to prepare directly from acids by substitution with an amine because amines are bases, which convert acidic carboxyl groups into their unreactive carboxylate anions. Thus, the –OH must be activated by making it a better,

nonacidic leaving group. In practice, amides are usually prepared by treating the carboxylic acid with dicyclohexylcarbodiimide (DCC) to activate it, followed by addition of the amine. We'll see in Section 15.7 that this DCC method for preparing amides is particularly useful for the laboratory synthesis of proteins from amino acids.



Conversion of Acids into Alcohols ($RCO_2H \rightarrow RCH_2OH$)

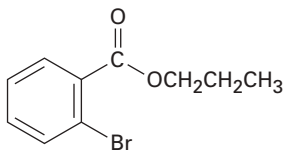
As we saw in Section 8.3, carboxylic acids are reduced by lithium aluminum hydride ($LiAlH_4$) to yield primary alcohols. The reaction occurs by initial substitution of the acid –OH group by –H to give an aldehyde intermediate that is further reduced to the alcohol.



Worked Example 10.3

Synthesizing an Ester from an Acid

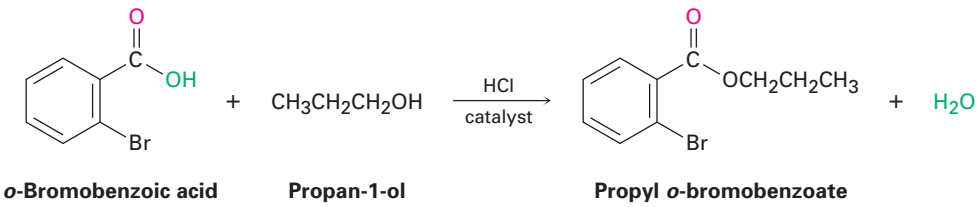
How might you prepare the following ester using a Fischer esterification reaction?



Strategy

Begin by identifying the two parts of the ester. The acyl part comes from the carboxylic acid, and the –OR part comes from the alcohol. In this case, the target molecule is propyl *o*-bromobenzoate, so it can be prepared by treating *o*-bromobenzoic acid with propan-1-ol.

Solution

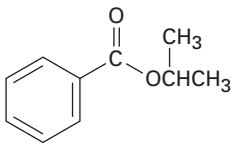


Problem 10.11 What products would you obtain by treating benzoic acid with the following reagents?

(a) $SOCl_2$ **(b)** CH_3OH, HCl **(c)** $LiAlH_4$ **(d)** NaOH

Problem 10.12 Show how you might prepare the following esters using a Fischer esterification reaction:

(a) $CH_3COCH_2CH_2CH_2CH_3$ **(b)** $CH_3CH_2CH_2COCH_3$ **(c)**



10.7 Acid Halides and Their Reactions

Acid chlorides are prepared from carboxylic acids by reaction with thionyl chloride, $SOCl_2$, as we saw in the previous section.

Acid halides are among the most reactive of the various carboxylic acid derivatives and can be converted into many other kinds of substances. The halogen can be replaced by –OH to yield an acid, by –OR to yield an ester, or by $-NH_2$ to yield an amide. In addition, acid halides can be reduced by $LiAlH_4$ to give primary alcohols or allowed to react with Grignard reagents to give tertiary alcohols (Figure 10.6). Neither of these latter two processes is often used, however, because the product alcohols can be made more conveniently from esters. Although illustrated only for acid chlorides, similar reactions take place with other acid halides.

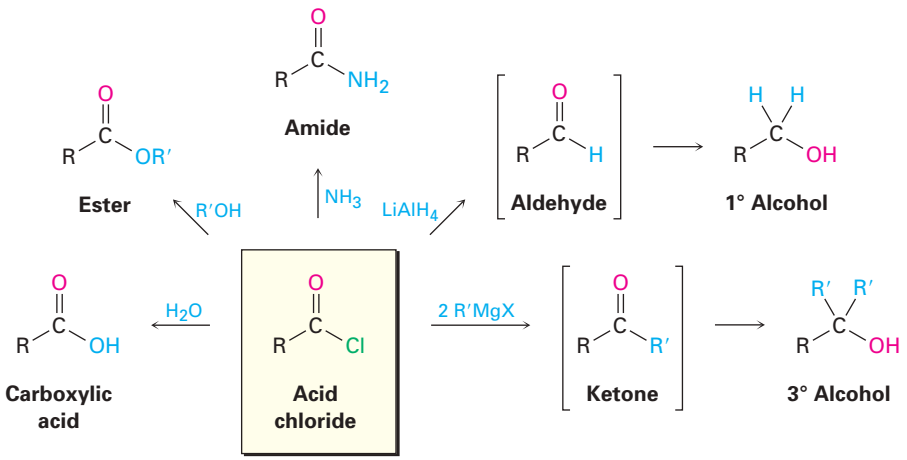
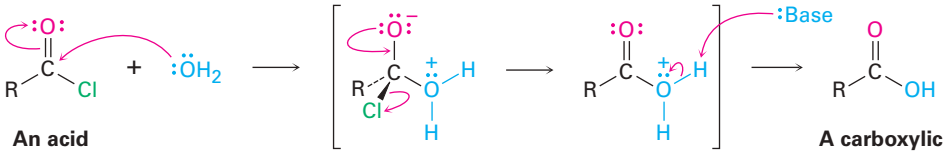


Figure 10.6 Some nucleophilic acyl substitution reactions of acid chlorides.

Conversion of Acid Chlorides into Acids (RCOCl → RCO_2H)

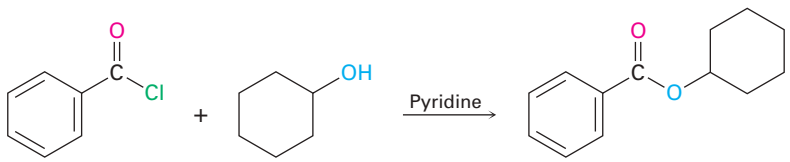
Acid chlorides react with water to yield carboxylic acids—the substitution of –Cl by –OH. This hydrolysis reaction is a typical nucleophilic acyl substitution process and is initiated by attack of the nucleophile water on the acid chloride carbonyl group. The initially formed tetrahedral intermediate undergoes loss of HCl to yield the product.



An acid chloride **A carboxylic acid**

Conversion of Acid Chlorides into Esters (RCOCl → RCO_2R')

Acid chlorides react with alcohols to yield esters in a reaction analogous to their reaction with water to yield acids.

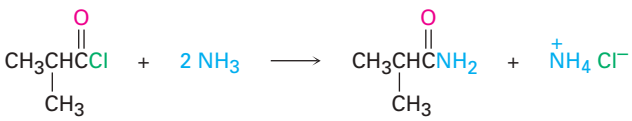


Benzoyl chloride **Cyclohexanol** **Cyclohexyl benzoate (97%)**

Because HCl is generated as a by-product, the reaction is usually carried out in the presence of an amine base such as pyridine (see Section 12.6), which reacts with the HCl as it's formed and prevents it from causing side reactions.

Conversion of Acid Chlorides into Amides (RCOCl → $RCONH_2$)

Acid chlorides react rapidly with ammonia and with amines to give amides—the substitution of –Cl by $-NR_2$. Both monosubstituted and disubstituted amines can be used. For example, 2-methylpropanamide is prepared by reaction of 2-methylpropanoyl chloride with ammonia. Note that one extra equivalent of ammonia is added to react with the HCl generated.



2-Methylpropanoyl chloride **2-Methylpropanamide (83%)**

Worked Example 10.4

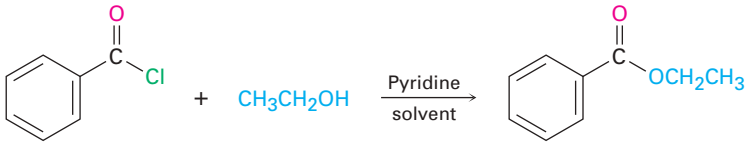
Synthesizing an Ester from an Acid Chloride

Show how you could prepare ethyl benzoate by reaction of an acid chloride with an alcohol.

Strategy

As its name implies, ethyl benzoate can be made by reaction of *ethyl* alcohol with the acid chloride of *benzoic* acid.

Solution



Benzoyl chloride **Ethanol** **Ethyl benzoate**

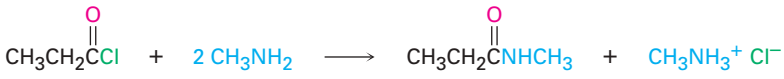
Worked Example 10.5 Synthesizing an Amide from an Acid Chloride

Show how you would prepare *N*-methylpropanamide by reaction of an acid chloride with an amine.

Strategy

The name of the product gives a hint as to how it can be prepared. Reaction of *methyl*amine with *propanoyl* chloride gives *N*-methylpropanamide.

Solution



Propanoyl chloride **Methylamine** ***N*-Methylpropanamide**

Problem 10.13 How could you prepare the following esters using the reaction of an acid chloride with an alcohol?

(a) $CH_3CH_2CO_2CH_3$ **(b)** $CH_3CO_2CH_2CH_3$ **(c)** Cyclohexyl acetate

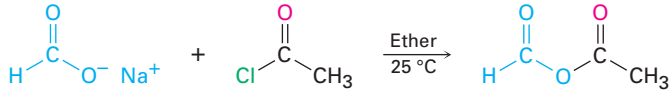
Problem 10.14 Write the steps in the mechanism of the reaction between ammonia and 2-methylpropanoyl chloride to yield 2-methylpropanamide.

Problem 10.15 What amines would react with what acid chlorides to give the following amide products?

(a) $CH_3CH_2CONH_2$ **(b)** $(CH_3)_2CHCH_2CONHCH_3$
(c) *N,N*-Dimethylpropanamide **(d)** *N,N*-Diethylbenzamide

10.8 Acid Anhydrides and Their Reactions

The best method for preparing acid anhydrides is by a nucleophilic acyl substitution reaction of an acid chloride with a carboxylic acid anion. Both symmetrical and unsymmetrical acid anhydrides can be prepared in this way.

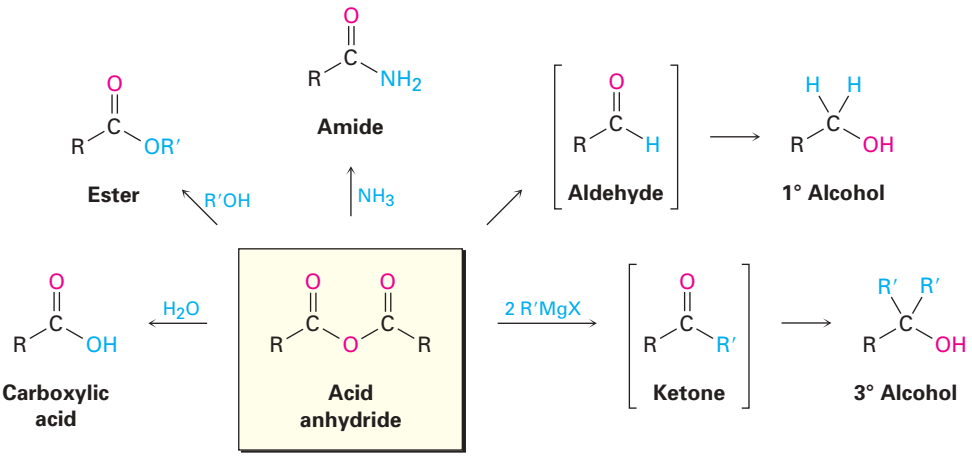


Sodium formate **Acetyl chloride** **Acetic formic anhydride (64%)**

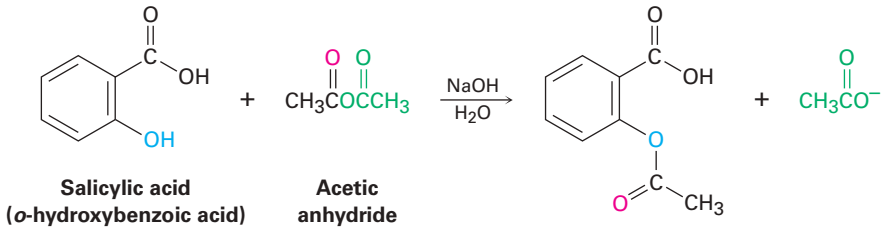
The chemistry of acid anhydrides is similar to that of acid chlorides. Thus, acid anhydrides react with water to form acids, with alcohols to form esters, and with amines to form amides (Figure 10.7). They also undergo reduction

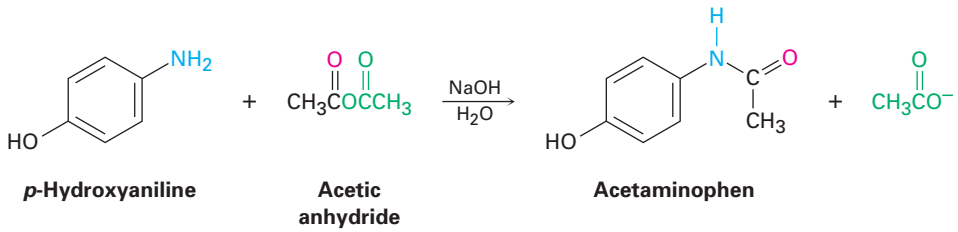
with $LiAlH_4$ to give primary alcohols and Grignard reaction to give tertiary alcohols, but neither of these reactions is often used since the alcohol products can be made more conveniently from esters.

Figure 10.7 Some reactions of acid anhydrides.



Acetic anhydride is often used to prepare acetate esters of complex alcohols and to prepare substituted acetamides from amines. For example, aspirin (an ester) is prepared by reaction of acetic anhydride with *o*-hydroxybenzoic acid. Similarly, acetaminophen (an amide; the active ingredient in Tylenol) is prepared by reaction of acetic anhydride with *p*-hydroxyaniline.

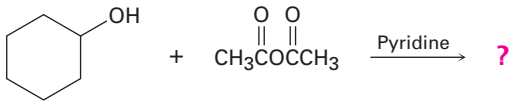




Notice in both of these examples that only "half" of the anhydride molecule is used; the other half acts as the leaving group during the nucleophilic acyl substitution step and produces carboxylate anion as a by-product. Thus, anhydrides are inefficient to use, and acid chlorides are normally used instead.

Worked Example 10.6 **Predicting the Product of a Nucleophilic Acyl Substitution Reaction**

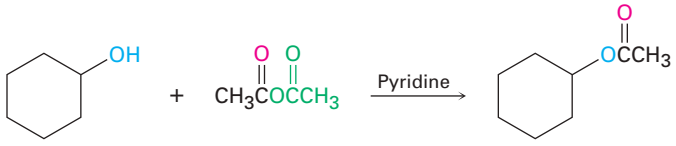
What is the product of the following reaction?



Strategy

Acid anhydrides undergo a nucleophilic acyl substitution reaction with alcohols to give esters. Reaction of cyclohexanol with acetic anhydride yields cyclohexyl acetate by nucleophilic acyl substitution of the $-OCOCH_3$ group of the anhydride by the $-OR$ group of the alcohol.

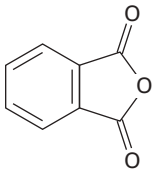
Solution



Cyclohexanol **Cyclohexyl acetate**

Problem 10.16 Write the steps in the mechanism of the reaction between *p*-hydroxyaniline and acetic anhydride to prepare acetaminophen.

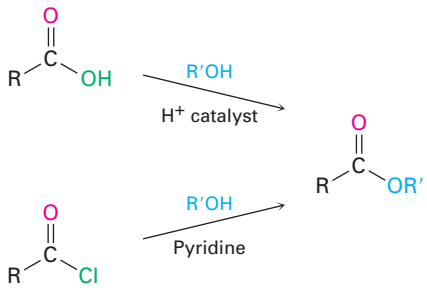
Problem 10.17 What product would you expect to obtain from the reaction of 1 equivalent of methanol with a cyclic anhydride such as phthalic anhydride?



Phthalic anhydride

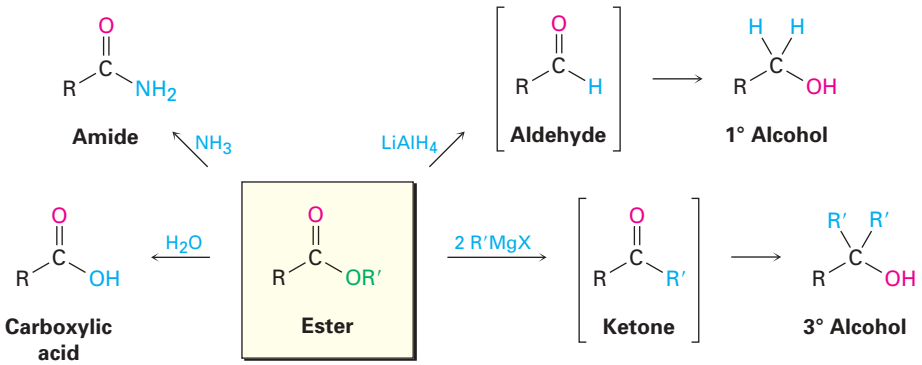
10.9 Esters and Their Reactions

Esters are usually prepared either from acids or acid chlorides by the methods already discussed. Thus, carboxylic acids are converted directly into esters by Fischer esterification with an alcohol (Section 10.6), and acid chlorides are converted into esters by reaction with an alcohol in the presence of pyridine (Section 10.7).



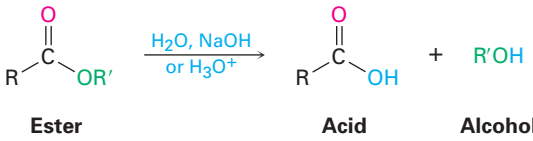
Esters show the same kinds of chemistry we've seen for other acyl derivatives, but they're less reactive toward nucleophiles than acid chlorides or anhydrides. Figure 10.8 shows some general reactions of esters.

Figure 10.8 Some reactions of esters.

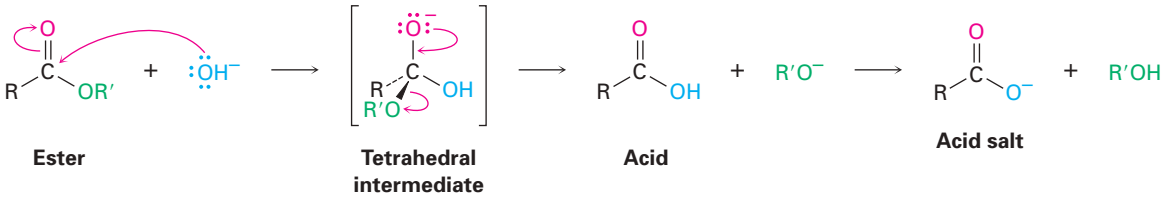


Conversion of Esters into Acids ($RCO_2R' \rightarrow RCO_2H$)

Esters are hydrolyzed either by aqueous base or by aqueous acid to yield a carboxylic acid plus an alcohol.



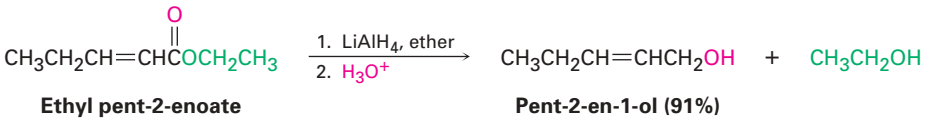
Hydrolysis in basic solution is called *saponification,* after the Latin word *sapo,* "soap." (As we'll see in Section 16.2, soap is made by the base-induced ester hydrolysis of animal fat.) Ester hydrolysis occurs by a typical nucleophilic acyl substitution pathway in which OH^- nucleophile adds to the ester carbonyl group, yielding a tetrahedral alkoxide intermediate. Loss of RO^- then gives a carboxylic acid, which is deprotonated to give the acid carboxylate plus alcohol.



Conversion of Esters into Alcohols by Reduction ($RCO_2R' \rightarrow RCH_2OH$)

Esters are reduced to primary alcohols by treatment with $LiAlH_4$ (Section 8.3). The reaction occurs by an initial nucleophilic acyl substitution reaction in which hydride ion adds to the carbonyl group followed by

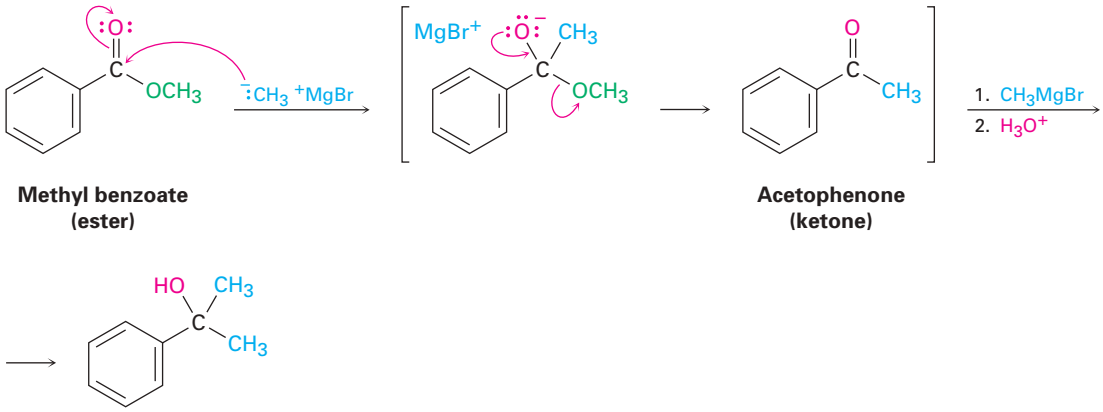
elimination of an alkoxide ion to give an aldehyde intermediate. Further reduction of the aldehyde by a typical nucleophilic addition process gives the primary alcohol.



Ethyl pent-2-enoate **Pent-2-en-1-ol (91%)**

Conversion of Esters into Alcohols by Grignard Reaction ($RCO_2R' \rightarrow R_3COH$)

Grignard reagents react with esters to yield tertiary alcohols in which two of the substituents on the hydroxyl-bearing carbon are identical (Section 8.3). For example, methyl benzoate reacts with 2 equivalents of CH_3MgBr to yield 2-phenylpropan-2-ol. The reaction occurs by nucleophilic addition of a Grignard reagent to the ester, elimination of alkoxide ion to give an intermediate ketone, and further nucleophilic addition to the ketone to yield the tertiary alcohol (Figure 10.9).



Methyl benzoate (ester) **Acetophenone (ketone)**

2-Phenylpropan-2-ol (3° alcohol)

Figure 10.9 Mechanism of the reaction of a Grignard reagent with an ester to yield a tertiary alcohol. A ketone intermediate is involved.

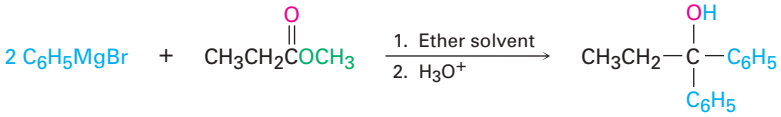
Worked Example 10.7 Synthesizing an Alcohol from an Ester

How could you use the reaction of a Grignard reagent with an ester to prepare 1,1-diphenylpropan-1-ol?

Strategy The product of the reaction between a Grignard reagent and an ester is a tertiary alcohol in which the alcohol carbon and one of the attached groups have come from the ester and the remaining two groups bonded to the alcohol carbon have come from the Grignard reagent. Since 1,1-diphenylpropan-1-ol has two phenyl groups and one ethyl group bonded to the alcohol carbon, it must be

prepared from reaction of a phenylmagnesium halide with an ester of propanoic acid.

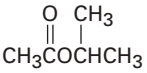
Solution



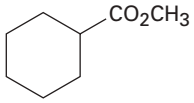
1,1-Diphenylpropan-1-ol

Problem 10.18 Show the products of hydrolysis of the following esters:

(a)



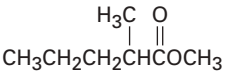
(b)



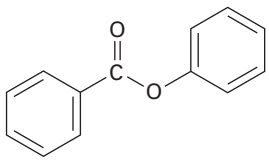
Problem 10.19 Why do you suppose the saponification of esters is not reversible? In other words, why doesn't treatment of a carboxylic acid with an alkoxide ion give an ester?

Problem 10.20 Show the products you would obtain by reduction of the following esters with $LiAlH_4$:

(a)

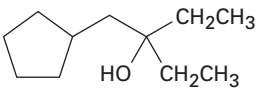


(b)

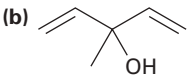


Problem 10.21 What ester and what Grignard reagent might you use to prepare the following alcohols?

(a)

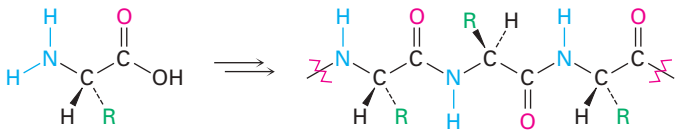


(b)



10.10 Amides and Their Reactions

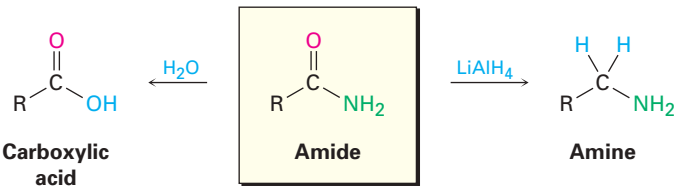
Amides are usually prepared by reaction of an acid chloride with an amine (Section 10.7). They are much less reactive than acid chlorides, acid anhydrides, and esters, and the amide bond is stable enough to link different amino acids together to form proteins.



An amino acid **A protein**

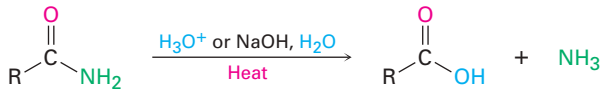
The most common reactions of amides are their hydrolysis to give carboxylic acids and their reduction with $LiAlH_4$. Interestingly, though, the reduction product of an amide is an *amine* rather than the expected alcohol (Figure 10.10).

Figure 10.10 Some reactions of amides.



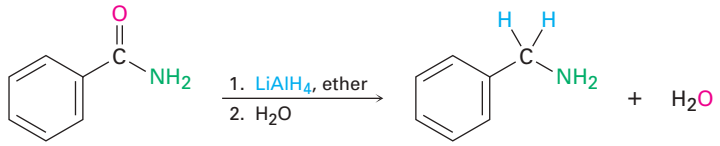
Conversion of Amides into Acids ($RCONH_2 \rightarrow RCO_2H$)

Amides undergo hydrolysis in either aqueous acid or base to yield carboxylic acids plus amine. Although the reaction is slow and requires prolonged heating, the overall transformation is a typical nucleophilic acyl substitution of $-OH$ for $-NH_2$. In biochemistry, the reaction is particularly useful for hydrolyzing proteins to their constituent amino acids.



Conversion of Amides into Amines by Reduction ($RCONH_2 \rightarrow RCH_2NH_2$)

Like other carboxylic acid derivatives, amides are reduced by $LiAlH_4$. The product of this reduction, however, is an amine rather than an alcohol. For example:

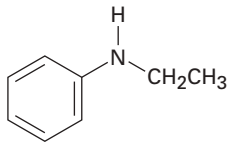


The effect of amide reduction is to convert the amide carbonyl group into a methylene group ($C{=}O \rightarrow CH_2$). This kind of reaction is specific for amides and does not occur with other carboxylic acid derivatives.

Worked Example 10.8

Synthesizing an Amine from an Amide

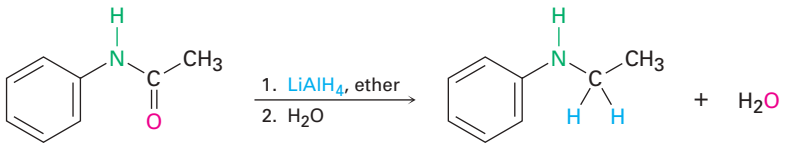
How could you prepare *N*-ethylaniline by reduction of an amide with $LiAlH_4$?



***N*-Ethylaniline**

Strategy Reduction of an amide with $LiAlH_4$ yields an amine. To find the starting material for synthesis of *N*-ethylaniline, look for a CH_2 position next to the nitrogen atom and replace that CH_2 by C=O. In this case, the amide is *N*-phenylacetamide.

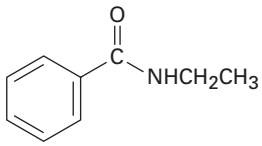
Solution



***N*-Phenylacetamide** ***N*-Ethylaniline**

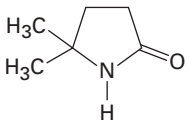
Problem 10.22 How would you convert *N*-ethylbenzamide into the following substances?

(a) Benzoic acid
(b) Benzyl alcohol
(c) *N*-Ethylbenzylamine, $C_6H_5CH_2NHCH_2CH_3$



***N*-Ethylbenzamide**

Problem 10.23 The reduction of an amide with $LiAlH_4$ to yield an amine occurs with both acyclic and cyclic amides (*lactams*). What product would you obtain from reduction of 5,5-dimethylpyrrolidin-2-one with $LiAlH_4$?



5,5-Dimethylpyrrolidin-2-one (a lactam)

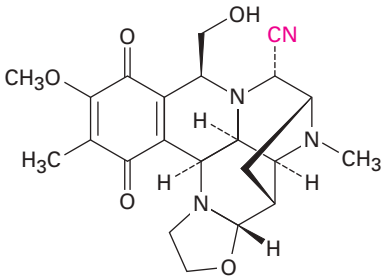
10.11 Nitriles and Their Reactions

Nitriles, R—C≡N, are analogous to carboxylic acids in that both have a carbon atom with three bonds to electronegative atoms and both contain a multiple bond.

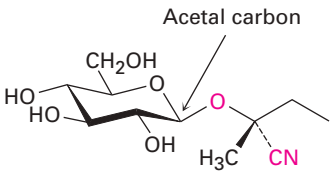
A nitrile—three bonds to nitrogen **An acid—three bonds to two oxygens**

Nitriles occur less frequently in living organisms than do acid derivatives, although more than 1000 examples are known. Cyanocycline A, for instance, has been isolated from the bacterium *Streptomyces lavendulae* and found to

have both antimicrobial and antitumor activity. Lotaustralin, isolated from the cassava plant, contains a sugar with an acetal carbon, one oxygen of which is bonded to a nitrile-bearing carbon (Sugar—O—C—CN). On hydrolysis of the acetal, hydrogen cyanide is released, thereby acting as a natural insecticide to protect the plant.



Cyanocycline A



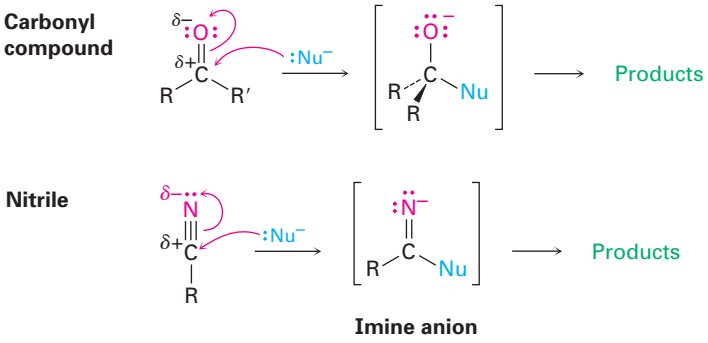
Lotaustralin
(a cyanogenic glycoside)

The simplest method of preparing nitriles is by the S_N2 reaction of cyanide ion with a primary alkyl halide, as discussed in Section 7.5.

$$RCH_2Br + Na^+ {}^-CN \xrightarrow[\text{reaction}]{S_N2} RCH_2C{\equiv}N + NaBr$$

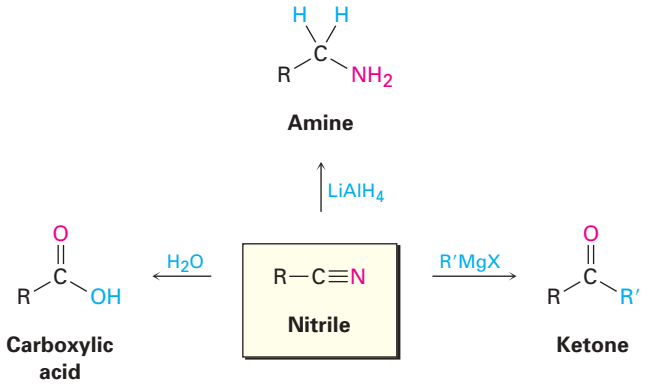
Reactions of Nitriles

Like a carbonyl group, a nitrile group is strongly polarized and has an electrophilic carbon atom. Nitriles therefore react with nucleophiles to yield sp^2-hybridized imine anions in a reaction analogous to the formation of an sp^3-hybridized alkoxide ion by nucleophilic addition to a carbonyl group. The imine anion then goes on to yield further products.



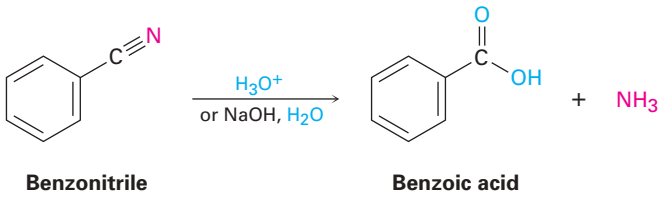
Among the most useful reactions of nitriles are hydrolysis to give a carboxylic acid plus ammonia, reduction to yield an amine, and Grignard reaction to give a ketone (Figure 10.11).

Figure 10.11 Some reactions of nitriles.



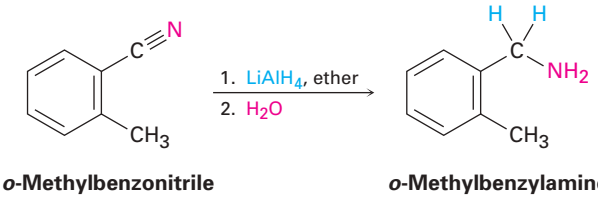
Conversion of Nitriles into Carboxylic Acids (RCN → RCO_2H)

Nitriles are hydrolyzed in either acidic or basic solution to yield carboxylic acids and ammonia (or an amine). For example, benzonitrile gives benzoic acid.



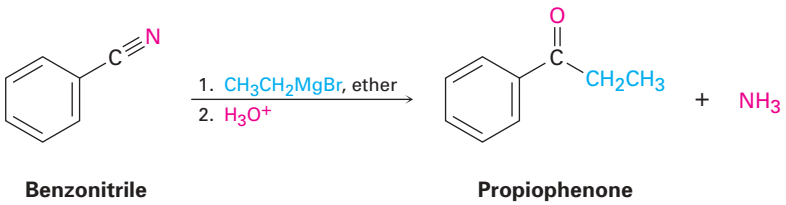
Conversion of Nitriles into Amines by Reduction (RCN → RCH_2NH_2)

Reduction of a nitrile with $LiAlH_4$ gives a primary amine, RNH_2, just as reduction of an ester gives a primary alcohol, ROH. For example:



Conversion of Nitriles into Ketones by Reaction with Grignard Reagents

Grignard reagents, RMgX, add to nitriles to give intermediate imine anions that can be hydrolyzed to yield ketones. For example, benzonitrile reacts with ethylmagnesium bromide to give propiophenone.



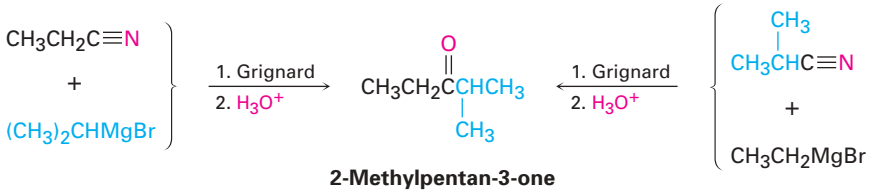
Worked Example 10.9 Synthesizing a Ketone from a Nitrile

Show how you could prepare 2-methylpentan-3-one by reaction of a Grignard reagent with a nitrile.

Strategy

Look at the structure of the target ketone. The C=O carbon comes from the C≡N carbon, one of the two attached groups comes from the Grignard reagent, and the other attached group was present in the nitrile. Thus, there are two ways to prepare a ketone from a nitrile by Grignard addition.

Solution

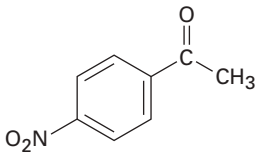


2-Methylpentan-3-one

Problem 10.24 How would you prepare the following ketones by reaction of a Grignard reagent and a nitrile?

(a) $CH_3CH_2CCH_2CH_3$ (O)

(b)



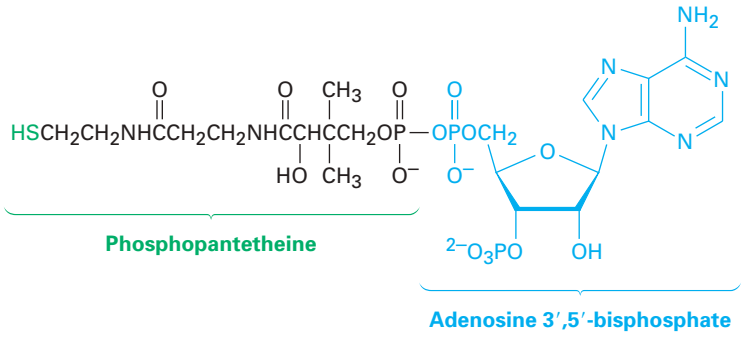
Problem 10.25 How would you prepare 1-phenylbutan-2-one, $C_6H_5CH_2COCH_2CH_3$, from benzyl bromide, $C_6H_5CH_2Br$? More than one step is needed.

10.12 Biological Carboxylic Acid Derivatives: Thioesters and Acyl Phosphates

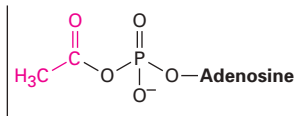
As mentioned in the chapter introduction, the substrate for nucleophilic acyl substitution reactions in living organisms is generally either a **thioester (RCOSR′)** or an **acyl phosphate** (**$RCO_2PO_3^{2-}$** or **$RCO_2PO_3R'^-$**). Both are intermediate in reactivity between acid chlorides and esters. Thus, they are stable enough to exist in living organisms but reactive enough to undergo acyl substitution.

Acetyl coenzyme A, abbreviated acetyl CoA, is the most common thioester in nature. Coenzyme A is a thiol (RSH) that contains a phosphoric anhydride linkage (O═P—O—P═O) between phosphopantetheine and adenosine 3′,5′-bisphosphate. (The prefix *bis-* means "two" and indicates that adenosine 3′,5′-bisphosphate has two phosphate groups, one on C3′ and one on C5′.) Reaction of coenzyme A with an acyl phosphate gives the acyl CoA (Figure 10.12).

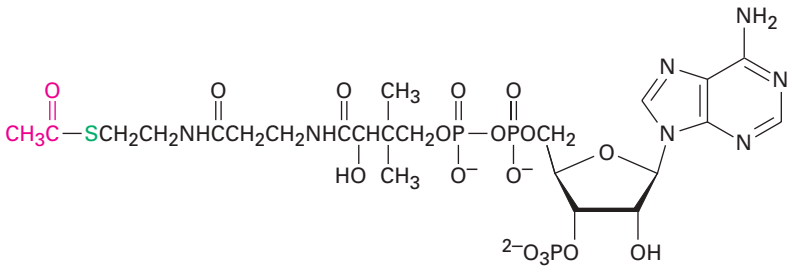
Figure 10.12 Formation of the thioester acetyl CoA by nucleophilic acyl substitution reaction of coenzyme A (CoA) with acetyl adenylate.



Coenzyme A (CoA)

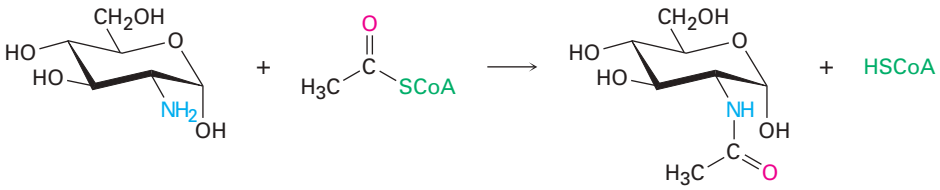


Acetyl adenylate
(an acyl phosphate)



Acetyl CoA

Once formed, an acyl CoA is a substrate for numerous nucleophilic acyl substitution reactions. For example, *N*-acetylglucosamine, a component of cartilage and other connective tissues, is synthesized by an aminolysis reaction between glucosamine and acetyl CoA.



Glucosamine
(an amine)

***N*-Acetylglucosamine**
(an amide)

Problem 10.26 Write the mechanism of the reaction shown in Figure 10.12 between coenzyme A and acetyl adenylate to give acetyl CoA.

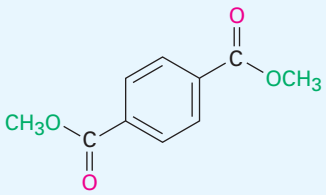
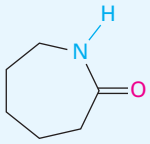
10.13 Polymers from Carbonyl Compounds: Polyamides and Polyesters

Now that we've seen the main classes of carboxylic acid derivatives, it's interesting to note how some of these compounds are used in daily life. Surely their most important such use is as polymers, particularly polyamides (*nylons*) and polyesters.

There are two main classes of synthetic polymers: *chain-growth polymers* and *step-growth polymers*. Polyethylene and other alkene polymers like those we saw in Section 4.7 are called **chain-growth polymers** because they are prepared in chain-reaction processes. An initiator first adds to the double bond of an alkene monomer to produce a reactive intermediate, which then adds to a second alkene monomer unit, and so on. The polymer chain lengthens as more monomer units add successively to the end of the growing chain.

Step-growth polymers are prepared by polymerization reactions between two difunctional molecules, with each new bond formed in a discrete step, independent of all other bonds in the polymer. The key bond-forming step is often a nucleophilic acyl substitution of a carboxylic acid derivative. Some commercially important step-growth polymers are shown in Table 10.3.

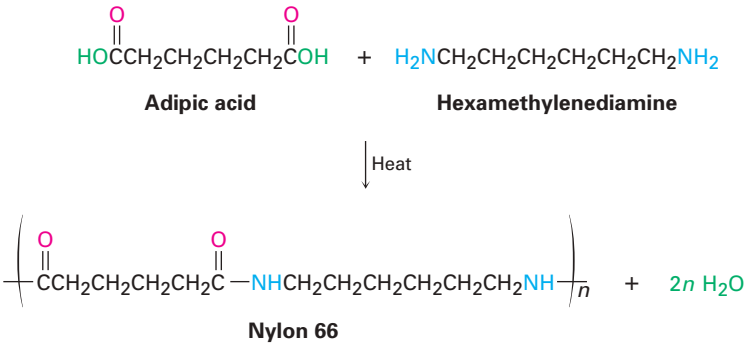
Table 10.3 Some Important Step-Growth Polymers and Their Uses

Monomers	Structure	Polymer	Uses
Adipic acid + Hexamethylenediamine	$HOCCH_2CH_2CH_2CH_2COH$ (O, O) + $H_2NCH_2CH_2CH_2CH_2CH_2CH_2NH_2$	Nylon 66	Fibers, clothing, tire cord
Dimethyl terephthalate + Ethylene glycol	 + $HOCH_2CH_2OH$	Dacron, Mylar, Terylene	Fibers, clothing, films, tire cord
Caprolactam		Nylon 6, Perlon	Fibers, castings

Polyamides

The best-known step-growth polymers are the *polyamides*, or **nylons**, prepared by reaction of a diamine with a diacid. For example, nylon 66 is prepared by reaction of adipic acid (hexanedioic acid) with hexamethylene-

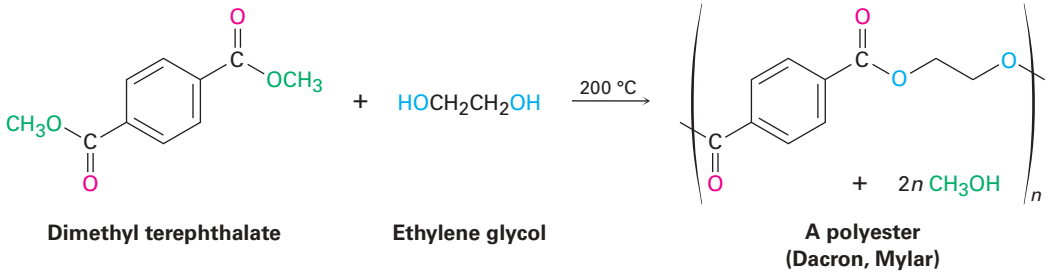
diamine (hexane-1,6-diamine) at 280 °C. The designation "66" tells the number of carbon atoms in the diamine (the first 6) and the diacid (the second 6).



Nylons are used both in engineering applications and in making fibers. A combination of high impact strength and abrasion resistance makes nylon an excellent metal substitute for bearings and gears. As fiber, nylon is used in a variety of applications, from clothing to tire cord to ropes.

Polyesters

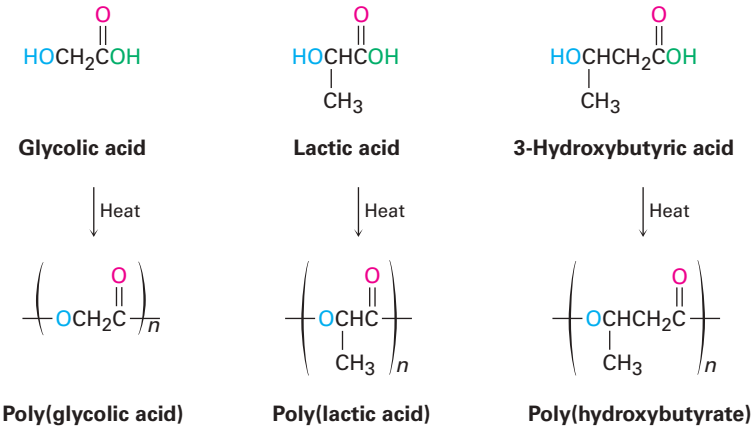
Just as a polyamide is made by reaction between a diacid and a diamine, a **polyester** is made by reaction between a diacid and a dialcohol. The most generally useful polyester is that made by reaction between dimethyl terephthalate (dimethyl benzene-1,4-dicarboxylate) and ethylene glycol (ethane-1,2-diol). The product is used under the trade name Dacron to make clothing fiber and tire cord, and under the name Mylar to make recording tape. The tensile strength of poly(ethylene terephthalate) film is nearly equal to that of steel.



Biodegradable Polymers

Because plastics are too often thrown away rather than recycled, much work has been carried out on developing *biodegradable* polymers, which can be broken down rapidly in landfills by soil microorganisms. Among the most common biodegradable polymers are poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and polyhydroxybutyrate (PHB). All are polyesters and are therefore susceptible to hydrolysis of their ester links. As an example, biodegradable

sutures made of poly(glycolic acid) are hydrolyzed and absorbed by the body within 90 days after surgery.

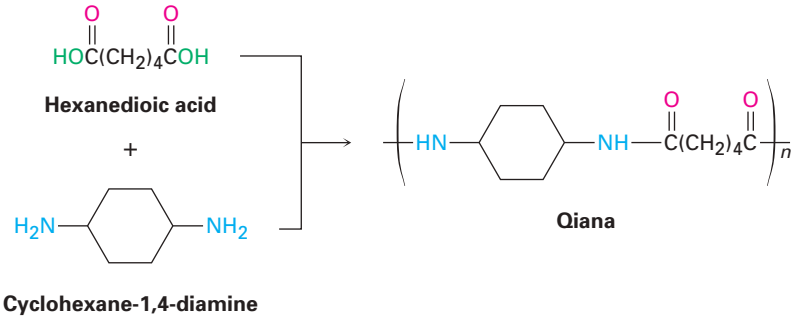


Worked Example 10.10 Predicting the Structure of a Polymer

Draw the structure of Qiana, a polyamide made by high-temperature reaction of hexanedioic acid with cyclohexane-1,4-diamine.

Strategy Reaction of a diacid with a diamine gives a polyamide.

Solution



Problem 10.27 Kevlar, a nylon polymer used in bulletproof vests, is made by reaction of benzene-1,4-dicarboxylic acid with benzene-1,4-diamine. Show the structure of Kevlar.

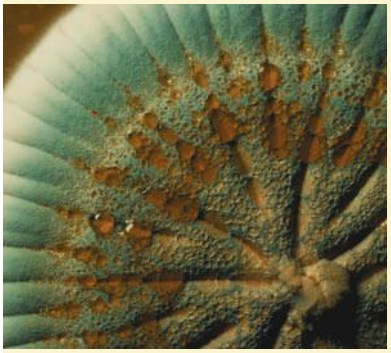
INTERLUDE

β-Lactam Antibiotics

You should never underestimate the value of hard work and logical thinking, but it's also true that blind luck plays a role in most real scientific breakthroughs. What has been called "the supreme example of luck in all scientific history" occurred in the late summer of 1928, when the

continued

INTERLUDE



Andrew McClenaghan/Photo Researchers, Inc.

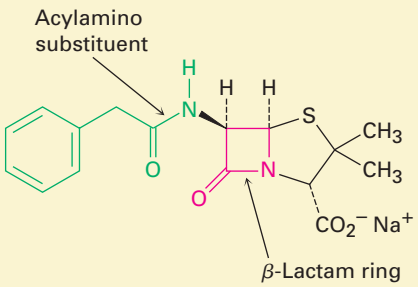
***Penicillium* mold growing in a petri dish.**

Scottish bacteriologist Alexander Fleming went on vacation, leaving in his lab a culture plate recently inoculated with the bacterium *Staphylococcus aureus.*

While Fleming was away, an extraordinary chain of events occurred. First, a 9-day cold spell lowered the laboratory temperature to a point where the *Staphylococcus* on the plate could not grow. During this time, spores from a colony of the mold *Penicillium notatum* being grown on the floor below wafted up into Fleming's lab and landed in the culture plate. The temperature then rose, and both *Staphylococcus* and *Penicillium* began to grow. On returning from vacation, Fleming discarded the plate into a tray of antiseptic, intending to sterilize it. Evidently, though, the plate did not sink deeply enough into the antiseptic, because when Fleming happened to glance at it a few days later, what he saw changed the course of history. He noticed that the growing *Penicillium* mold appeared to dissolve the colonies of staphylococci.

Fleming realized that the *Penicillium* mold must be producing a chemical that killed the *Staphylococcus* bacteria, and he spent several years trying to isolate the substance. Finally, in 1939, the Australian pathologist Howard Florey and the German refugee Ernst Chain managed to isolate the active substance, called *penicillin.* The dramatic ability of penicillin to cure infections in mice was soon demonstrated, and successful tests in humans followed shortly thereafter. By 1943, penicillin was being produced on a large scale for military use in World War II, and by 1944 it was being used on civilians. Fleming, Florey, and Chain shared the 1945 Nobel Prize in Medicine.

Now called benzylpenicillin, or penicillin G, the substance first discovered by Fleming is but one member of a large class of so-called β-lactam antibiotics, compounds with a four-membered lactam (cyclic amide) ring. The four-membered lactam ring is fused to a five-membered, sulfur-containing ring, and the carbon atom next to the lactam carbonyl group is bonded to an acylamino substituent, RCONH–. This acylamino side chain can be varied in the laboratory to provide many hundreds of penicillin analogs with different biological activity profiles. Ampicillin, for instance, has an α-aminophenylacetamido substituent [$PhCH(NH_2)CONH–$].



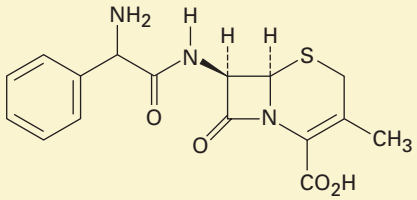
Benzylpenicillin (penicillin G)

Closely related to the penicillins are the *cephalosporins,* a group of β-lactam antibiotics that contain an unsaturated six-membered, sulfur-containing ring. Cephalexin, marketed under the trade name Keflex, is an

continued

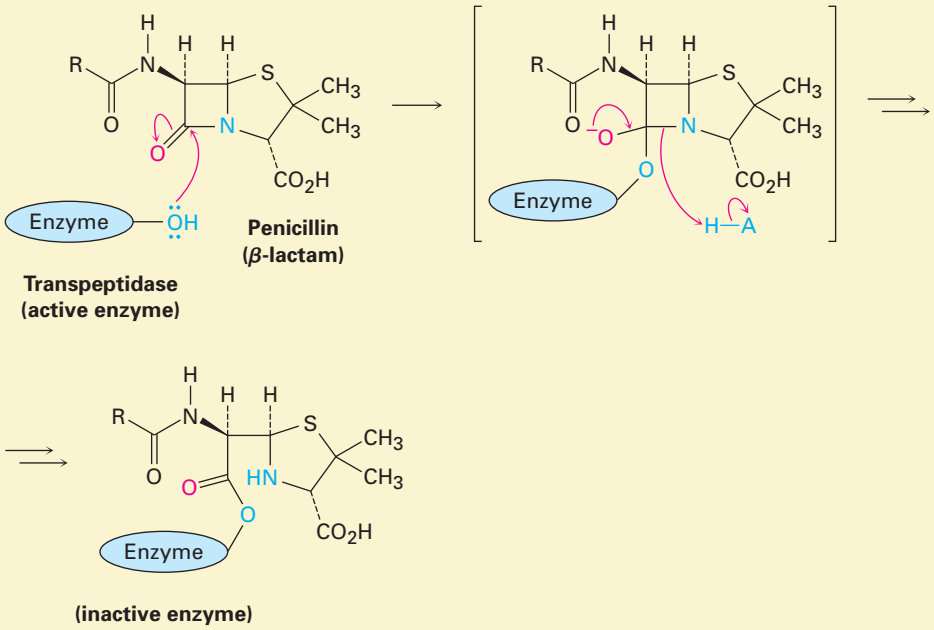
INTERLUDE

example. Cephalosporins generally have much greater antibacterial activity than penicillins, particularly against resistant strains of bacteria.



Cephalexin (a cephalosporin)

The biological activity of penicillins and cephalosporins is due to the presence of the strained, unusually reactive β-lactam ring, which undergoes an irreversible nucleophilic acyl substitution reaction with the transpeptidase enzyme needed to synthesize and repair bacterial cell walls. With the enzyme thus inactivated, the cell walls remain either incomplete or weakened, so the bacteria die.



Penicillin (β-lactam)

Transpeptidase (active enzyme)

(inactive enzyme)

Summary and Key Words

acid anhydride (RCO_2COR') 325
acid halide (RCOCl) 325
acyl phosphate ($RCO_2PO_3^{2-}$) 354
amide ($RCONH_2$) 325
carboxyl group 326
carboxylate ion 332
carboxylic acid (RCO_2H) 325
chain-growth polymer 356
ester (RCO_2R') 325

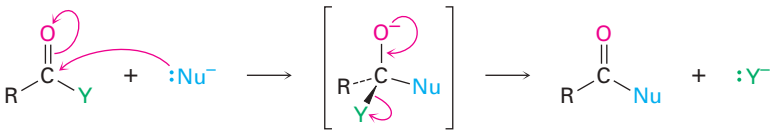
Carboxylic acids and their derivatives are among the most widely occurring of all molecules, both in nature and in the chemical laboratory. In this chapter, we covered the chemistry necessary for understanding them and thus also necessary for understanding the chemistry of living organisms.

The distinguishing characteristic of carboxylic acids is their acidity. Although weaker than mineral acids like HCl, carboxylic acids are much more acidic than alcohols because carboxylate ions are stabilized by resonance.

Carboxylic acids can be transformed into a variety of carboxylic acid derivatives in which the acid –OH group has been replaced by another substituent.

Fischer esterification reaction 339
nitrile (RCN) 325
nucleophilic acyl substitution reaction 335
nylon 356
polyester 357
step-growth polymer 356
thioester (RCOSR′) 354

Acid chlorides, **acid anhydrides**, **esters**, and **amides** are the most common. The chemistry of all these derivatives is similar and is dominated by a single general reaction type: the **nucleophilic acyl substitution reaction**. These substitutions take place by addition of a nucleophile to the polar carbonyl group of the acid derivative, followed by expulsion of a leaving group. The reactivity order of acid derivatives is acid halide > acid anhydride > ester > amide.



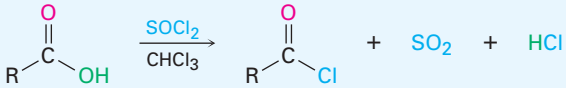
The most common reactions of carboxylic acid derivatives are substitution by water (*hydrolysis*) to yield an acid, by an alcohol (*alcoholysis*) to yield an ester, by an amine (*aminolysis*) to yield an amide, by hydride ion to yield an alcohol (*reduction*), and by an organometallic reagent to yield an alcohol (*Grignard reaction*).

Nitriles, R—C≡N, are related to carboxylic acid derivatives because they undergo nucleophilic additions to the polar C≡N bond in the same way carbonyl compounds do. The most important reactions of nitriles are their hydrolysis to yield carboxylic acids, their reduction to yield primary amines, and their reaction with Grignard reagents to yield ketones.

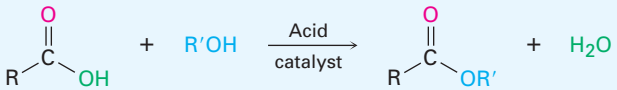
Step-growth polymers, such as polyamides and polyesters, are prepared by reactions between difunctional molecules. Polyamides (nylons) are formed by reaction between a diacid and a diamine; polyesters are formed from a diacid and a diol.

Summary of Reactions

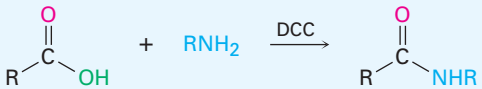
1. Reactions of carboxylic acids (Section 10.6)
   (a) Conversion into acid chlorides



   (b) Conversion into esters (Fischer esterification)



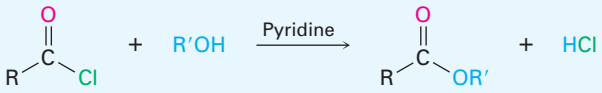
   (c) Conversion into amides



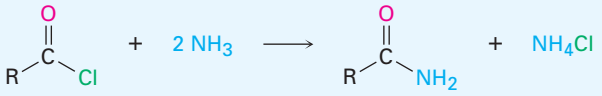
2. Reactions of acid halides (Section 10.7)
   (a) Conversion into carboxylic acids

continued

(b) Conversion into esters

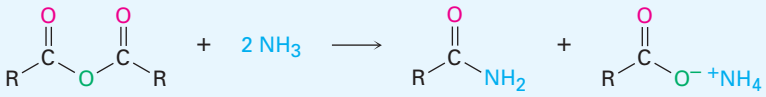


(c) Conversion into amides

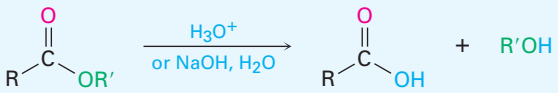


3. Reactions of acid anhydrides (Section 10.8)
(a) Conversion into esters

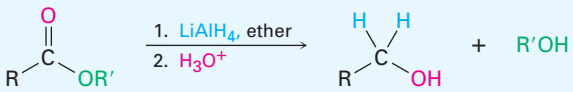
(b) Conversion into amides



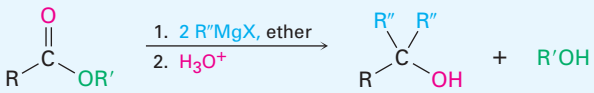
4. Reactions of esters (Section 10.9)
(a) Conversion into acids



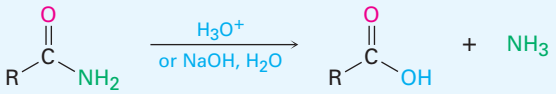
(b) Conversion into primary alcohols by reduction



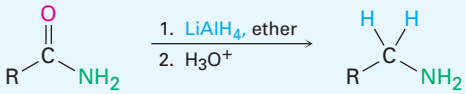
(c) Conversion into tertiary alcohols by Grignard reaction



5. Reactions of amides (Section 10.10)
(a) Conversion into carboxylic acids

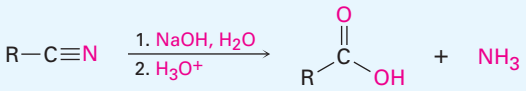


(b) Conversion into amines by reduction

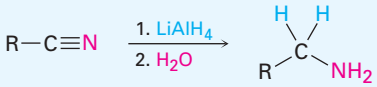


6. Reactions of nitriles (Section 10.11)

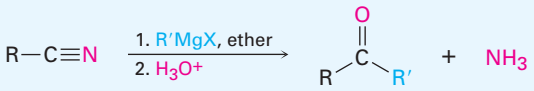
(a) Conversion into carboxylic acids



(b) Conversion into amines by reduction



(c) Conversion into ketones by Grignard reaction



Exercises

Visualizing Chemistry

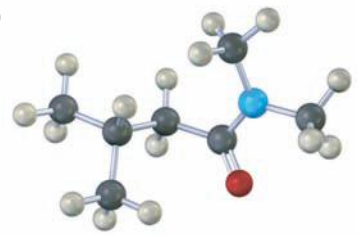
(Problems 10.1–10.27 appear within the chapter.)

OWL

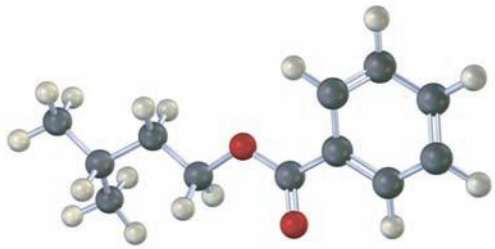
Interactive versions of these problems are assignable in OWL.

10.28 Name the following compounds (red = O, blue = N):

(a)

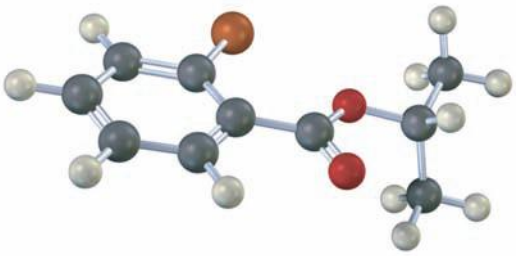


(b)

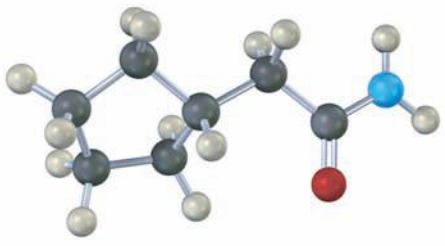


10.29 Show how you could prepare each of the following compounds starting with an appropriate carboxylic acid and any other reagents needed (red = O, blue = N, reddish brown = Br):

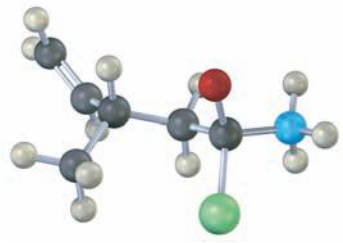
(a)



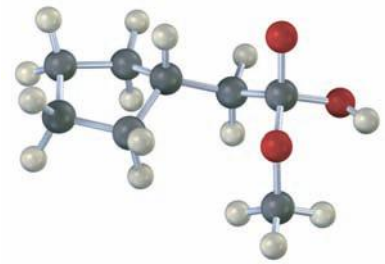
(b)



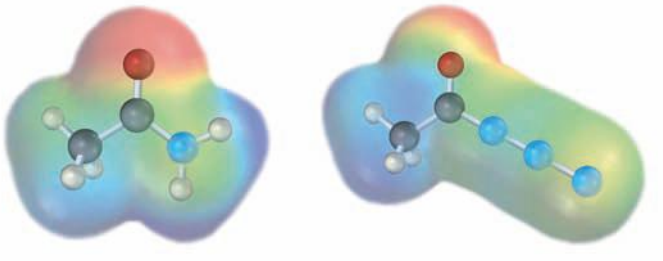
10.30 The following structure represents a tetrahedral alkoxide ion intermediate formed by addition of a nucleophile to a carboxylic acid derivative. Identify the nucleophile, the leaving group, the reactant, and the ultimate product (red = O, blue = N, yellow-green = Cl).



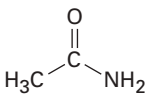
10.31 The following structure represents a tetrahedral alkoxide ion intermediate formed by addition of a nucleophile to a carboxylic acid derivative. Identify the nucleophile, the leaving group, the reactant, and the ultimate product (red = O, blue = N).

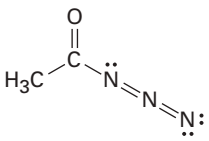


10.32 Electrostatic potential maps of a typical amide (acetamide) and an acyl azide (acetyl azide) are shown. Which of the two do you think is more reactive in nucleophilic acyl substitution reactions? Explain.



Acetamide





Acetyl azide

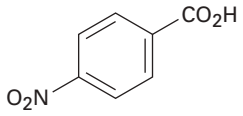
Additional Problems

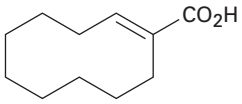
Naming Carboxylic Acids and Derivatives

10.33 Give IUPAC names for the following carboxylic acids:

(a) $CH_3CHCH_2CH_2CHCH_3$ (CO_2H at each end)

(b) CH_3CCO_2H (CH_3 and CH_3 on the carbon)

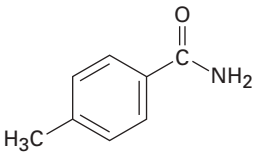
(c) 

(d) 

(e) $CH_3CH_2CH_2CHCH_2CH_3$ (CH_2CO_2H on the CH)

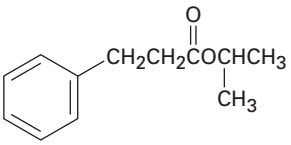
(f) $BrCH_2CHCH_2CH_2CO_2H$ (Br on the CH)

10.34 Give IUPAC names for the following carboxylic acid derivatives:

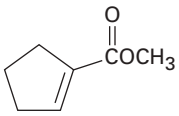
(a) 

(b) $CH_3CH_2CHCH{=}CHCCl$ (CH_2CH_3 and O on the CH; O on the CCl)

(c) $CH_3OCCH_2CH_2COCH_3$

(d) 

(e) $CH_3CHCH_2CNHCH_3$ (O on the CH; Br on the CH)

(f) 

10.35 Draw structures corresponding to the following IUPAC names:

(a) 4,5-Dimethylheptanoic acid
(b) *cis*-Cyclohexane-1,2-dicarboxylic acid
(c) Heptanedioic acid
(d) Triphenylacetic acid
(e) 2,2-Dimethylhexanamide
(f) Phenylacetamide
(g) Cyclobut-2-enecarbonitrile
(h) Ethyl cyclohexanecarboxylate

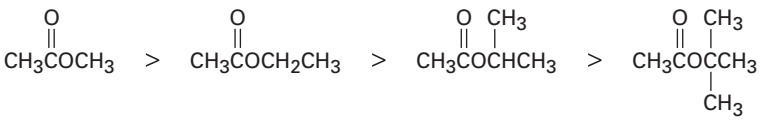
10.36 Draw and name the eight carboxylic acids with formula $C_6H_{12}O_2$. Which are chiral?

10.37 Draw and name compounds that meet the following descriptions:

(a) Three acid chlorides, C_6H_9ClO
(b) Three amides, $C_7H_{11}NO$
(c) Three nitriles, C_5H_7N
(d) Three esters, $C_5H_8O_2$

Reactivity and Acidity

10.38 The following reactivity order has been found for the saponification of alkyl acetates by aqueous NaOH:



How can you explain this reactivity order?

10.39 Rank the following compounds in order of their reactivity toward nucleophilic acyl substitution:

(a) CH_3COCH_3 **(b)** CH_3CCl **(c)** CH_3CNH_2 **(d)** CH_3COCCH_3

10.40 Citric acid has $pK_a = 3.14$, and tartaric acid has $pK_a = 2.98$. Which acid is stronger?

10.41 Order the compounds in each of the following sets with respect to increasing acidity:
(a) Acetic acid, chloroacetic acid, trifluoroacetic acid
(b) Benzoic acid, *p*-bromobenzoic acid, *p*-nitrobenzoic acid
(c) Acetic acid, phenol, cyclohexanol

10.42 How can you explain the fact that 2-chlorobutanoic acid has $pK_a = 2.86$, 3-chlorobutanoic acid has $pK_a = 4.05$, 4-chlorobutanoic acid has $pK_a = 4.52$, and butanoic acid itself has $pK_a = 4.82$?

10.43 Methyl trifluoroacetate, $CF_3CO_2CH_3$, is more reactive than methyl acetate, $CH_3CO_2CH_3$, in nucleophilic acyl substitution reactions. Explain.

REACTIONS

10.44 Predict the product(s) of the following reactions:

(a) $CO_2CH_2CH_3$ → 1. CH_3CH_2MgBr 2. H_3O^+ → ?

(b) $CH_3CHCH_2CH_2C{\equiv}N$ → 1. $LiAlH_4$ 2. H_2O → ?

(c) $COCl$ → CH_3NH_2 → ?

(d) CO_2H, H, CH_3, H → CH_3OH, H_2SO_4 → ?

(e) $H_2C{=}CHCHCH_2CO_2CH_3$ (CH_3) → 1. $LiAlH_4$ 2. H_3O^+ → ?

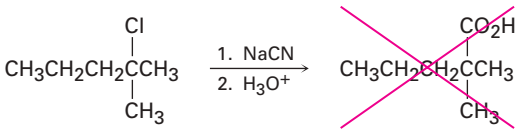
(f) OH → $CH_3CO_2COCH_3$, Pyridine → ?

(g) $CONH_2$, CH_3 → 1. $LiAlH_4$ 2. H_2O → ?

(h) CO_2H, Br → $SOCl_2$ → ?

10.45 Predict the product of the reaction of *p*-methylbenzoic acid with each of the following reagents:
(a) $LiAlH_4$ **(b)** CH_3OH, HCl **(c)** $SOCl_2$ **(d)** NaOH, then CH_3I

10.46 A chemist in need of 2,2-dimethylpentanoic acid decided to synthesize some by reaction of 2-chloro-2-methylpentane with NaCN, followed by hydrolysis of the product. After carrying out the reaction sequence, however, none of the desired product could be found. What do you suppose went wrong?



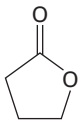
10.47 If 5-hydroxypentanoic acid is treated with an acid catalyst, an intramolecular esterification reaction occurs. What is the structure of the product? (*Intramolecular* means within the same molecule.)

$HOCH_2CH_2CH_2CH_2CO_2H$ **5-Hydroxypentanoic acid**

10.48 How can you explain the observation that an attempted Fischer esterification of 2,4,6-trimethylbenzoic acid with methanol/HCl is unsuccessful? No ester is obtained, and the starting acid is recovered unchanged.

10.49 Acid chlorides undergo reduction with $LiAlH_4$ in the same way that esters do to yield primary alcohols. What are the products of the following reactions?

10.50 What product would you expect from the reaction of a cyclic ester such as butyrolactone with $LiAlH_4$?

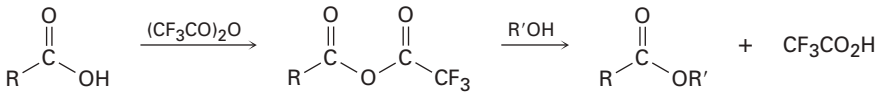


Butyrolactone

MECHANISMS

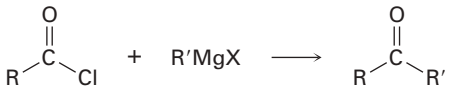
10.51 The reaction of an acid chloride with $LiAlH_4$ to yield a primary alcohol (Problem 10.49) takes place in two steps. The first step is a nucleophilic acyl substitution of H^- for Cl^- to yield an aldehyde, and the second step is nucleophilic addition of H^- to the aldehyde to yield an alcohol. Write the mechanism of the reduction of CH_3COCl.

10.52 Reaction of a carboxylic acid with trifluoroacetic anhydride leads to an unsymmetrical anhydride that rapidly reacts with alcohol to give an ester.



(a) Propose a mechanism for formation of the unsymmetrical anhydride.
(b) Why is the unsymmetrical anhydride unusually reactive?
(c) Why does the unsymmetrical anhydride react as indicated rather than giving a trifluoroacetate ester plus carboxylic acid?

10.53 Acid chlorides undergo reaction with Grignard reagents at −78 °C to yield ketones. Propose a mechanism for the reaction.



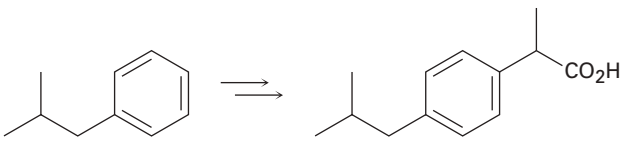
10.54 If the reaction of an acid chloride with a Grignard reagent (Problem 10.53) is carried out at room temperature, a tertiary alcohol is formed.
(a) Propose a mechanism for this reaction.
(b) What are the products of the reaction of CH_3MgBr with the acid chlorides given in Problem 10.49?

SYNTHESIS

10.55 How can you prepare acetophenone (methyl phenyl ketone) from the following starting materials? More than one step may be needed.
(a) Benzonitrile **(b)** Bromobenzene
(c) Methyl benzoate **(d)** Benzene

10.56 How might you prepare the following products from butanoic acid? More than one step may be needed.
(a) $CH_3CH_2CH_2CH_2OH$ **(b)** $CH_3CH_2CH_2CHO$
(c) $CH_3CH_2CH_2CH_2Br$ **(d)** $CH_3CH_2CH_2CH_2CN$
(e) $CH_3CH_2CH{=}CH_2$ **(f)** $CH_3CH_2CH_2CH_2NH_2$

10.57 Show how you might prepare the anti-inflammatory agent ibuprofen starting from isobutylbenzene. More than one step is needed.



Isobutylbenzene **Ibuprofen**

GENERAL PROBLEMS

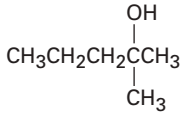
10.58 When dimethyl carbonate, $CH_3OCO_2CH_3$, is treated with phenylmagnesium bromide, triphenylmethanol is formed. Explain.

10.59 Predict the product, if any, of reaction between propanoyl chloride and the following reagents. (See Problems 10.49 and 10.53.)
(a) Excess CH_3MgBr in ether **(b)** NaOH in H_2O
(c) Methylamine, CH_3NH_2 **(d)** $LiAlH_4$
(e) Cyclohexanol **(f)** Sodium acetate

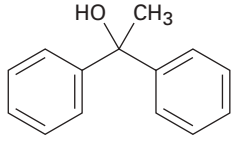
10.60 Answer Problem 10.59 for reaction between methyl propanoate and the listed reagents.

10.61 What esters and what Grignard reagents would you use to make the following alcohols? Show all possibilities.

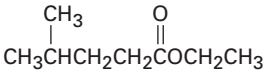
(a)

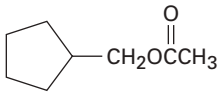


(b)

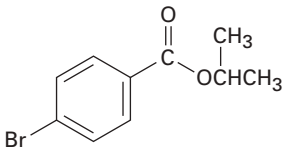


10.62 How could you make the following esters:

(a) 

(b) 

10.63 What products would you obtain on saponification of the following esters?

(a) 

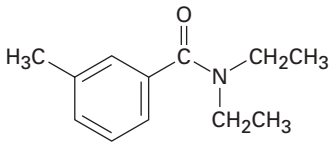
(b) Cyclohexyl propanoate

10.64 When *methyl* acetate is heated in pure ethanol containing a small amount of HCl catalyst, *ethyl* acetate results. Explain.

10.65 *tert*-Butoxycarbonyl azide, an important reagent used in protein synthesis, is prepared by treating *tert*-butoxycarbonyl chloride with sodium azide. Propose a mechanism for this reaction.

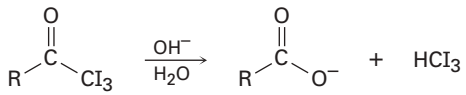
10.66 What product would you expect to obtain on treatment of the cyclic ester butyrolactone with excess phenylmagnesium bromide? (See Problem 10.50.)

10.67 *N,N*-Diethyl-*m*-toluamide (DEET) is the active ingredient in many insect repellents. How might you synthesize DEET from *m*-bromotoluene?

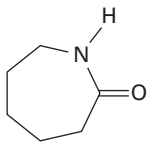


***N,N*-Diethyl-*m*-toluamide**

10.68 In the *iodoform reaction,* a triiodomethyl ketone reacts with aqueous NaOH to yield a carboxylate ion and iodoform (triiodomethane). Propose a mechanism for this reaction.



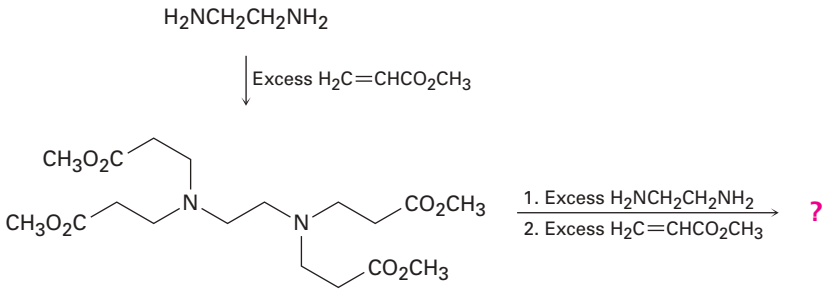
10.69 The step-growth polymer called nylon 6 is prepared from caprolactam. The reaction involves initial reaction of caprolactam with water to give an intermediate amino acid, followed by heating to form the polymer. Propose mechanisms for both steps, and show the structure of nylon 6.



Caprolactam

10.70 Draw a representative segment of the polyester that would result from reaction of pentanedioic acid ($HO_2CCH_2CH_2CH_2CO_2H$) and pentane-1,5-diol.

10.71 A *dendrimer,* unlike a linear polymer, is a highly branched, tree-shaped molecule. An example is formed by reaction of ethylenediamine ($H_2NCH_2CH_2NH_2$) with methyl acrylate ($H_2C{=}CHCO_2CH_3$). The synthesis begins with initial formation of a tetraester, which is allowed to react with more diamine to give a tetraamino tetraamide. The tetraamino tetraamide then reacts again with excess methyl acrylate to form an octaester, which reacts again with excess diamine, and so on.



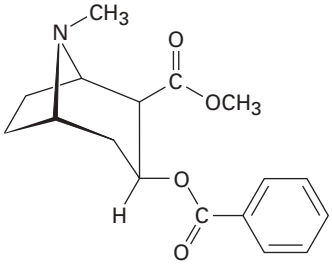
A tetraester

(a) What kind of reaction is involved in the initial reaction of the diamine with methyl acrylate?

(b) What kind of reaction is involved in the reaction of the tetraester with diamine? Show the product.

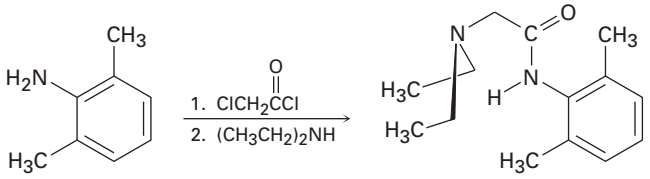
IN THE MEDICINE CABINET

10.72 Yesterday's drug can be today's poison. Cocaine enjoyed a much better reputation 100 years ago, when it was used as a stimulant in many products (including Coca-Cola) as well as in drops to treat toothaches and depression. What three molecules are produced by hydrolysis of cocaine?



Cocaine

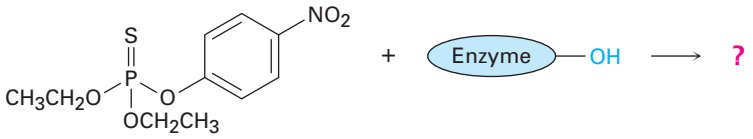
10.73 Cocaine's addictive properties led researchers to look for less addictive alternatives to relieve pain. Lidocaine, for instance, has many of the structural features of cocaine (Problem 10.72) but doesn't have the same risk. Lidocaine is prepared by the reaction sequence shown. Indicate the type of reaction in each step, and draw a mechanism.



Lidocaine

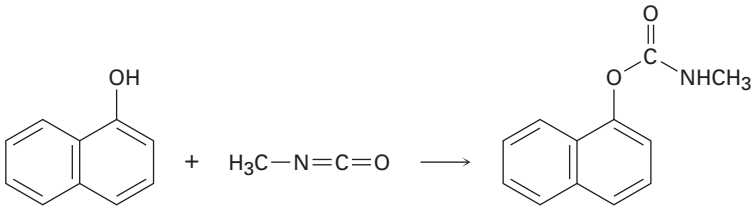
IN THE FIELD

10.74 Parathion was one of the first organophosphate insecticides. Assuming that the P=S group shows the same chemistry as a C=O group and that *p*-nitrophenoxide ion is a good leaving group, show how parathion can inactivate its target enzyme (acetylcholine esterase) by forming a stable enzyme intermediate.



Parathion

10.75 Carbaryl, an insecticide marketed under the trade name Sevin, is prepared by reaction between a phenol and methyl isocyanate, $H_3C{-}N{=}C{=}O$. Propose a mechanism for the reaction.



Methyl isocyanate **Carbaryl**